Drug Discovery and Drug Development

I. RATIONALE

The infectious disease burden inflicted by tropical diseases continues to exact a huge price both in human suffering and in contributing to poverty and underdevelopment.

For the diseases within TDR’s mandate [African trypanosomiasis, Chagas disease, dengue, leishmaniasis, leprosy, lymphatic filariasis, malaria, onchocerciasis, tuberculosis, schistosomiasis (http://www.who.int/tdr)], no vaccines are available and there are no prospects for vaccines becoming available soon. Thus, drugs will remain the mainstay of disease control.

The vast majority of drugs available to date have at least one of the following drawbacks (1) insufficient efficacy or increasing loss of effectiveness, (2) high level of toxicity, (3) inaccessibility, and/or (4) high costs. New drugs are desperately needed and will continue to be needed for the foreseeable future. TDR has generated generic target product profiles for drugs for each of the diseases within its mandate based on the medical need as defined by properties of existing drugs, disease burden and epidemiological trends, infrastructure available in the endemic countries for drug distribution and administration, as well as affordability (http://www.who.int/tdr/grants/strategic-emphases/default.htm).

The tropical diseases within TDR’s mandate occur primarily or exclusively in developing countries, and many are endemic in the Least Developed Countries. The commercial return from marketing a drug for these diseases is very low relative to the costs for research and development (R&D) of new drugs. This has resulted in a withdrawal of the pharmaceutical industry from R&D in these diseases.

The objectives of the Product Research and Development unit (PRD) within TDR are to promote, enable and conduct development and registration of new drugs for neglected tropical diseases. TDR/PRD actively initiates, funds, coordinates, and manages projects at all stages of drug discovery and development, generally working in close collaboration with academic institutions and/or pharmaceutical companies.

II. OBJECTIVES

PRD aims to have a portfolio of both Drug discovery and Drug development projects whose composition is determined by:

- medical need as determined by current availability of drugs, disease burden and epidemiological trends (including development of disease refractory/resistance to available treatments),
- properties of the available drugs in terms of efficacy, safety, costs
- opportunities available through R&D activities in academia and the pharmaceutical industry,
- activities outside TDR to discover and develop new drugs for the diseases within TDR’s mandate.
2.1 Drug Discovery Research

The objectives of the Drug Discovery Research (DDR) group within TDR/PRD are:

1. Discovery of new compounds that are effective against one or more of the diseases within TDR’s mandate.

   Each project aims to identify one compound, and perhaps one or two related back-up compounds, considered to be ready to enter preclinical evaluation as the first step in a dedicated drug development project. Minimum qualifications for a drug candidate are demonstration of:
   a. good efficacy in a relevant animal model of the disease
   b. acceptable initial data on toxicity and pharmacokinetics

In practice, TDR is not always able to fully and independently support a project all the way from early discovery research through lead optimization to identification of a drug candidate. TDR may fund and manage part of the drug discovery process with other organizations taking responsibility for earlier or later phases. For example, TDR has supported investigators in early lead identification and optimization projects where, on the basis on the results obtained under TDR’s support, final lead optimization and drug candidate selection were undertaken with support from TDR-affiliated public private partnerships.

2. Research Capacity Strengthening (RCS) in disease-endemic countries (RCS Plus)

   DDR is working with the RCS unit in TDR to identify and support researchers in disease-endemic countries in their evaluation of natural products as the source of new classes of compounds with activity against the TDR diseases of interest.

   DDR is seeking to identify researchers in disease-endemic countries who can set up and run compound-screening centres capable of evaluating compounds that are sent to them by TDR for activity against one or more of the TDR diseases of interest.

2.2 Drug Development

The objectives of the Drug Development group within PRD are

1. Development and regulatory registration of new drugs for the treatment and control of the diseases within TDR’s mandate. This requires:
   a. Evaluation of development candidates for inclusion in the TDR Drug Development Portfolio at any of the following stages of development (pre-clinical development to be initiated, first-in-man study to be initiated, Phase I, Phase II or Phase III).
   b. Formation of product development teams comprising all the scientific and drug development expertise needed, based on the stage of development of a particular compound or compound combination.
   c. Generation of rational development strategies in collaboration with regulatory agencies in developed as well as the disease-endemic target countries with input from the end-users (primarily disease control programmes, national health services).
   d. Identification of preclinical and clinical investigators as well as organizations offering operational expertise in drug development (e.g. generation of investigator brochure, protocols, study reports, and submission documents, database, data management, statistical analysis).
   e. Implementation of the drug development strategy
      • through contracting of work to qualified investigators, and
      • through application of the technical, scientific, drug development as well as drug development management expertise within PRD (e.g. clinical protocol generation, investigator brochure generation).
2. Research Capacity Strengthening in disease-endemic countries (RCS Plus)
   a. Training of investigators from disease-endemic countries participating in product development teams (see section 5.2) in drug development for regulatory registration.
   b. Generation and dissemination of guidance documents for different aspects of drug development (e.g.
      
      Handbook: Good Laboratory practice;
      Good laboratory practice: training manual (TRAINEE);
      Good laboratory practice: training manual (TRAINER);
      Workbook for investigator;
      Operational guidelines for ethics committee that review medical research;
      Surveying and evaluating ethical review practices
   c. Training of clinical investigators participating in the clinical development programmes in Good Clinical Practice.
   d. Training and qualification of clinical monitors from disease endemic countries.
   e. Creation of clinical data management capacity in disease endemic countries.
   f. GLP training of laboratories conducting preclinical pharmacology and toxicology studies for drug development.

III. ROLES AND RESPONSIBILITIES OF THE STEERING COMMITTEE

The Steering Committee that reviews drug discovery and development projects in PRD is referred to as the Chemotherapy Portfolio Review Committee (CPR).

It is composed of experts in the different areas of discovery (e.g. target identification, medicinal chemistry, \textit{in vitro} and \textit{in vivo} assay systems, lead optimization) and development (e.g. animal and human pharmacokinetics, clinical development, clinical expertise in the TDR target diseases) from both industry and academia in the North and in the South.

A general overview of the roles and responsibilities of Steering Committees within TDR is provided in the TDR General Operations Guide.

The specific roles and responsibilities of the CPR Committee are:

1. Review of existing drug discovery activities operating within PRD with particular emphasis on the network of centres testing and evaluating compounds as potential new hits or leads.
2. Review of drug development projects with particular emphasis on development strategy and feasibility of achieving the objectives determined by the Product Development Teams (see section 4.2).
3. Identification of new drug discovery and development projects that PRD should target for its portfolio.
4. Assessment of the strategic balance of the portfolio regarding:
   - discovery vs. development
   - disease focus in both discovery and development
   - innovation vs. risk (likelihood of success)
   - target product profiles of individual drugs in development, including accessibility post-registration and positioning within the currently existing tools to treat and control the target disease.
5. Review of Research Capacity Strengthening projects

6. Review of and recommendation on PRD resources and procedures for co-ordination, management and implementation of projects.

7. Strategic management of individual drug development projects. This is conducted through delegation to Product Development Teams (see section 4.2.1)

IV. PROJECT MANAGEMENT

4.1 Drug Discovery Research

In its efforts to identify new classes of compounds with activity against the TDR diseases, DDR supports two approaches.

1. The first is based on testing compounds that may have activity against certain parasites within TDR’s mandate (in vitro analysis). If activity is detected, and no serious general cytotoxicity is observed, the compound is progressed to in vivo testing for efficacy against the disease in a relevant animal model. Using this approach, the number of compounds that can be tested is limited by the complexity and the cost of the assay.

   TDR supports several laboratories with expertise in in vitro and in vivo screening of compounds against the TDR diseases. In most cases, compounds are first analyzed for in vitro effects against several parasites (Plasmodium, Leishmania, Trypanosoma, Onchocerca) as well as for mammalian cell toxicity. If the results are encouraging, further, more focused in vitro and in vivo analyses can be undertaken by laboratories with expertise in the specific disease(s). A flowchart outlining the typical sequence of events in analyzing newly submitted compounds and examples of the protocols that are employed by the TDR-supported screening centres are now available.

2. The second approach is based on identifying molecular drug targets that are relevant for the TDR diseases and then screening large compound libraries or collections for compounds that “hit” the target. The hits from a molecular target screen are then fed back into the in vitro and in vivo screening described above. This approach is being relied on more and more as the genome sequences of the parasites become available and as modern drug discovery as carried out in pharmaceutical companies moves in this direction.

   TDR is expanding its efforts in this area. One centre has been funded to carry out high-throughput screening-using (HTS) a compound collection of approximately 100,000 compounds. Critical to the success of this approach is the identification and validation of good molecular targets for the TDR diseases. TDR welcomes, either through the Genomes to Drugs and Diagnostics group in the STR unit or through DDR in the PRD unit, inquiries from investigators who have identified molecular targets of interest, are developing assays that are amenable to HTS, and are seeking access to HTS expertise and facilities.

   Compounds for hypothesis-driven investigation are obtained from several sources. In some cases the Principal Investigators heading these laboratories source compound of interest themselves. TDR/DDR is taking an active role in sourcing compounds itself, either by requesting compounds from academic groups or companies, or by purchasing compounds from commercial suppliers. In addition, TDR/DDR invites investigators with compounds that they consider to have potential to be active against the TDR diseases to contact DDR regarding the evaluation of the compounds by TDR. All results of the TDR-supported analyses are reported back to the investigator supplying the compound(s). All compounds and related information are treated as confidential and the investigator retains all rights or intellectual property associated with the compounds. There are no charges to investigators submitting compounds other than shipping fees. Detailed information on how to submit compounds is available under Request for compounds. This includes template confidentiality and material transfer/confidentiality agreements.
All on-going activities in Drug Discovery Research are managed and coordinated by a team of internal PRD staff working in close collaboration with external consultants. The team, referred to as Chemcore, meets monthly. Many of the TDR-funded drug discovery projects are focused on testing and evaluating compounds for their activity against the TDR diseases. The principal investigators from these projects report data back to TDR on a monthly basis. This data is stored in a TDR-managed database. All new data is reviewed at the monthly meetings and comments/recommendations from the Chemcore team passed back to the principal investigators supervising the evaluation of the compounds as well as to the investigators that have sent in compounds for analysis. Twice a year, the Chemcore team meets in person with the Principal Investigators from the key TDR-supported compound evaluation centers to review progress and plan future work.

4.2 Drug Development

The CPR committee delegates the strategic management of the development of a specific drug or drug combination to a dedicated Product Development Team (PDT) which collaborates with WHO/TDR secretariat. The implementation of development strategy and plan is the responsibility of PRD staff.

1. Product Development Teams

Depending on the stage of the development of the product, the PDT includes external scientists with expertise in pharmaceutical development, animal toxicology, pharmacokinetics and pharmacodynamics, and clinicians with expertise in the target disease and regulatory experts. PDT members are selected based on their expertise and with consideration of geographical and gender representation. The PDT includes representatives of all public and private organizations that collaborate on the development of the product.

The responsibilities of the PDTs are:

- To design the overall development strategy and target product profile
- To design the development plan
- To design the strategic elements of individual projects within the development (e.g., preclinical studies, clinical studies)
- To identify suitable investigators and contractors for individual projects within the development
- To oversee the implementation of the development plan.

2. WHO/TDR secretariat

The PDT manages the drug development in collaboration with a WHO/TDR secretariat. The WHO/TDR secretariat consists of PRD staff including the Project Manager, Clinical Coordinator, Preclinical Coordinator, CPR committee Manager, and PRD planner, and of WHO disease control staff and WHO Regional Office field staff.

The responsibilities of the WHO/TDR secretariat are:

- To provide input from disease control as well as field experience so that development strategy, target product profile and development plan are consistent with field conditions and requirements (WHO disease control and WHO regional office field staff)
- To provide PRD experience in drug development for registration for tropical disease indications
- To provide PRD experience in collaboration in public-private partnerships.

3. PRD staff

The PRD staff are responsible for implementation of the development strategy and plan developed by the PDT as well as for ensuring that the implementation is performed according to applicable guidelines and regulations.

Implementation is achieved through:
• Contracting of individual projects within a drug development plan (e.g. specific preclinical studies, clinical studies) to investigators or organizations selected and qualified by the PDT according to WHO guidelines and rules.
• Project work performed by PRD staff (e.g. writing of clinical protocols, investigator brochures, design of case report forms and data analysis plans, import permits for investigational drugs, investigator training on protocol, clinical study data analysis, writing of regulatory documents for submission to regulatory agencies).
• Operational support of the PDT as well as individual projects through knowledge management and administration of funds.

PRD staff ensure that individual projects are performed according to relevant guidelines and regulations through
• Review and sign off of preclinical and clinical protocols by the PRD preclinical and clinical coordinator, respectively
• Investigator site qualification and investigator training on protocols
• GLP and GCP training of the investigators selected to conduct a preclinical and clinical study, respectively
• Clinical monitoring (source data verification)
• Submission of all protocols involving human subjects to the WHO Secretariat Committee for Research in Human Subjects (SCRIHS).
• Depending on budget and staff availability, these tasks are either performed by PRD staff or are contracted to suitable qualified individuals or organizations.
• The PRD staff is also responsible for reporting back to the CPR committee on any issues the committee has asked the PDT to address.

V. FUNDING

5.1 Funding opportunities for investigators

At its annual meeting in March/April, the CPR committee reviews Letters of Interest for both drug discovery research and drug development projects. Deadline for the receipt of Letters of Interest is in January. A Call for Letters of Interest with instructions on the information to be provided by the researchers/investigators will be posted on the TDR website (http://www.who.int/tdr/) in December before the CPR committee meeting.

Principal Investigators for projects identified as promising are contacted soon after the CPR committee meeting for further discussion on how to proceed toward the development of a more complete proposal and, if necessary, how to develop a broader project partnership that includes other development partners. If a complete proposal is requested, the Principal Investigator may be asked to use the TDR standard form for a Collaborative Research Project (http://www.who.int/tdr/grants/forms.htm).

5.1.1 Drug Discovery Research

Letters of Interest should be directed toward the identification of a candidate compound for entry into preclinical development.
• Projects may be at an early or late stage of the discovery process but must clearly outline the steps that will be followed and the issues that will be addressed to identify a candidate molecule.
• Projects that have already established a partnership between an academic centre and a pharmaceutical company are welcome. However, this should not be seen as restrictive and applications are also welcome from stand-alone academic groups or from biotechnology or pharmaceutical companies.
• The key determinant for funding will be the perceived chance of project success and the feasibility of use and equitable accessibility in disease endemic countries.
Where it is thought that a project would benefit from the establishment of a partnership, TDR will make efforts and offer its services to facilitate this.

5.1.2. Drug Development

Drug development is a process that requires input and research from numerous disciplines ranging from discovery research, via animal metabolism and toxicology, clinical development, and regulatory affairs to the end user (market, health systems, control programmes). Furthermore, drug development requires constant review of the data accumulated and adjustment of the development strategy and plans based on the conclusions from these reviews. Thus, drug development exceeds the capacity of individual investigators and does not lend itself to a ‘Letter of interest – review - research proposal – review – funding decision’ process.

Thus, response to a Call for Letters of Interest is primarily an opportunity for the investigator to provide TDR/PRD with the basic information on a possible development candidate/project. The CPR committee will provide recommendations to TDR/PRD on whether to pursue the development opportunity and to initiate more in-depth discussions with the investigator on the generation of a development strategy and plan, and on raising funds for the development.

Letters of Interest should define a single molecule or combination (perhaps with a back-up compound) that has been identified and has demonstrably acceptable preclinical pharmacology properties and a potential for clinical development.

- The molecule (or combination) may be at either a preclinical or clinical stage of development. It must have well documented efficacy in an appropriate animal model and/or in humans.
- An established partnership or organization to take forward the candidate drug through clinical development to registration is desirable, but not an essential prerequisite for funding.
- TDR can assist in establishing the product development team and partnerships required to organize preclinical and clinical development to registration.
- The key determinant for funding will be the perceived chance of project success and the feasibility of use and equitable accessibility in disease-endemic countries.

There are selected circumstances in which a Letter of Interest – review - research proposal – review – funding decision process may be applicable e.g. the conduct of specific toxicity studies to finalize qualification of a lead compound for development or even the conduct of a first-in-man study or a proof-of-concept study if the investigator feels that such a study is required to approach TDR or other organizations for adoption of the compound into their portfolio.

Letters of interest of such a scope will be reviewed by the CPR committee for funding, as are the Discovery Research proposals described in section 5.1.1 above.

For on-going drug development projects where a Product Development Team (PDT) has been established (see Section 5.2.1), grants are awarded to carry out specific tasks/studies as determined necessary by the PDT. In this case, the PDT seeks out organizations or institutes that have the necessary expertise to carry out the defined task (i.e. toxicity or metabolism studies, formulation work, production, clinical studies) through specific Letters of Interest. These will be posted on the TDR website at the time the need for a particular study has been identified.

5.2 Fundraising by TDR/PRD

TDR obtains funding from the TDR co-sponsors and member countries (see: Governance), charitable foundations, national government programmes for supporting international development and even individual or small groups of concerned citizens (see: Funding and Resources). Pharmaceutical companies contribute to funding of specific projects either through donating money or through active collaboration in the development.
5.2.1 Drug Discovery Research

Much of the funding that supports drug discovery research in TDR comes from undesignated funding that TDR receives from its donors to support all TDR activities, only one of which is Drug Discovery research. In efforts to increase the level of funding for drug discovery, DDR seeks designated funding from countries to support compound-screening centres in their respective countries.

Recently, more emphasis has been placed on contacting biotechnology and pharmaceutical companies to seek their assistance and in-kind services rather than financial donations. This approach has been increasingly successful. For example, TDR has agreements with several companies which donate compounds of interest for evaluation for activity against named TDR diseases.

DDR also maintains close contact with other public organizations funding drug discovery research on these diseases in an effort to bring in additional funding as well as an effort to coordinate activities and maximize value.

5.3 Drug Development and Public-Private and Public-Public Partnerships

The majority of PRD drug development projects are performed in public-private or public-public partnerships (http://www.who.int/tdr/publications/publications/partnerships.htm). In these partnerships scientific expertise, clinical know-how, public health knowledge and drug development experience of partners from the North and the South, from publicly funded research institutions and pharmaceutical industry, are brought together for discovery of new drug candidates and their optimization to development candidates, toxicological testing, clinical development, and ultimately regulatory submission in all disease endemic countries. Both the public and the private partners contribute funding directly or through in-kind contributions.

The funding of part of drug development by a public partner in a PPP changes the economics of drug development since it reduces the cost of development for the private partner. This can result in drug prices compatible with the financial capacity of the disease endemic countries for which the drug is developed. In some cases purchase commitments of these countries provide an additional commercial incentive for the pharmaceutical companies to collaborate in a PPP.

TDR/PRD raises funds through grant applications and through direct collaboration with other public or with private organizations.

To date, all drugs brought to registration in which TDR was involved are based on public-private partnerships.

VI. ON-GOING ACTIVITIES

6.1 Discovery Research

DDR supports the following investigators who are carrying out compound screening and evaluation as part of the TDR network of screening centers. For information on the assays carried out at these centres and on how to submit compounds for evaluation, please refer to section 4.1.
<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institute</th>
<th>Project Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Reto Brun</td>
<td>Swiss Tropical Institute; Basel, Switzerland</td>
<td><em>in vitro</em> screening against a panel of parasites (<em>Leishmania</em>, <em>Plasmodium</em>, <em>Trypanosoma</em>), focus on <em>in vitro</em> and <em>in vivo</em> evaluation for African trypanosomiasis</td>
</tr>
<tr>
<td>Dr Simon Croft</td>
<td>London School of Hygiene and Tropical Medicine; London, UK</td>
<td><em>in vitro</em> and <em>in vivo</em> evaluation for malaria, leishmaniasis, and Chagas disease</td>
</tr>
<tr>
<td>Dr Simon Townson</td>
<td>Northwick Park Institute for Medical Research; London, UK</td>
<td><em>in vitro</em> and <em>in vivo</em> evaluation for onchocerciasis</td>
</tr>
<tr>
<td>Dr Kazuhiko Otoguro</td>
<td>Kitasato Institute; Tokyo, Japan</td>
<td><em>in vitro</em> and <em>in vivo</em> evaluation for malaria</td>
</tr>
<tr>
<td>Dr Quentin Bickle</td>
<td>London School of Hygiene and Tropical Medicine; London, UK</td>
<td><em>in vitro</em> and <em>in vivo</em> evaluation for schistosomiasis</td>
</tr>
<tr>
<td>Dr Fouad Yousif</td>
<td>Theodor Bilharz Research Institute; Cairo, Egypt</td>
<td><em>in vitro</em> and <em>in vivo</em> evaluation for schistosomiasis</td>
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</tbody>
</table>

DDR is supporting discovery based on the identification/validation of molecular targets and subsequent high-throughput screening of compound libraries. Projects that are currently active are:

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institute</th>
<th>Project Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Michael Kron</td>
<td>Michigan State University; East Lansing, Michigan, USA</td>
<td>Investigation/validation of aminoacyl tRNA synthetases from <em>Brugia</em> and <em>Wolbachia</em> as molecular drug targets for filariases</td>
</tr>
<tr>
<td>Dr Carolyn Behm</td>
<td>The Australian National University; Canberra, Australia</td>
<td>Identification and validation of molecular drug targets for filariases using RNAi in <em>C. elegans</em></td>
</tr>
<tr>
<td>Dr Ian Street</td>
<td>Walter and Eliza Hall Institute of Medical Research; Melbourne, Australia</td>
<td>High-throughput screening against molecular targets to identify hits, hit to lead expansion and early profiling of leads</td>
</tr>
</tbody>
</table>

In addition, DDR supports focused meetings of scientists to discuss particular topics and make recommendations to TDR and the CPR committee on future actions that will further the DDR objective of discovering more compounds that can be progressed into development. In 2003, DDR sponsored a meeting to discuss if and how new technologies such as RNAi can be used to identify and validate new molecular drug targets for filariases. A report from this meeting is being prepared for publication in a major journal.
### 6.2 Drug Development

The PRD Drug Development portfolio currently comprises the following products:

<table>
<thead>
<tr>
<th>Compound/Combination</th>
<th>TDR Disease Indication</th>
<th>Stage</th>
<th>Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal Artesunate</td>
<td><strong>Malaria</strong>&lt;br&gt;Initial Management of acute malaria patients who cannot take oral drugs and to whom parenteral drugs are not available</td>
<td>Registration</td>
<td>Knoll/Abbott, Scherer, ScanPharm</td>
</tr>
<tr>
<td>Artemether-lumefantrine (Co-artemether)</td>
<td><strong>Malaria</strong>&lt;br&gt;Uncomplicated <em>P. falciparum</em> malaria in very young infants</td>
<td>Label extension</td>
<td>Novartis, RBM</td>
</tr>
<tr>
<td>Chlorproguanil/Dapsone/Artesunate</td>
<td><strong>Malaria</strong>&lt;br&gt;Treatment of adults and children (primarily in Africa) with acute uncomplicated <em>P. falciparum</em> malaria</td>
<td>Phase II</td>
<td>GSK, MMV</td>
</tr>
<tr>
<td>Pyronaridine plus Artesunate</td>
<td><strong>Malaria</strong>&lt;br&gt;Paediatric and adult acute uncomplicated <em>P. falciparum</em> malaria</td>
<td>Phase 0</td>
<td>Shin Poong Pharmaceuticals, MMV</td>
</tr>
<tr>
<td>Eflornithine</td>
<td><strong>African trypanosomiasis</strong>&lt;br&gt;First line oral treatment for late-stage <em>T. b. gambiense</em> disease</td>
<td>Phase II</td>
<td>Aventis</td>
</tr>
<tr>
<td>Miltefosine</td>
<td><strong>Leishmaniasis</strong>&lt;br&gt;Post kala-azar dermal leishmaniasis</td>
<td>Phase II</td>
<td>Zentaris</td>
</tr>
<tr>
<td>Miltefosine</td>
<td><strong>Leishmaniasis</strong>&lt;br&gt;Visceral Leishmaniasis</td>
<td>Phase IV, label extension</td>
<td>Zentaris</td>
</tr>
<tr>
<td>Paromomycin</td>
<td><strong>Leishmaniasis</strong>&lt;br&gt;Visceral Leishmaniasis</td>
<td>Phase III</td>
<td>Thammasat University, Thailand; Kalazar Research Center, Kala-azar Medical Research Center and Rajendra Memorial Research Institute of Medical; Institute for One World Health</td>
</tr>
<tr>
<td>Moxidectin</td>
<td><strong>Onchocerciasis</strong>&lt;br&gt;</td>
<td>Phase I/II</td>
<td>Wyeth</td>
</tr>
</tbody>
</table>

Legal agreements are currently being negotiated for initiation/continuation of several other products in the disease areas of malaria and tuberculosis.
VII. FURTHER INFORMATION AND CONTACTS

Further information on TDR is available on the TDR website including a review of major TDR activities over the past 25 years.

7.1 How to apply

Researchers interested in collaborating on drug discovery or development projects for the TDR diseases are invited to send in a Letter of Interest in response to a specific Call for Letters of Interest. A broad Call for Letters of Interest is generally made in November prior to the annual meeting of the Steering Committee (the CPR Committee) in March/April. For more information on the LoI review see section 5.1.

Additional Calls for Letters of Interest with a more narrow definition are also possible at other times during the year.

7.2 Contacts

Drug Discovery Research

Informal inquiries can be made to:
Dr Mary M. Bendig
Acting Manager, Drug Discovery Research
WHO/TDR
20 Avenue Appia
1211 Geneva 27
Switzerland
Tel: +41 (0)22 791-3960
Fax: +41 (0)22 791-4854
E-mail: bendigm@who.int

Drug Development

Informal inquiries can be made to:
Dr Annette C. Kuesel
Manager, Drug Development Portfolio
Acting Manager, CPR committee
WHO/TDR
20 Avenue Appia
1211 Geneva 27
Switzerland
Tel: +41 (0)22 791-1541
Fax: +41 (0)22 791-4854
E-mail: kuesela@who.int