BL 6

Business Plan

2008-2013

Drug development and evaluation for helminths and other neglected tropical diseases

Draft Business Plan for JCB

May, 2007

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Needs and Opportunities

Helminthiases are responsible for an enormous burden of disease in developing countries. This has been highlighted in recent years through WHO's development and promotion of an integrated strategy to address neglected tropical diseases. Although many new PPP's have been established for the development of drugs against certain neglected infectious diseases, none of them addresses the drug needs for human helminths and a variety of other diseases. The control of helminthiases is based on preventive mass chemotherapy of populations at risk. Effective drugs are available, but they are few, and their extended use carries the risk of drug resistance development. Further research is also required to support their scaled-up use in combinations. The situation is particularly critical for onchocerciasis for which annual mass treatment with ivermectin has brought the disease under control but has not eliminated the adult parasites. The development of a safe macrofilaricide that would allow onchocerciasis eradication is therefore a top research priority. The drugs for lymphatic filariasis and schistosomiasis control have also limited effect on the adult or immature stages of the parasites, and more potent drugs would be of immense value for more effective control or elimination of these diseases.

Overall Objective

To develop new and optimize the use of currently available drugs for helminths and other neglected tropical diseases (NTDs).

Specific Objectives

- Development and registration of new drugs for onchocerciasis, lymphatic filariasis, schistosomiasis and other helminthiasis and field evaluation of their effectiveness to achieve the control programme objectives they are being developed for.
- Generation of evidence for improved use of currently available drugs to support disease control, elimination or eradication strategies for NTDs with emphasis on integrated disease management or prophylactic chemotherapy including:
  - Evaluation of the efficacy and safety of modifications of currently used doses or treatment regimens
  - Evaluation of efficacy and safety of combinations of currently available drugs
  - Assessment of safety and efficacy of co-administration of drugs
  - Evaluation of product safety and efficacy in children and pregnant women
- Development of products for other neglected diseases when an opportunity emerges and no other organization is available or has the know-how to do so.

Activities

The activities of the business line will involve the identification of development drug candidates and their progression into development, building on the work of BL 3. Product development will be undertaken according to a development strategy and plan, and legal agreement between WHO and Pharmaceutical partners, to generate evidence on efficacy and safety for drug registration by partners. Once a new drug is registered, the business line will proceed with field studies to determine the safety and effectiveness of the drugs in real-life settings, and their operational value for disease control and/or elimination. Clinical studies will be undertaken to provide data for improved use of currently available drugs for diseases targeted in integrated intervention strategies in line with WHO strategy. To optimize the effectiveness and relevance of the research activities, there will be close interaction with disease control programs and with Bio/Pharma companies in the North and South, while expounding and utilizing capacity and infrastructure in disease endemic countries.

End-Products

- Pre-clinical and clinical evidence of efficacy and safety of new drugs against helminths that support registration by pharmaceutical partners (e.g. registration of moxidectin by 2013).
- Evidence that the registered drugs are safe for large scale use and more effective than currently used drugs in the control of onchocerciasis, lymphatic filariasis. schistosomiasis and other helminthic diseases (e.g. impact of moxidectin on onchocerciasis transmission).
- New information for the utilization of drugs for diseases targeted for the integrated approach and multi intervention packages for disease control (e.g. combined use of praziquantel and oxamniquine).
- Evidence for improved use of currently available drugs to support disease control, elimination or eradication strategies (e.g. effect of benznidazole on chronic Chagas' disease).
- Capacity in centres in developing countries for conducting clinical trials and capacity of developing country regulatory authorities to review and approve clinical trial exemptions and new drug applications.

Comparative Advantage

TDR has around 25 years of experience and track record in discovery, development and operational evaluation of drugs for onchocerciasis, lymphatic filariasis and schistosomiasis; it has provided the evidence on which the global control and elimination strategies for these diseases are based. TDR has been supporting research on drug resistance and has clinically evaluated 5 drug candidates for onchocerciasis in the last 8 years. TDR has a track record of motivating pharmaceutical companies to provide their drug compounds for development for

tropical diseases and to collaborate in and co-fund the development of these compounds. TDR has conducted key clinical research of the safety and efficacy of concomitant administration of key drugs for integrated disease control. It has a track record in building, strengthening and utilizing capacity for Good Clinical Practices, Good Laboratory Practices, and Ethical review in disease endemic countries and conducting clinical trials according to internationally accepted standards. Finally, TDR has particularly close links with the African Programme for Onchocerciasis Control (APOC), the Lymphatic Filariasis Elimination programmes and Schistosomiasis Control programmes which consider TDR to be their research arm. TDR works very closely with WHO's Neglected Tropical Diseases department in this area and responds to, informs and builds on its strategies for NTD control and elimination.

1. OBJECTIVE

1.1. OVERALL OBJECTIVE

The overall objective of "Business Line 6" is to develop new and optimize the use of currently available drugs for helminths and other neglected tropical diseases (NTDs).

This TDR "Business Line 6" is being proposed in the context of the innovative strategy that the World Health Organization (WHO), together with its partners, has formulated to ensure cost-effective, ethical and sustainable control towards elimination or eradication of several NTDs[1]. The strategy encompasses the following components:

- a multi-pronged approach;
- focus on populations and interventions rather than specific diseases;
- use of a quasi-immunization model for preventive chemotherapy;
- introduction of innovative tools for disease control;
- a multi-disease, intersectoral and inter-programmatic approach.

1.2. SPECIFIC OBJECTIVES

The objective of BL 6 will be in line with the strategic areas for action proposed in the WHO Global Plan to Combat Neglected Tropical Diseases (2008-2015), in particular in the area of: "Access to innovation" (6.6) and in the "Integrated approach and multi-intervention packages for disease control" (6.2).

BL 6 will pursue 3 specific objectives:

1. Development and registration of new drugs for onchocerciasis, lymphatic filariasis, schistosomiasis and other helminthiasis and field evaluation of their effectiveness to achieve the control programme objectives they are being developed for.
2. Generation of evidence for improved use of currently available drugs to support disease control, elimination or eradication strategies for NTDs with emphasis on integrated disease management or prophylactic chemotherapy including:
   - Evaluation of the efficacy and safety of modifications of currently used doses or treatment regimens with a view towards enhancing their efficacy
   - Evaluation of efficacy and safety of combinations of currently available drugs to enhance efficacy

[1] Global Plan to Combat Neglected Tropical Diseases (Draft), WHO, 2008-2015

- Assessment of safety and efficacy of co-administration of drugs used for control / management of different diseases
- Evaluation of product safety and efficacy in special populations (children and pregnant women)

3 Development of products for other neglected diseases when an opportunity emerges and no other organization is available or has the know-how to do so.

An integral part of the activities conducted or sponsored to achieve BL6 objectives will be the building and utilization of capacity in the disease endemic countries for drug development, in particular the planning, preparation, conduct and analysis of clinical trials according to internationally accepted standards and the review of regulatory dossiers. In addition and depending on the types of development projects being included in the BL portfolio, capacity for preclinical toxicology studies will be built and utilized.

2. NEEDS AND OPPORTUNITIES

Access to innovation is an integral part of control activities because it allows optimization of NTD control strategies. TDR trough BL 6 is well positioned to address the following needs of the WHO global strategy for NTDs:

- define the profile of key new tools enabling implementation of new strategies for NTD control (for either diagnosis (BL6) or treatment or prevention or all of them);
- facilitate the implementation of clinical trials at field level by involving and mobilizing national control programme capacities;
- ensure strong coordination between national authorities in charge of control activities and groups engaged in research and development;
- ensure rapid dissemination of the new or optimized tools as soon as the registration or evaluation process is completed.

2.1 ONCHOCERCIASIS

Around 120 Million people live in areas meso- or hyperendemic for onchocerciasis with around 40 Million infected. Control is based on annual ivermectin mass treatment in most of these areas which can reduce, but not interrupt transmission throughout Africa. Maintaining current achievements in onchocerciasis control will require sustaining mass treatment for an unforeseeable number of years, a major challenge for the health systems. Furthermore, prolonged ivermectin treatment brings an increased risk of ivermectin resistance. If resistance should emerge, all achievements in controlling this disease would be lost. Consequently, the development of a safe and easily administered macrofilaricide (a drug which kills or permanently sterilizes adult Onchocerca volvulus) for eradication of onchocerciasis is a key research priority.

Opportunities

- In collaboration with Wyeth Research, moxidectin has already passed four of the six major milestones to registration (pre-clinical pharmacology suggesting its potential to be macrofilaricidal and/or permanently macrofilaria sterilizing in O. volvulus, animal toxicology, cost effective formulation, safety studies in healthy volunteers) and is currently undergoing the first clinical trial in subjects infected with Onchocerca volvulus.
- Emodepside, a new anthelminthic compound with a novel mechanism of action being developed by Bayer for animal health, is currently undergoing the final TDR sponsored pre-clinical testing for its potential utility in onchocerciasis. The results of

this testing taken together with the animal toxicology data obtained by Bayer will allow to make the decision whether to progress emodepside to development.

- The TDR supported Drug Discovery Network (BL3) has recently identified several compounds that warrant further evaluation for their potential to result in drug candidates.

2.2 LYMPHATIC FILARIASIS

Around 1.1 Billion people live in areas with lymphatic filariasis (LF) transmission, around 120 Million people are infected worldwide. Control of LF is based on the mass drug administration of albendazole plus ivermectin or diethylcarbamazine (DEC). These combinations are effective in killing the microfilaria but are not very potent in terms of their effect on the adult worm. The need to administer two separate drugs poses operational difficulties.

The stakeholders of the LF elimination initiatives stressed during the 'LF Research Forum': Towards a Strategic Plan for Research to Support the Global Programme to Eliminate Lymphatic Filariasis (Philadelphia, 2003) and during the TDR Scientific Working Group on Lymphatic Filariasis (Geneva, 10-12 May 2005) the value of more potent macrofilaricidal drugs both for LF elimination and for halting progression of morbidity which is largely due to adult worms.

Opportunities

- The in vitro and animal model data obtained on moxidectin by the TDR supported Drug Discovery Network show that moxidectin has at least as much promise for LF as for onchocerciasis.
- The TDR supported Drug Discovery Network (BL3) has recently identified several compounds that will be optimized to obtain potential drug candidates.
- Wolbachia (endosymbiont of filarial worms) has been recently identified as a drug target against adult worms. This has prompted other institutions to establish an active drug discovery program. The experience and infrastructure available at TDR may provide an appropriate clinical evaluation platform to conduct the necessary clinical research able to address the regulatory requirements.

2.3 SCHISTOSOMIASIS

More than 600 million people are at risk of schistosomiasis worldwide, and close to 200 million are actually infected. Disease control is based on large scale treatment with praziquantel (PZQ) the only drug available for disease control since oxamniquine, the other drug available, is too expensive for most countries.

Praziquantel has only limited efficacy against immature worms which is a problem particularly in areas with high disease transmission. Parasites with decreased susceptibility to PZQ have been isolated. It is unclear whether these isolates represent natural variation of parasite susceptibility to praziquantel or whether they herald emerging resistance which has to be expected for any anti-infective used on a large scale for a long period of time. The control efforts of the past 25 years have reduced the intensity of infection, but have not reduced disease transmission.

The need for new drugs with a different mechanism of action, including those which kill immature stages of the parasite and could thus significantly impact disease transmission as well as optimization of praziquantel treatment were identified as a high priority during the TDR Scientific Working Group on Schistosomiasis (Geneva, 14-16 November 2005).

Opportunities

- Several clinical and pre-clinical studies show that artemisinin derivatives (including synthetic peroxides) have the potential to kill the immature stages of the schistosomes.
- Data available to date suggest that the stereo-selective synthesis of L-praziquantel is feasible and could be cost effective.
- Oxamniquine analogues, acridone derivatives, benzodiazepine derivatives/analogues and cyclosporines, alkylamino octane thio sulfuric acids and plant derivatives have been discussed in the past as potential drug development candidates, but were not further pursued because of the availability of praziquantel. These compounds may be worthwhile revisiting.
- The TDR supported Drug Discovery Network (BL3) has recently identified several compounds that could be considered new leads.

2.4 SOIL TRANSMITTED HELMINTHS

Soil-transmitted helminths (STH) continue to impose an excessive disease burden on poor populations primarily in the tropics and sub-tropics. It is estimated that more than 1 billion have roundworm infections. Hookworms and whipworms each infect more than 700 million people and pinworms infect more than 200 Million. STHs cause anaemia in those heavily

infected, especially by hookworms. Women of children-bearing age in endemic areas also have an additional burden of iron-deficiency anaemia due to hookworm infections. STHs furthermore cause malnutrition, growth retardation and reduced learning capacity in children.

Four drugs are currently recommended for the treatment of STH infections: the benzimidazoles albendazole and mebendazole are easy to administer and used on a wide scale by most endemic countries. Only a few countries use pyrantel and levamisole on a wide-scale.

Based on experience in veterinary practice the scale up of albendazole and mebendazole mass treatment to treat at least 75% of the school-age children at risk of infection by 2010 (WHA resolution 54.19) may result in development of drug resistance in the human parasites. To avoid or address benzimidazole resistance, additional drugs with a different mechanism of action and suitable for prophylactic mass treatment (ease of administration, safety profile, affordability) are needed. Furthermore, given the potential teratogenic effect of the available drugs when used during the first trimester, affordable drugs without any potential risk during pregnancy are highly desirable. Despite this need, discovery and development of new drug candidates for STHs is one of the most neglected research areas within the neglected diseases. Within the developed country pharmaceutical industry no recent drug candidates have emerged nor are drug development programs being pursued.

Opportunities

- TDR initiative (BL 3) to discover new leads and candidates against Helminths ("Helminth initiative") will provide a pipeline with development candidates.
- Tribendimidine is a new anthelminthic drug that was developed in China. It is a potentially interesting compound, because it belongs to a different family than the broad-spectrum anthelminthics currently on the WHO essential medicines list.
- New products currently used in managing animal helminth infections
- The biology and molecular basis for benzimidazole resistance is well understood. This could provide an opportunity to develop tools to monitor emergence of resistance in human parasites.
- Pregnancy registries are being developed for neglected diseases (malaria, AIDS) to determine the real teratogenic potential of the drugs used for these diseases when inadvertently used during pregnancy. This experience provides an opportunity to address similar concerns with some of the drugs for the STHs.

2.5 INTEGRATED APPROACH AND MULTI-INTERVENTION PACKAGES

Most of the tropical diseases share many features that make integrated interventions and technical guidance both feasible and advantageous, in particular: concentration in under-served communities, endemic areas are frequently overlapping and use of same staff, delivery systems, and opportunities for contact with populations

WHO is working towards integration of the control strategies in national health systems and international development policies. The prophylactic use of chemotherapy is being promoted to increase the impact of disease control activities. This requires thorough examination of pharmacological suitability and risk / benefit especially when the drugs are to be administered to uninfected individuals or those at increased risk for adverse events due to underlying diseases or physiological conditions.

Opportunities

- TDR has developed a network of experts and infrastructure in developed and developing countries capable of conducting and interpreting human pharmacology studies (pharmacokinetics, pharmacodynamics, drug-drug interaction).

2.6 "TOOL DEFICIENT" DISEASES

The WHO Global Plan to Combat Neglected Tropical Diseases (2008-2015) has identified the need for intensified efforts for NTDs other than lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiasis, i.e.: Buruli ulcer, Chagas disease, cholera, dracunculiasis, leishmaniasis, leprosy, yaws, human African trypanosomiasis, dengue as well as zoonoses such as anthrax, brucellosis, cysticercosis, echinococcosis, and rabies. For these diseases intervention tools are either not existent or inadequate for the health systems.

TDR BL 6 will address development and evaluation of tools for these diseases on a case by case basis when opportunities arise and when no other institution is addressing them.

Opportunities

- Potential of PAFR (platelet activating factor receptor) antagonists to prevent progression of dengue towards shock and haemorrhagic syndrome.
- Moxidectin and ivermectin may provide an opportunity to develop an indication against other helminths, cysticercosis or equinococcosis.
- TB drug development candidates may provide opportunities for Buruli ulcer
- New generation azoles for Chagas disease

3. COMPARATIVE ADVANTAGE

3.1 TDR COMPARATIVE ADVANTAGE

TDR is well positioned to address product development through partnerships with the public and private sectors. TDR has around 25 years of experience and track record in discovery, development and field evaluation of drugs for onchocerciasis, lymphatic filariasis and schistosomiasis working in collaboration with disease control programmes.

Proven technical and field experience

- TDR has been supporting research on developing tools and assessing the potential for emergence of resistance against ivermectin and benzimidazoles.
- TDR has an extensive network of collaborators in developed and developing countries for drug discovery, development and field evaluation of products for tropical diseases. Thus, TDR has a proven capacity to work in partnership with the pharmaceutical "for profit" industry to obtain chemical entities for the initial research that leads to identification of drug candidates. TDR has a track record of motivating pharmaceutical companies (Merck, Wyeth, Bayer, Pfizer, Novartis, GSK) to provide their drug compounds for development for tropical diseases and to collaborate in and co-fund the development of these compounds, resulting in regulatory registration of the drugs by the pharmaceutical companies and ensuring accessibility of the products. TDR played a cardinal role in the development and evaluation of ivermectin as a tool to control onchocerciasis by working in partnership with Merck and the onchocerciasis control programmes.
- TDR supported drug development has clinically evaluated 5 drug candidates for onchocerciasis in the last 8 years.
- TDR has conducted key clinical research of the safety and efficacy of concomitant administration of key drugs (albendazole, DEC, ivermectin, and praziquantel) for integrated disease control.

Capacity building capabilities in developing countries

- TDR has a track record in building, strengthening and utilizing capacity for Good Clinical Practices (GCP), Good Laboratory Practices (GLP), and Ethical review required for countries, health care centres and staff in the disease endemic countries to conduct clinical trials according to internationally accepted standards:
- Onchocerciasis Chemotherapy Research Centre in Hohoe, Ghana

- LF: Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, Mumbai, India)
- Schistosomiasis: China, Mauritania, Tanzania, Philippines, Brazil and Sudan

Demonstrated stewardship/facilitation of agenda setting

- TDR has particularly close links with the African Onchocerciasis Control Programme (APOC), the Lymphatic Filariasis elimination programmes and Schistosomiasis Control programmes which consider TDR to be their research arm.

4. ACTIVITIES AND END PRODUCTS

4.1 KEY ACTIVITIES

Portfolio management and priority setting

The project portfolio will be actively managed through regular scientific and management review of:

- project strategy, plan and feasibility of achieving its objectives
- project implementation, progress and resource requirements
- continued relevance and relative priority within the BL activities

This review will be conducted by the BL Scientific Advisory Committee (BL 6 SAC) and the STAC.

Based on the BL objectives as well as portfolio and project management requirements, the portfolio will consist of two groups of projects:

- Long term projects addressing objectives 1 (Development, registration and field evaluation of new drugs for diseases targeted for integrated disease control) and objective 3 (Development and registration of drugs for other NTDs) with an anticipated project life time of 5-10 years. This part of the portfolio is consequently anticipated to be relatively 'stable' and will consume the major part of the financial resources for the BL. Project initiation will have a relatively long 'lead time' to ensure thorough assessment of project options and feasibility (including financial and staffing resource assessment and provision) and to put in place the legal agreement with the development partners.
- Short term projects addressing objective 2 (Generation of evidence for improved use of available drugs) with an anticipated project duration of 1-3 years. This part of the portfolio will be very dynamic with relatively short lead times to project initiation and each project consuming a relatively small fraction of the overall BL budget.

Priority setting will be decided upon by Director TDR and the JCB and is expected to be based on:

- Disease control programme needs, as emerging either from TDR Stewardship or from issues that NTD control programmes experience during the implementation of their strategies.
- Opportunities.
- Anticipated impact of the results of the research.

- Level of engagement of other organizations (determined e.g. via TDR Stewardship).
- Availability of resources (partners, funding, personnel).
- Review and approval/recommendation by BL 6 SAC and STAC from a scientific and TDR strategic point of view and by Director TDR from a management (including personnel and financial resource) point of view.

Table on activities within BL6

Objective	Activities
Across all objectives	• Strengthen the interaction with (NTD) disease control programs and initiatives • Expand network of collaborators (public and private) for preclinical and clinical development and evaluation of drugs • Engage Bio / Pharma companies (north and south) in development candidate identification, drug development and registration of new chemical entities • Expand and utilize capacity and infrastructure in disease endemic countries for conducting product development activities and/or product evaluation activities • Provide support to conduct the clinical and community studies of new and existing drugs aimed at interruption of disease transmission and reduction of disease manifestations. • Develop fund raising strategy to finance these activities. • Consultation of BL Scientific Advisory Committee
Objective 1: Development and registration of new drugs for onchocerciasis, lymphatic filariasis, schistosomiasis and other helminthiasis and field evaluation of their effectiveness to achieve the control programme objectives they are being developed for. **Objective 3:** Development of products for other neglected diseases when an opportunity emerges and no other organization is available or has the know-how to do so.	**Identification of development drug candidates and progression into development in collaboration with BL 3 (Lead discovery for infectious diseases of poverty).** • Obtain expert advice on available data, the product profile they suggest and its fit with global research priorities and needs of control programmes (in line with TDR role in stewardship). • Identify relevant potential development partners • Generate draft development strategy with financial and staff requirements and fund raising strategy for discussion with potential partners, including funding agencies • Establish the necessary business agreements and contracts, including funding of development activities. **Product development as per the development strategy and plan (agreed upon as part of the legal agreement between WHO and the company) to generate evidence of efficacy and safety for drug registration by pharma partners.** • Develop study plans according to development strategy and regulatory requirements • Identify investigators and centres, strengthen their human capacity and infrastructure • Initiate and manage study conduct and analysis **Field studies for drugs for community based/integrated treatment *** • Establish framework and objectives with disease control partners • Define study strategy and study plans • Identify investigators and centre, strengthen their human capacity and infrastructure • Initiate and manage study conduct and analysis

Objective	Activities
Objective 2: Generation of evidence for improved use of currently available drugs to support disease control, elimination or eradication strategies for NTDs with emphasis on integrated disease management or prophylactic chemotherapy	**Clinical studies to provide data for** **(a) the utilization of drugs for diseases targeted for the integrated approach and multi intervention packages for disease control and** **(b) improved use of currently available drugs to support disease control, elimination or eradication strategies** • Establish framework and objectives with disease control partners • Define study strategy and study plans • Identify investigators and centres and strengthen their human capacity and infrastructure • Initiate and manage study conduct and analysis

* This may include both drugs developed with and without engagement of TDR

4.2. END-PRODUCTS

Table below provides an overview of the objects and end products of the currently planned and potential future projects within BL6. More details on the products are provided further below.

Objectives	End Products	Ongoing Projects	Projects to be initiated after BL formation	Potential projects based on options assessment, e.g.
Objectives 1 and 3	*1) Pre-clinical and clinical evidence of efficacy and safety of new drugs that support registration by pharma partners*	Moxidectin for onchocerciasis and lymphatic filariasis		Emodepside for onchocerciasis L-Praziquantel for schistosomiasis Tribendimidine for STH Platelet activating factor receptor (PAFR) antagonists for Hemorrhagic dengue fever and dengue shock syndrome
Objective 1	*2) Evidence that the registered drugs are safe for large scale use and more effective than currently used drugs in the control of onchocerciasis, lymphatic filariasis. schistosomiasis and other helminthic diseases*	Moxidectin for onchocerciasis and lymphatic filariasis	Pregnancy registers for drugs for onchocerciasis, LF, schistosomiasis and STH contra-indicated for use in pregnancy	
Objective 2	*3) New information for the utilization of drugs for diseases targeted for the integrated approach and multi intervention packages for disease control.*	Proof-of-concept for the efficacy and safety of albendazole in reducing Loa loa microfilaremia Impact of early treatment on LF disease manifestations in children Efficacy and safety of increased praziquantel dose and praziquantel combination with oxamniquine and praziquantel and artemisinin derivatives.		
Objective 2	*4) Evidence for improved use of currently available drugs to support disease control, elimination or eradication strategies*	Efficacy and safety of the combination of nifurtimox and eflornithine for the treatment of 2nd stage HAT Evidence on the effect of benznidazole in indeterminate T. cruzi infection on chronic disease onset or progression		
Cross-objective	*5) Capacity in developing countries for conducting clinical trials and to review and approve clinical trial exemptions and new drug applications*			

Objective 1: Development and registration of new drugs for onchocerciasis, lymphatic filariasis, schistosomiasis and other helminthiasis and field evaluation of their effectiveness to achieve the control programme objectives they are being developed for

End product 1: Pre-clinical and clinical evidence of efficacy and safety of new drugs that support registration by pharma partners.

Current portfolio

- **Moxidectin for onchocerciasis and lymphatic filariasis**

The development strategy and plan agreed upon between Wyeth and TDR is anticipated to result in registration in for treatment of onchocerciasis the target countries between 2013 and 2014.

Following proof of efficacy and safety of moxidectin in onchocerciasis, clinical development for lymphatic filariasis or other helminth diseases will be pursued on the basis of the preclinical pharmacology data, animal toxicology, pharmaceutical development, and human volunteer data conducted for development for onchocerciasis. The safety data obtained in the clinical studies conducted for onchocerciasis, if indicating the safety profile required for a drug designed for mass treatment, will provide the basis for a large efficacy and safety study in LF infected subjects that will complete the registration dossier.

Potential future projects based on options assessment

- **Back-up compounds for onchocerciasis**

Success rates in drug development are low. Thus, development of a 'back-up' compound is advisable even when a promising compound such as moxidectin has already reached Phase 2 clinical development.

The cyclooctadepsipeptide 'Emodepside' (Bayer) is a new anthelmintic compound currently under development as a veterinary drug by Bayer of Germany that has shown exceptionally good activity against onchocerciasis models.

Should emodepside qualify as a candidate for development (through BL 3), TDR will work to engage Bayer in the development for onchocerciasis.

- **L-Praziquantel for schistosomiasis**

Praziquantel (PZQ) is the only drug currently available/affordable to schistosomiasis control programmes in the majority of endemic countries.

The available formulation is a racemate containing 50% of D-praziquantel which is parasitologically inactive but contributes to toxicity. Preliminary work in China shows L-PZQ to be superior to racemic PZQ since a comparable level of efficacy is associated with fewer side effects. If large scale manufacturing of a formulation of L-PZQ is shown to be cost-effective, L-PZQ could be developed with different objectives: (a) same dose of L-PZQ as currently with smaller tablet size and less frequent/severe adverse events, (b) higher dose

of L-PZQ with similar tablet size and possibly similar adverse event profile as current treatment which could reduce the probability of or delay the development of resistance, or (c) a combination of these two objectives.

- **Tribendimidine for STH**

A drug (N,N'-bis(4-(1-dimethylamino) ethylidene aminophenyl)-1,4-phenylene imethylidyne amine) belonging to a new chemical class of antihelmintic drugs is currently being developed in PR China. It has a broad activity against intestinal helminths and is potentially safe for use during 1st trimester of pregnancy as well as amenable to use in children.

End product 2: Evidence that the registered drugs are safe for large scale use and more effective than currently used drugs in the control of onchocerciasis, lymphatic filariasis. schistosomiasis and other helminthic diseases

This will build on TDR's experience in community trials (ivermectin trials which established the efficacy and safety of ivermectin during large scale use and led to the community directed treatment paradigm of the onchocerciasis control programmes, ongoing community studies which evaluate under which conditions ivermectin mass treatment can be discontinued in selected areas because of local interruption of transmission, ongoing community trials which evaluate integration of additional health interventions into the community directed treatment with ivermectin, and the community trials which evaluated the use of drug combinations for LF).

Current portfolio

Community effectiveness studies of moxidectin will be conducted to determine moxidectin's effect on disease transmission and its safety profile under conditions of community directed treatment. They will thus provide the data required for the final milestone in moxidectin development: determination of moxidectin's potential for integration into disease control programmes for eradication of onchocerciasis.

Studies with the equivalent objectives will be conducted for moxidectin for lymphatic filariasis.

Potential future projects based on options assessment

Studies with equivalent objectives will be conducted for any other drug that will potentially be developed (by TDR or other organizations).

Objective 2: Generation of evidence for improved use of currently available drugs to support disease control, elimination or eradication strategies for NTDs with emphasis on integrated disease management or prophylactic chemotherapy

End product 3 : New information for the utilization of drugs for diseases targeted for the integrated approach and multi intervention packages for disease control.

Current portfolio

- **Onchocerciasis:** Data on the feasibility of using albendazole to reduce the burden of Loa loa microfilaremia to avoid the encephalopathy that results from the use of ivermectin in individuals with heavy Loa loa infection.
- **LF**: LF disease manifestations in children and the impact of early treatment provided by the control programs.
- **Schistosomiasis**: Efficacy and safety of increased praziquantel dose regimens, and of the combined use of praziquantel and oxamniquine and praziquantel with artemisinin derivatives.

Future project pending BL 6 SAC, STAC and JCB endorsement

For drugs that are used in the treatment of STH, LF, onchocerciasis or schistosomiasis that are contraindicated during early pregnancy the establishment of pregnancy registries (inadvertent exposures) will provide information on the real risk/benefit of these drugs when used during pregnancy.

Potential future projects

Based on prior experience within TDR e.g. as the research arm of the Onchocerciasis Control Programme for West Africa and the African Programme for Onchocerciasis Control, this part of the portfolio will be very dynamic with capacity freed through completion of one project being immediately utilized for the next project to address the research needs emerging during the implementation of integrated approaches and multi-intervention packages.

End product 4: Evidence for improved use of currently available drugs to support disease control, elimination or eradication strategies

Current portfolio

- **Chagas disease**: Evidence on the effect of currently available drugs (benznidazole or nifurtimox) on chronic disease onset or progression.
- **Human African Trypanosomiasis**: Efficacy and safety of the combined use of nifurtimox and eflornithine in comparison with standard eflornithine treatment of 2nd stage HAT patients and evidence for the efficacy of a shortened pentamidine treatment of 1st stage HAT patients as a basis for treatment recommendation.

Objective 3: Development of products for other neglected diseases when an opportunity emerges and no other organization is available or has the know-how to do so

Platelet activating factor receptor (PAFR) antagonists for Hemorrhagic dengue fever and dengue shock syndrome.

Currently there are drug discovery efforts targeting the dengue virus. It will be several years before new candidates will be available for clinical development. Recently it has been described that PAFR play a role during experimental dengue infection. Using these animal models several PAFR antagonists developed by pharma industry for asthma (but failed to show efficacy for this indication) have been tested. The experimental data suggest that the compound prevented all the major pathophysiological changes induced by the infection, including thrombocytopenia. Such antagonists may provide an opportunity to address the progression of dengue infection towards Hemorrhagic dengue fever or Dengue shock syndrome.

This line of work will require: establishment of an agreement with the pharma industry for access to key compounds, synthesis of clinical grade material, evaluation in experimental animals of the efficacy of the synthesized material; definition of the format of and regions where to perform the first clinical trial; design of a clinical development plan including a small proof of concept study to evaluate the ability of PAFR antagonists of prevent thrombocytopenia and larger trials required for regulatory approval.

Across Objectives 1-3

End product 5: Capacity in centres in developing countries for conducting clinical trials and capacity of Developing country regulatory authorities to review and approve clinical trial exemptions and new drug applications

Clinical evaluation of products in the setting of low resource countries requires a high level of human resource and infrastructure development. This investment and the resulting capacity for conducting clinical trials is an asset on its own. The principals underlying design and conduct of preclinical studies and clinical trials are identical across diseases. Thus, the capacity built in the context of the development programme within this BL will allow institutions in developing countries to engage in pharmaceutical research not only for helminthic diseases but also other diseases endemic in these countries. This end product is of particular value in the context of objectives 1 and 3 given that drug development is inherently associated with a high risk of failure related to the pharmacological properties of the compound under evaluation.

4.3. INTERIM IMPLEMENTATION MILESTONES

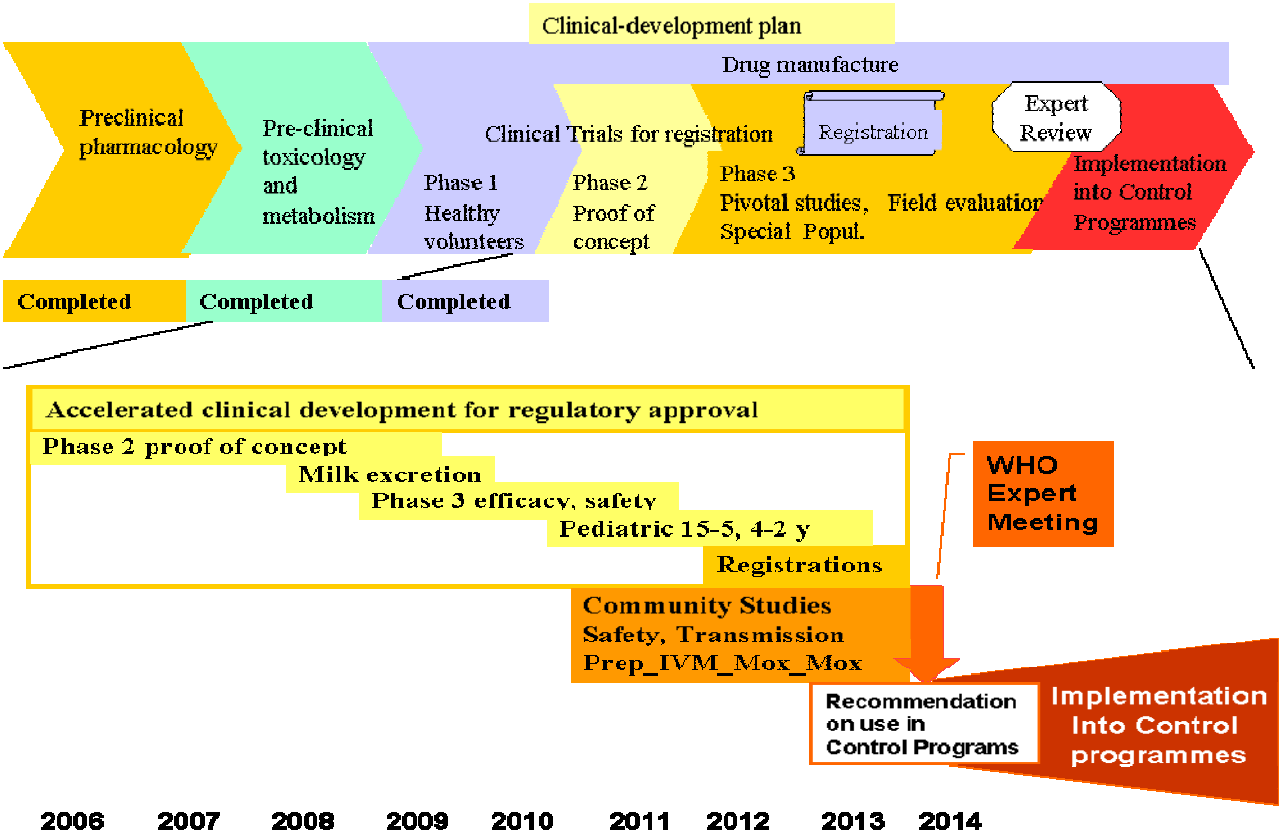
Moxidectin for onchocerciasis

Implementation of development of moxidectin for onchocerciasis control will proceed according to the accelerated development strategy (

Figure **1** and Appendix 1) agreed upon with Wyeth, the pharmaceutical company partner. Personnel to manage the project on the TDR side and financial resources for operations expenses to registration are available. It is anticipated that based on Proof-of-Concept data fund raising for the community studies will not delay the initiation of these studies.

Figure **1** shows both the major milestones already passed and the major standard 'drug development for public health' milestones still to be achieved (initiation of Phase 3, proof-of-concept, initiation of the paediatric study, decision for submission of a dossier for registration, initiation of community studies and decision on implementation into the control programmes.

Figure 1: Development plan elements for moxidectin for eradication of onchocerciasis



Moxidectin for lymphatic filariasis

Latest at the time a decision has been made to submit a registration dossier for moxidectin in onchocerciasis and assuming that lymphatic filariasis disease control continues to need a more potent macrofilaricidal drug than is currently available, a Phase 3 study of the efficacy and safety of moxidectin in lymphatic filariasis will be initiated.

The milestones applicable are: decision to initiate the Phase 3 study, Proof-of-Concept (built into the Phase 3 study, approximately 3-4 years after initiation of the study taking into account fund raising and site identification and capacity building requirements), decision for submission of registration dossier (approximately 1 year after proof of concept), initiation of community studies and decision on implementation into the control programmes.

Personnel to manage this activity is available. It is anticipated that based on the strength of the preclinical pharmacology data in lymphatic filariasis models and the data anticipated from development for onchocerciasis the requirement for fund raising will not constitute an obstacle to initiation of these activities.

1. **Implementation of ongoing studies to generate evidence that the registered drugs are safe and efficacious for large scale use (including multi intervention packages for disease control and prophylactic use of chemotherapy) (Objective 2)**

The majority of the work in this area will initially be based on currently ongoing studies with defined workplans and target dates:

- Albendazole to reduce the burden of Loa loa infection (completion end 2008)
- LF disease manifestations in children and the impact of early treatment (completion 2009)
- Efficacy and safety of increased praziquantel doses and praziquantel pcombination with oxamniquine and praziquantel and artemisinin derivatives (completion 2009).
- Benzimidazole resistance in helminths (completion of pilot project 2008).
- Effect of benznidazole treatment during indeterminate T. cruzi infection on chronic disease onset or disease progression (completion of pilot study 2009).
- Evidence for the combined use of nifurtimox with eflornithine in the treatment of 2nd stage HAT patients (completion 2009).
- Evidence for efficacy of shortened pentamidine treatment for 1st stage HAT patients (completion 2009)

2. New projects for Objective 2

A new area that has been identified as very relevant for the control programs is the establishment of Pregnancy registry for 1st trimester safety of antihelminthic drugs. This work will take advantage of the currently ongoing TDR activities in malaria and addressed in BL 9.

Upon formation of the BL, priority will be given to the design of a strategy and plan for pregnancy registries for drugs used for the diseases targeted for integrated disease control and contraindicated for use in pregnancy. Once a strategy and plan have been approved by BL 6 SAC and STAC and endorsed by JCB and Director TDR, the strategy will be implemented in collaboration with the control programmes.

3. New projects for Objectives 1 and 3

Tribendimidine for STH.

WHO has been recently approached by the Swiss Tropical Institute (Basel, CH) to explore the possibility to participate in the development of Tribendimidine, a broad spectrum antihelmintic drug from the Shandong Xinhua Pharmaceutical Company Ltd., PR of China. The drug has undergone proof of principle trials. TDR participated in these discussions identifying several areas within the current development plan where TDR could contribute. Discussions on further development are in progress. A decision on whether or not and if yes to what extent TDR will be involved in this development will be taken once a development strategy and plan has been established. Funds for the development activities and for personnel to manage it will need to be raised.

Given the data already available for tribendimidine, standard drug development milestones may not all apply. Thus, the first milestone will be a development plan to registration agreed upon with the regulatory authorities. This plan will define further milestones and the time required to reach them.

Emodepside for onchocerciasis.

The final pre-clinical pharmacology data required to decide on transition of emodepside into development will become available in 2Q07.

If emodepside qualifies as a development candidate, the first milestone beyond engagement of the pharma partner will be a development strategy agreed upon between all partners and regulatory authorities. Development will initially be pursued to qualification for the first study in humans. Development beyond this milestone will be contingent upon moxidectin not meeting its target profile.

Other potential development candidates

Other development candidates (e.g. L-praziquantel, synthetic trioxanes -OZ series - oxamniquine analogues, acridine derivatives (e.g. Roche RO 15-5458)), benzodiazepine (3-methyl clonazepam RO11-3128 derivatives/analogues, PFAR antagonists) will be evaluated within TDR and by outside experts for potential review by the CEC during the first year after establishment of BL 6.

For all drug development candidates, the first milestone will be engagement of institutions and companies for development and manufacturing/license holding. Following milestones will be the standard drug development milestones based on development strategies and plans agreed upon with all partners and relevant regulatory authorities, complemented, where appropriate by those for qualifying the newly registered drugs for large scale use.

5. FUNDING

5.1 RESOURCE REQUIREMENTS

The overall plan and costs for the BL 6 are shown in Table 1.

The budget and human resources required will depend on:

- the number of drug developments initiated (Objectives 1 and 3), the phase in which they will be initiated, the disease targeted and whether and in what phase their development and evaluation is discontinued. Since drug development is a long term, extensive engagement, development activities are anticipated to require the vast majority of the budget.
- the number of projects for Objective 2.

The budgets below for projects for objectives 1 and 3 are based on the planned budget for the continuation of moxidectin development (phase 2 onwards) through to all data required for a recommendation on use in onchocerciasis control and previous TDR experience in product development. They include the costs typically assumed by TDR in collaborations with pharmaceutical industry.

Based on prior experience in TDR, costs for projects for Objective 2 may vary between US$ 100,000 and US$ 2,000,000 depending on the type of research question addressed.

Table 1: Activities, time lines and operational budget for BL6 by year

US $ x 1000

Objective	Description	2008	2009	2010	2011	2012	2013
1	**Development and registration of new helminth drugs**	**835**	**1,065**	**1,863**	**3,636**	**3,109**	**2,903**
1.1	Moxedectin for onchocerciasis	800	700	1,148	1,326	1,529	1,140
1.2	Moxedectin for LF	-	-	70	1,510	420	783
1.3	Back-up for Oncho to Clin Dev (e.g. empodepside)	-	110	100	100	-	-
1.4	Schistosomiasis drug candidate (e.g. L-PZQ)	30	30	20	275	525	745
1.5	STH drug candidate	5	225	525	425	635	235
2	**Evidence for improved use of currently available drugs**	**600**	**780**	**600**	**600**	**600**	**600**
2.1	Loa Loa	50	-	-	-	-	-
2.2	LF disease manifestations	100	50	-	-	-	-
2.3	Nifurtimox - eflorinithine	200	150	-	-	-	-
2.4	Benznidazole in Chagas disease	150	150	-	-	-	-
2.5	Benzimadazole resistance	50	30	-	-	-	-
2.6	New projects (pregnancy register, other TBD)	50	400	600	600	600	600
3	**Development of products for other NTDs**	**5**	**215**	**715**	**693**	**2,885**	**1,023**
3.1	Candidate 1 (e.g. PFAR dengue)	5	215	715	693	2,885	1,023
4	**Other**	**50**	**50**	**50**	**50**	**50**	**50**
4.1	Strengthening of networks, clinical monitor training	20	20	20	20	20	20
4.2	Scientific advisory committee	30	30	30	30	30	30
	Activities	**1,490**	**2,110**	**3,228**	**4,979**	**6,644**	**4,576**
	Personnel Costs	**901**	**901**	**1,195**	**1,301**	**1,301**	**1,301**
	No. of professional staff	3	3	4	4	4	4
	No. of support staff	1.5	1.5	2.5	3.5	3.5	3.5
	Total	**2,391**	**3,011**	**4,423**	**6,280**	**7,945**	**5,877**

6. RISKS

1. Inherent risk of drug development of not delivering the desired agent (industry experience: out of 10 drug candidates entering development 1 reaches regulatory approval).
2. Slippage of development time lines due to uncertainties associated with work in developing countries (political and socioeconomic instability, infrastructure related challenges (e.g. time to repair of critical equipment for clinical trials, clinical trial capacity building, etc)).
3. Sustainability of a strong interaction with disease control programmes and product research and discovery initiatives (including BL3).
4. Adequate funding, fundraising will depend on advocating funds on a case by case basis for each product development opportunity and may depend on delivery of product development milestones, which will lead to significantly increase development time lines.
5. Lack of suitable personnel: Key human resources will be professionals with experience and expertise in drug development project management, a resource mainly available within the pharmaceutical industry and highly sought after (e.g. hired much more quickly than feasible based on WHO procedures and paid substantially above WHO salary levels).

ANNEX

ID	Task Name
2	Phase 2 enrollment and 18 months follow up
3	Phase 2, 2 mg treatment and 30 day safety follow up
38	Dose progression decision 2 mg to 4 mg
63	Phase 2, 4 mg treatment and 30 day safety follow up
97	Dose progression decision 4 mg to 8 mg
122	Phase 2, 8 mg treatment and 30 day safety follow up
155	Assessment 30 day safety 8 mg and 2 mg 12 mo PI, Wyeth, TDR, CERT
167	Phase 2, 6-18 months efficacy follow up,
255	PK data
287	Final Data and Report
290	PDT-Advisory committee meetings
297	EMEA scientific advice Article 58
314	Preparation of Phase 3 study
350	Phase 3 enrollment and 18 months follow up
351	Phase 3, 4 mg treatment arm, enrollment and 18 months FU
408	Phase 3, 8 or 2 mg treatment arm (or 4 mg) and 18 months FU
465	Phase 3 final data analysis and study report
472	Milk excretion study
473	Study preparation
479	Study conduct
481	PK and efficacy data availability and analysis
486	Milk excretion study report
489	Decisions based on final Phase 2 data, all safety Phase 3, 300 pat efficacy Phase 3
501	Drug interaction studies (most likely not necessary)
516	Pediatric study, initiation based on DSMB
517	Site selection and preparation
520	DSMB for decision on pediatric study
525	Protocol preparation
526	Draft Pediatric protocol
527	DSMB feedback on protocol
528	Protocol finalization and sign off
529	Regulatory, ethics and WHO approvals
530	CTX preparation
533	Pediatric PK and safety study (with 12 months efficacy follow up)
534	Site preparation
537	15-5 year olds (enrollment and 30 day follow up)
538	15-5 year old dose 1
542	Dose progression decision
567	15-5 year old dose 2
570	Final safety data base, CDRs and study report 15-5 year olds
578	Final 12 months efficacy data base, CDRs and study report 15-5 year olds
589	Age degression decision decision
613	2-4 year olds (enrollment and 30 day follow up)
614	2-4 year olds dose 1
617	Dose progression decision
642	2-4 year olds dose 2
645	Final safety data base, CDRs and study report 4-2 year olds
652	Final 12 months efficacy data base, CDRs and study report 2-4 year olds
663	Submissions and registration
664	Base case: submission, 18 mo eff P3 with 5 year pediatric safety
665	Initial MAA (P2, P3 18 mo eff. P3, ME, 5+ safety)
687	Supplemental submission(s) for pediatric data (2-4 year safety, all efficacy)
702	Upside 1: submission (P2, P3 12 months, ME),
703	Initial MAA (P2, P3 12 mo eff. P3, ME,)
708	Supplemental submissions (Pediatric)
714	Upside 2: Accelerated Approval based on P2 efficacy and P3 safety data
715	Initial MAA (P2, safety data P3, ME)
722	Supplemental submissions
730	Community effectiveness studies (4 parallel studies), assuming base case regulatory
731	Preparation of community studies
732	Site selection and preparation
733	CTX preparation/submission/approval in countries for community studies
744	Study conduct
753	Data reporting
757	WHO Expert review