Business Plan 2007-2014

DNDi

Drugs for Neglected Diseases *initiative*

PROCESS

The revision of the business plan, with methodological support and coaching by Ernst & Young, was prepared over a period of 8 months with extensive internal & external consultation, and 4 workshops. The plan, which has been reviewed once by the Board of Directors (December 2006) and twice by its Executive Committee (November 2006, March 2007), was approved by the Board of Directors in July 2007.

CONTENTS

1. EXECUTIVE SUMMARY

DNDi has developed the following business plan to outline the process by which the organisation will make significant progress between now and 2014 toward accomplishing its mission to develop new treatments for patients suffering from the most neglected diseases. Acting in the public interest, DNDi will continue to bridge existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.

DNDi TODAY

DNDi has grown from the four projects described in the 2003 business plan to a portfolio of 22 projects in 2007. The current portfolio primarily focuses on the three kinetoplastid diseases of leishmaniasis, human African trypanosomiasis or HAT (sleeping sickness), and Chagas disease. Discovery projects initially test compounds against all of these diseases. By proactively identifying critical R&D challenges and opportunities in exploration with academia, pharma, biotech, and other product development partnerships (PDPs), DNDi is building a portfolio which already contains strong projects for two of the target diseases.

For visceral leishmaniasis (VL) and Human African Trypanosomiasis (HAT) in Africa, DNDi has facilitated the establishment of two disease-specific platforms that develop clinical research capacity in endemic regions by involving relevant scientists, research organisations, international organisations, NGOs, and national programmes. In 2007, as a result of the multi-partner FACT project, two fixed-dose artemisinin combination therapies (ACTs) will become available as non-patented public goods and will offer the first-ever paediatric strengths in fixed-dose antimalarials.

Through advocacy efforts, DNDi has influenced public policy agendas, from the WHA Resolution 59.24 on Essential Health R&D to political and financial commitments to neglected diseases by the G8 and EU respectively. As part of its policy success, DNDi has secured funding for neglected diseases' drug R&D from several governments including France, the Netherlands, and the UK. Having reached a number of milestones in its short life, DNDi must remain vigilant about proactively identifying the optimal balance between research, development, and access, so as to best address enduring unmet patient needs. A number of critical challenges remain as DNDi moves forward.

A CHANGED LANDSCAPE FOR NEGLECTED DISEASES

Neglected tropical diseases continue to cause significant morbidity and mortality in the developing world. Yet, of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4% of the global disease burden. Due to a combination of market and public policy failures, drug development has largely been confined to the R&D-based pharmaceutical industry which focuses on global diseases and lifestyle conditions. Recently, the field of R&D for neglected diseases has seen the emergence of several new organisations, new donors, new financial mechanisms, and a new political environment.

By building partnerships in both the public and the private sector - based on existing capacity, expertise, and resources – such as DNDi are working to foster R&D for neglected diseases. More academic and public institutes are becoming involved, and some companies in the pharmaceutical/biotechnology sector have now created special R&D facilities or initiatives to develop new tools for neglected diseases. A number of emerging, developing countries have dedicated resources to building R&D capacity, and several donors have also become involved in research funding for tools to combat neglected diseases. Philanthropic organisations, notably the Bill & Melinda Gates Foundation, have been critical drivers in the increased R&D activity. Although greater international attention is now being paid to the most neglected diseases, there is not enough sustainable funding, and a global framework for essential health R&D is still needed.

AN INNOVATIVE MODEL

DNDi's primary objective is to deliver 6 - 8 new treatments by 2014 for VL, HAT, Chagas disease and malaria, and to establish a strong R&D portfolio that addresses patient treatment needs. The organisation will also use and strengthen existing capacity in disease-endemic countries via project implementation and will continue to raise awareness about the need to develop new drugs for neglected diseases and to advocate for increased public responsibility.

To achieve these objectives, the DNDi business model has been updated to have:

1) A stronger focus on the kinetoplastid diseases;

2) A stepwise, integrated model of drug R&D in which needs-driven projects are sourced at any stage of the pipeline;

3) A virtual organisation which manages collaborative R&D projects;

4) A needs-driven regulatory and access strategy;

5) R&D networks that utilise and strengthen research capacities in disease-endemic countries;

6) International advocacy to support DNDi's R&D objectives and to foster an improved global framework for essential health R&D.

R&D STRATEGY

DNDi's R&D strategy will seek to fill the pipeline at all stages of development through a mix of short-, medium-, and long-term projects. DNDi is proactively developing a portfolio through the identification of:

1) Enduring unmet patient needs;

2) R&D opportunities, such as candidate compounds and improved formulations to address such needs;

3) Possible organisations to partner with in the R&D process;

4) Adequate funding to secure.

Throughout this process, DNDi will work to strengthen capacity and contribute to R&D technology transfer by developing partnerships in countries where neglected diseases are endemic. Post-registration mechanisms will also be leveraged through partnerships to ensure treatment, utilisation, access, and timely handover of projects with commercial partners, international and national programmes. Project-associated quality and safety from screening through clinical development and into the field is a key success factor for DNDi.

The current portfolio contains seven clinical, four preclinical and eleven discovery projects. By 2014, DNDi will have developed six to eight new treatments (four to five drugs registered, two geographical extensions and two to three co-administrations recommended by WHO) and will have built a balanced pipeline that will have projects at all stages of development. Concerted efforts that will harness discovery activities targeting all three primary diseases will be taken such that the most promising anti-parasitic candidates are identified. In the long-term, a sustained programme of harnessing scientific innovation will ensure that each target disease has a selection of safe, effective, affordable, and easy-to-use treatments for all forms of the disease.

GOVERNANCE AND ORGANISATION

Today, DNDi is a team of committed people who are dedicated to maintaining the momentum achieved since the launch of the initiative in 2003. With DNDi's ambitious vision in mind, the team has made significant headway in achieving DNDi's mission. Governed by the Board of Directors with the Scientific Advisory Committee, Audit Committee, and Executive Board Committee providing key scientific and management guidance for decision-making, the DNDi Executive Team in Geneva implements the R&D strategy, manages the global portfolio, allocates resources, fundraises, and advocates.

The Board of Directors approves project selection and sets policies for intellectual property, financial control, and ethics. The Scientific Advisory Committee provides recommendations on all scientific aspects of drug discovery and development, project selection, and portfolio management. Four regional support offices have been established in developing countries to help identify patients' needs, support project managers, identify and support regional partners, seek funding, and undertake regional advocacy work for DNDi projects.

FINANCES

The annual budget is projected to grow from EUR 4 million in 2004 to EUR 40 million in 2014. The overall expenses during this time are projected to be EUR 274 million, with a possible outcome of six to eight new treatments for neglected diseases and the creation of a healthy portfolio with projects throughout the development pipeline. On average, the vast majority of funds will be devoted to R&D (84%), with a secondary programmatic focus on strengthening capacities (4%) and advocacy (3%). This focus shows a clear emphasis on the social mission with 91% of the funds allocated in this area. From a disease perspective, DNDi will dedicate the majority of funding towards the development of treatments for VL (33%), HAT (34%), and Chagas disease (16%).

To develop its activities and achieve its objectives, DNDi seeks different sources of funding from governments and international organisations (51% of projected income), Founding Partners (17%), private foundations and large donors (29%), and individuals (3%). The "Friends of DNDi", a group of individuals from around the world committed to DNDi's vision and mission, will equip DNDi with an additional tool to strengthen and to support the implementation of the fundraising strategy, as well as to raise awareness of the need for R&D for neglected diseases. DNDi is well-positioned to obtain the funds necessary to sufficiently support its mission, vision, and objectives, and to maintain independence.

2. DNDi IN 2007

Founded in 2003 to address the needs of patients with the most neglected diseases, DNDi is a collaborative, patients' needs-driven, virtual, not-for-profit drug R&D organisation.

2.1 VISION AND MISSION

DNDi's vision is:

To improve the quality of life and the health of people suffering from neglected diseases by using an alternative model to develop drugs for these diseases and by ensuring equitable access to new and field-relevant health tools.

In this not-for-profit model, driven by the public sector, a variety of players collaborate to raise awareness of the need to research and develop drugs for those neglected diseases that fall outside the scope of market-driven R&D. They also build public responsibility and leadership in addressing the needs of these patients.

DNDi's mission is:

To develop new drugs or new formulations of existing drugs for patients suffering from the most neglected communicable diseases. Acting in the public interest, DNDi will bridge existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners.

DNDi's primary focus will be the development of drugs for the most neglected diseases, such as HAT (sleeping sickness), visceral leishmaniasis (VL), and Chagas disease. The organisation will also consider engaging in R&D projects on other neglected diseases. DNDi will address unmet needs by taking on projects that others are unable or unwilling to pursue and, as means permit, will consider development of diagnostics and/or vaccines.

In pursuing these goals, DNDi will manage R&D networks built on South-South and North-South collaborations. While using the existing support capacities in countries where the diseases are endemic, DNDi will help to build additional capacity in a sustainable manner through technology transfer in the field of drug research and development for neglected diseases.

2.2 OBJECTIVES

The primary objective of DNDi is to deliver six - eight new treatments by 2014 for leishmaniasis, sleeping sickness (HAT), Chagas disease, and malaria, as well as to establish a strong R&D portfolio that addresses patient needs for treatment. Utilizing R&D networks built on South-South and North-South collaborations, DNDi aims to bring medical innovation to the patients by developing:

- New drugs from novel compounds identified through screening and lead optimisation;
- New drugs from compounds with known antimicrobial/antiparasitic activities (could start at lead optimisation or pre-clinical development);
- New indications for existing medicines in the field of the most neglected diseases (therapeutic switching);
- Reformulations and combinations better adapted to field conditions (paediatric, long-acting, new route of administration, fixed-dose combinations, co-packaging, or co-administration);
- Existing drugs for target diseases (geographical extension of registration; completion of regulatory dossiers of existing drug candidates).

In doing this, DNDi also has two other objectives:

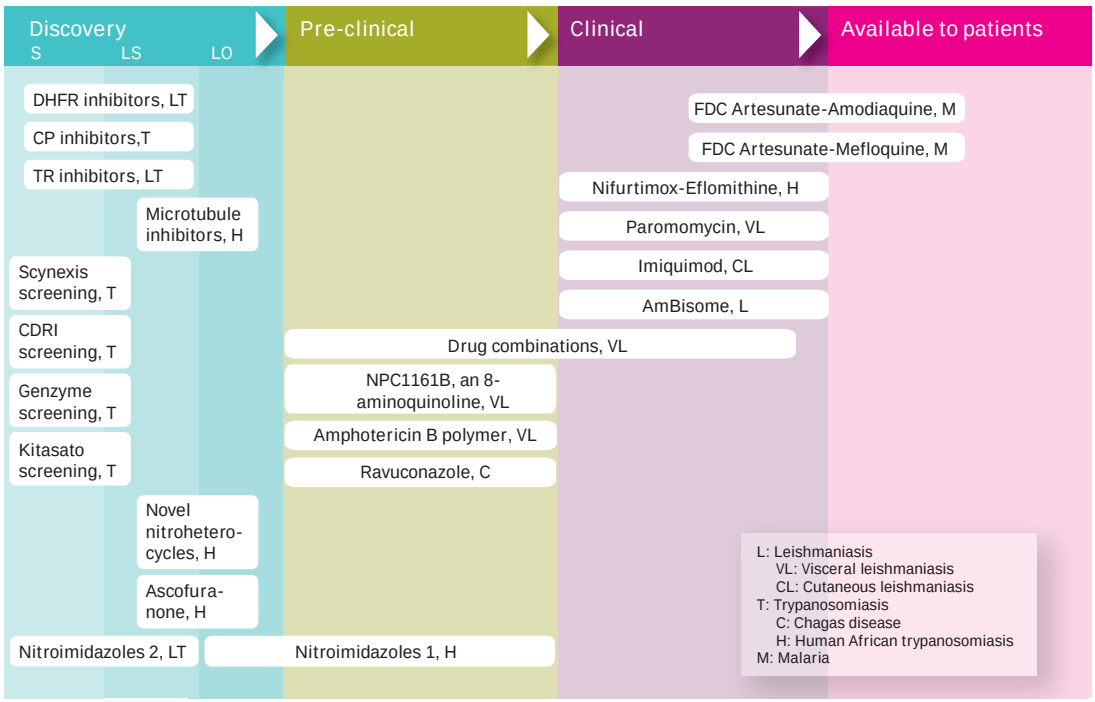
→ **To use and strengthen existing capacities in disease-endemic countries via project implementation.**

→ **To raise awareness about the need to develop new drugs for neglected diseases and advocate for increased public responsibility.**

2.3 PORTFOLIO

In 2007, the portfolio of DNDi has grown to 22 projects from the four projects described in the original Business Plan written in 2003. The current portfolio primarily focuses on the three kinetoplastid diseases (HAT, VL, and Chagas disease) and contains seven clinical, four preclinical, and eleven discovery projects (Figure 1). Through a continuous exploration and exchange with academia, pharma, biotech, and other PDPs, DNDi is building a portfolio that proactively identifies critical R&D challenges and opportunities (see Chapter 4).

Figure 1. DNDi portfolio, January 2007.



The portfolio already contains strong projects for HAT and VL (two of the three target diseases). The gains made in the past three years of building a portfolio must now be matched by a continuous supply of strong, new projects built through exploratory activities, rigorous selection, and a management process that enables efficient and effective project progression. More than ten exploratory activities are underway or in discussion.

2.4 ORGANISATION AT THE BEGINNING OF 2007

Today, DNDi is a team of committed people who are dedicated to maintaining the momentum achieved since the launch of the initiative in 2003. With DNDi's ambitious vision in mind, the small team of permanent staff in Geneva along with four regional support liaison offices, two project support offices, and several short-term consultants have made significant headway in achieving DNDi's mission.

Under the leadership of the Executive Director, the DNDi Executive team in Geneva oversees the implementation of the R&D strategy, manages the global portfolio, allocates resources, and leads fundraising and advocacy. Project managers, with experience in different aspects of pharmaceutical development, oversee the implementation of selected projects by managing a worldwide network of scientists actively involved in the R&D of new drugs for neglected diseases, principally in Asia, Africa, and Latin America. The four regional support liaison offices work primarily to help identify patients' needs, to support project management, and to identify and support regional partners. The Founding Partners play a critical role in the continuing development of DNDi, both with financial and in-kind contribution. Their historical involvement in tropical diseases, interest, and expertise in different aspects of R&D for neglected diseases (including advocacy, discovery, and drug development) are all valuable assets.

2.5 KEY ACCOMPLISHMENTS AND CHALLENGES

A number of achievements have been reached in a relatively short period of time. All such achievements are milestones along the way to achieving DNDi's vision:

■ Founding Partners

Underscoring the need for public leadership on and involvement in neglected diseases, DNDi drew Founding Partners primarily from the public sector in neglected disease-endemic countries: **the Oswaldo Cruz Foundation/Farmanguinhos** in Brazil, **the Indian Council for Medical Research (ICMR)**, **Kenya Medical Research Institute (KEMRI)**, and **the Malaysian Ministry of Health**, along with the international humanitarian organisation **Médecins Sans Frontières**, **the Institut Pasteur**, and with the **UNICEF-UNDP-World Bank-WHO's Special Programme for Research and Training in Tropical Diseases (TDR)** as permanent observer.

■ Portfolio

DNDi has built a portfolio, based around disease strategies for HAT, leishmaniases, and Chagas disease (Appendix C), which already contains strong projects for two of the target diseases and taps networks of expertise in many different fields. This portfolio serves the primary R&D objective of making six-eight new treatments available to patients by 2014, and of having a robust pipeline for all target diseases into the future.

■ Platforms

For HAT and VL in Africa, DNDi has helped to establish two disease-specific platforms that develop clinical research capacity in endemic regions by involving relevant scientists, research organisations, international organisations, NGOs, and national programmes. Such platforms have allowed for clinical research in extremely difficult, resource-poor, rural settings in Africa.

DNDi has also attracted quality R&D partners for all stages of drug development: from the many partners of the Pan-Asian Natural Products Screening Platform, which link top-notch research and institutes across the region in a collaborative network to explore natural products as potential drug candidates against kinetoplastids, to a late-stage industrial partner like sanofi-aventis to develop and distribute the new fixed-dose antimalarial co-formulation, artesunate-amodiaquine (ASAQ).

Products

In 2007, two fixed-dose artemisinin combination therapies (ACTs) will become available as products of the FACT project and will offer the first-ever paediatric strengths in fixed-dose antimalarials. These products, ASAQ and artesunate-mefloquine (ASMQ), are **easy to use** (fewer tablets in regimen to ensure drugs are taken **together** and **in correct proportions**), **affordable,** and **available as public goods**. Innovative partnerships have been built: in the case of ASAQ, sanofi-aventis has agreed to non-exclusive terms in the late-stage development and production; and in the case of ASMQ, two industrial partners in the South (Brazil and India) are working to make the combination available to the patients who need it most.

Policy

Through advocacy efforts, DNDi has influenced public policy agendas, from WHA Resolution 59.24 to G8 and EU political and financial commitments to neglected diseases. As part of its policy success, DNDi has secured funding of approximately EUR 22 million for neglected diseases' drug R&D from a number of governments including the UK, France, the Netherlands, and the European Union.

Having quickly reached a number of milestones, DNDi must remain vigilant about proactively identifying the optimal balance between research, development, and access to best address enduring unmet patient needs. A number of critical challenges are anticipated as DNDi moves forward into the future:

Product-related

- → sustainable delivery of products to neglected populations
- → access to chemical diversity
- → pragmatic identification and selection of promising candidates at all stages of drug R&D

Partner-related

- → recognition and choice of suitable partners at all stages of drug R&D, and access
- → successful negotiation of innovative agreements to in-source projects, manage partners, and deliver products
- → synergistic interaction with all neglected diseases players

Policy-related

- → encouraging policy change that will support adoption of and equitable access to new, essential health tools
- → securing adequate funding that will meet needs to cover R&D programmes

3. THE LANDSCAPE OF RESEARCH AND DEVELOPMENT FOR NEGLECTED DISEASES

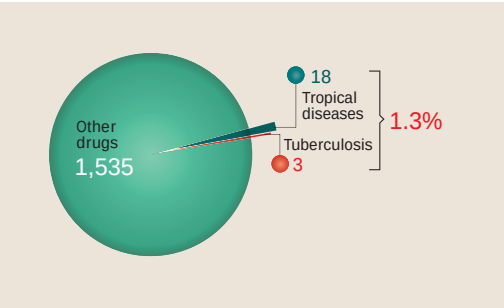
Since 2000, the R&D landscape has significantly changed for neglected diseases, including the most neglected. Even with the current players involved in the 2007 landscape, the need for new field-adapted drugs is far from being addressed for the kinetoplastid diseases.

3.1 INTRODUCTION

Over the past thirty years, global health has transformed at an unprecedented rate, with life expectancy increasing at an average of four months every year in developed countries. However, with few exceptions, people living in developing countries have not benefited from this revolution. Millions continue to die from preventable and treatable diseases, such as HIV/AIDS, malaria and tuberculosis; and many tropical diseases have been all but forgotten.

Tropical diseases, such as malaria, human African trypanosomiasis (HAT), Chagas disease, leishmaniasis, lymphatic filariasis, dengue fever and schistosomiasis, continue to cause significant morbidity and mortality. Yet, of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4% of the global disease burden (Figure 2).

Figure 2. Proportion of new drugs developed over the period from 1975 to 2004 that were for neglected tropical diseases and tuberculosis.



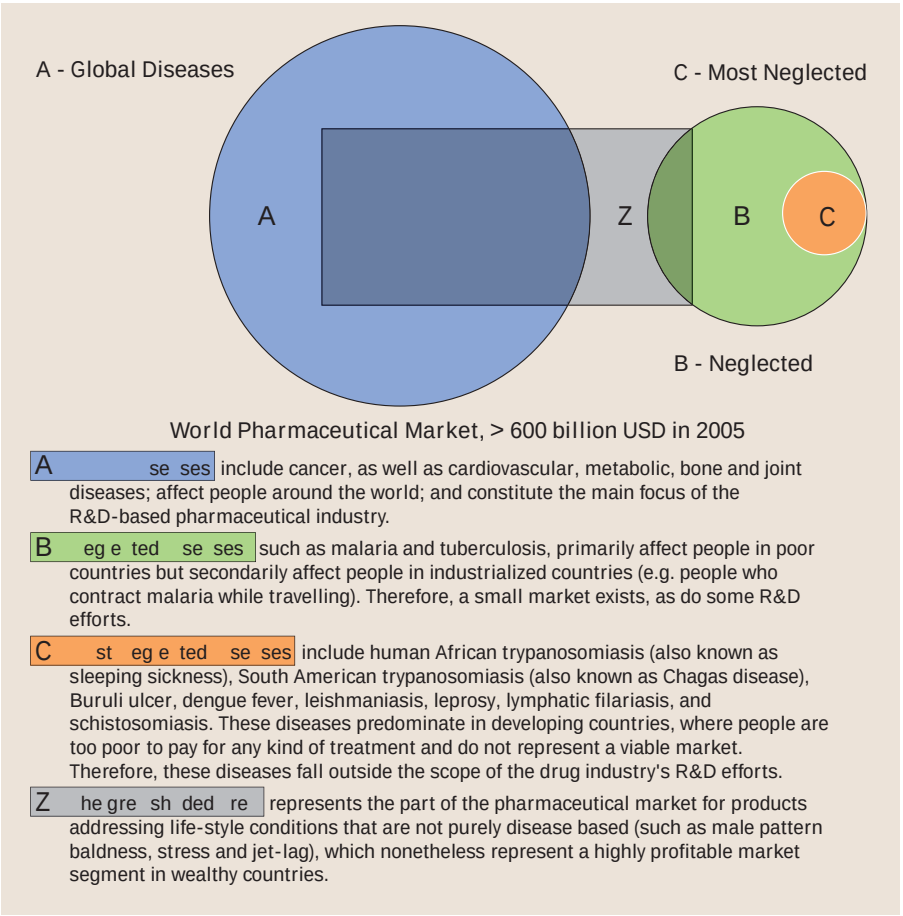
Source: Chirac P., Torreele E. Lancet. 2006 May 12; 1560-1561.

With progress made in the basic knowledge of many tropical diseases, drug discovery R&D for these diseases has significantly improved but has had little impact in development of new drugs. Most drugs currently used to treat kinetoplastid diseases were discovered decades ago. With few exceptions, the wealth of knowledge related to basic research of these parasites is not being translated into practical applications.

Why are some diseases more neglected than others?

Due to a combination of market and public policy failures, drug development has largely been confined to the R&D-based pharmaceutical industry. In neglected disease-endemic regions, the public sector has not been able to adequately cultivate drug development expertise and capacity. The dynamics of the market and public policy failures show that a distinction between "neglected" and "most neglected" diseases can be made (Figure 3).

Figure 3. Global pharmaceutical market and disease R&D targets.



Source: Médecins Sans Frontières Access to Essential Medicines Campaign and the Drugs for Neglected Diseases Working Group. (2001) Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases. Available: http://www.msf.org/content/page.cfm?articleid=032387D3-7D09-49E3-99FC231DBE03F7B7. Accessed 24 September 2007.

For the "most neglected" diseases, patients are so poor that they have virtually no purchasing power and cannot spark market interest in drug R&D among pharmaceutical companies.

3.2 NEEDS OF PATIENTS WITH NEGLECTED DISEASES

Even with the current players involved in the 2007 R&D landscape, the need for new field-adapted drugs is far from being addressed for the kinetoplastid diseases of HAT, VL, and Chagas disease. To provide a clear view of the landscape, a brief overview of each of these vector-borne parasitic diseases is provided below, followed by a sketch of current treatments and patient needs.

Human African Trypanosomiasis (HAT)

HAT, known as sleeping sickness, is caused by two sub-species of *Trypanosoma parasites*, which are transmitted to humans by tsetse flies. Sleeping sickness, which infects 50,000 to 150,000 people per year and threatens another 50 million at risk, occurs only in sub-Saharan Africa. The disease takes one of two forms, depending on the parasite sub-species (either *T.b. gambiense* or *T.b. rhodesiense*).

Sleeping sickness has two stages. The first stage entails bouts of fever, headaches, joint pains, and itching. The second stage, known as the neurological phase, begins when the parasite crosses the blood-brain barrier and invades the central nervous system. Without treatment, the disease is fatal.

Currently available treatments for HAT – melarsoprol, eflornithine, pentamadine, and suramin – are few and limited due to age-based dosing restrictions, toxicity, the difficulty of administration, cost, and lost efficacy in several regions. Treatment is stage-specific, with more toxic and more difficult-to-administer treatments (melarsoprol, eflornithine) for stage 2 disease. Few projects for improved treatments are currently in clinical development, and none has the potential to dramatically change either the treatment or control options for this disease.

■ Visceral Leishmaniasis (VL)

Transmitted by the sandfly, the protozoan parasite *Leishmania* causes three different forms of disease, of which visceral leishmaniasis (VL) is the most severe. Leishmaniasis affects over 12 million people and puts over 350 million people at risk in 88 countries.

Fatal if left untreated, VL (also known as black sickness or kala-azar in India) persists today in poor, remote, and sometimes politically unstable areas, where limited healthcare means that patients have little access to preventive measures and affordable drugs. A significant proportion of clinical cases occur in children. Approximately 500,000 new cases are reported to occur each year, though it is estimated that only 30% of cases are reported. VL is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anemia, and is complicated by co-infection with other infectious diseases, such as HIV or malaria.

Chemotherapy remains the most important element in the control of VL, with pentavalent antimonials used as the primary first-line treatment in most parts of the world (except in India which has a high level of drug resistance). However, the number of treatments available for VL has significantly increased during the past decade, with both new drugs and new formulations of old drugs either recently approved or in clinical development. These new treatments include:

- AmBisome™, an amphotericin B liposome formulation, that was registered for VL in the USA and Europe in the 1990s and has shown remarkable activity even in a single dose in India;
- oral miltefosine that was registered in India in 2002 and is now in Phase IV trials;
- a low-cost parenteral (intramuscular) formulation of paromomycin (aminosidine) that was registered in late 2006 in India (www.iowh.org) and is in Phase III in East Africa by DNDi.

Unfortunately, all these drugs have significant drawbacks – either in terms of route of administration, length of treatment (21 to 28 days), toxicity, or cost – all of which limit their utilization in disease-endemic areas.

■ Chagas Disease

Chagas disease, another human form of trypanosomiasis (human American trypanosomiasis), occurs almost exclusively in the Americas. Transmitted to humans by a triatomine insect containing the parasite *T. cruzi*, the disease is contracted through the bite of the insect widely known as «the kissing bug».

There are three stages of the disease: acute, indeterminate, and chronic. In the acute form (in which 5% of children die), Chagas disease manifests generally as fever, malaise, facial oedema, generalized lymphadenopathy, and hepatosplenomegaly. The acute illness often spontaneously resolves in four to six weeks, at which time patients enter an asymptomatic, 'indeterminate' phase that can last ten years to life. The chronic stage of Chagas disease develops in 10% to 30% of infected persons and most commonly affects the heart. Death usually results from cardiac arrhythmia or congestive heart failure.

The two current treatments, benznidazole (which requires 60 days of treatment in acute infections and is only effective in 50% of cases) and nifurtimox (used for acute and early indeterminate stages of the disease) are very limited. There are no treatments for indeterminate and chronic stages of the disease.

For Chagas disease, which infects 18 million and puts 100 million at risk in Central and South America, drugs are needed to treat both acute and chronic disease, as are safer and more effective drugs adapted to patient needs (i.e., paediatric formulation).

3.3 IN 2007, A CHANGED R&D LANDSCAPE FOR NEGLECTED DISEASES

Prior to 2000...

Very few players were involved in the field of the most neglected diseases. In addition to The Special Programme for Research and Training in Tropical Diseases (TDR), GlaxoSmithKline (GSK), and the Walter Reed Army Institute of Research (WRAIR) were involved in specific project-related activities.

UNDP / World Bank / WHO Special Programme for Research and Training in Tropical Diseases (TDR) was established in 1975. Initially, TDR addressed ten tropical diseases and had a two-fold mission: to develop new tools and methodologies to combat its target diseases, and to develop research capacity in developing countries so as to enable them to better address their needs and to contribute to sustainable long-term solutions. The work of TDR includes support for drug discovery and development, advocacy, agenda-setting, and professional training among other tasks. TDR has successfully partnered the development of several new treatments for tropical diseases over the past 25 years and remains active in this area.

Awareness of the lack of effective treatments for neglected diseases began to grow during the late 1990s, and some novel approaches emerged to stimulate R&D and to produce needs-adapted health tools. The first PDPs for neglected disease R&D, e.g. International AIDS Vaccine Initiative (IAVI) and Medicines for Malaria Venture (MMV), were established in the 1990s, but these PDPs were not mandated to address the unique characteristics of the most neglected diseases.

In parallel, market push and pull mechanisms include various financial and economic incentives designed to encourage the R&D-based pharmaceutical industry to develop drugs for otherwise neglected diseases. "Push" mechanisms, such as R&D grants, lower the costs and risks of companies' R&D efforts; "pull" mechanisms, such as market exclusivity and patent extension, secure the profitability of the market. While such mechanisms proved successful in stimulating R&D for rare ("orphan") diseases, a recent study2 by the London School of Economics (LSE) showed that these mechanisms do not attract pharmaceutical companies to engage in neglected diseases R&D. Moreover, market push and pull mechanisms are of limited use for the most neglected diseases where the market is non-existent because neither governments nor patients have the ability to pay.

Now in 2007...

At the turn of the millennium, increasing pressure and attention have turned to addressing the needs of patients with neglected diseases (i.e., Millenium Development Goals). Several new actors, new donors, new financial mechanisms, and a new political environment have become increasingly active in the field of R&D for neglected diseases (Figure 4, p.15).

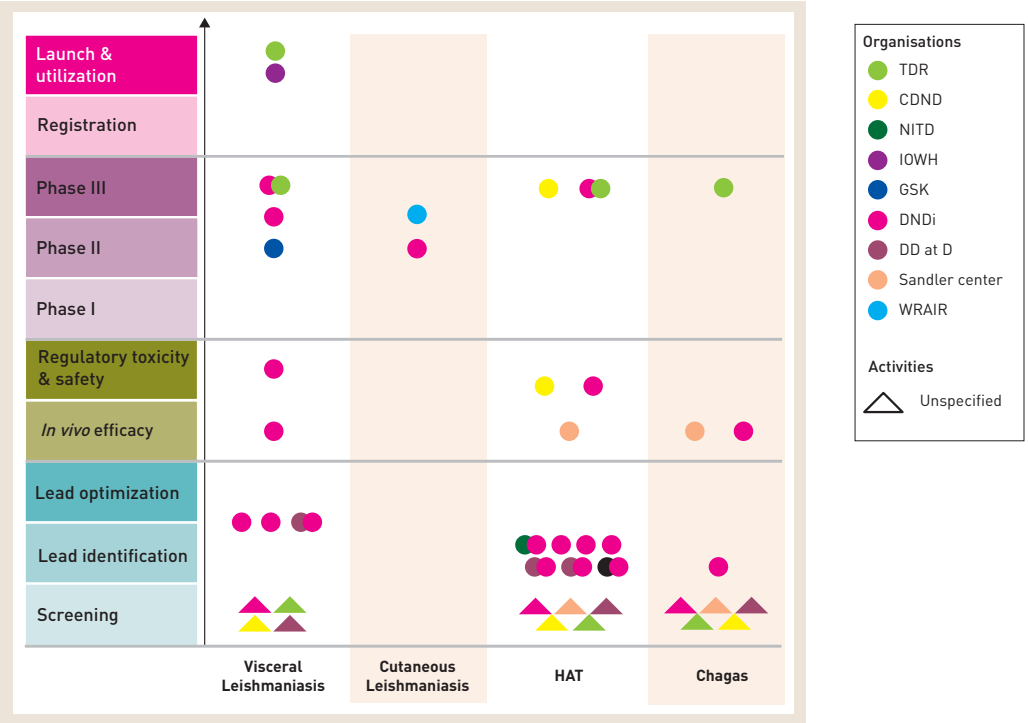
New players though more activity is still needed

Product Development Partnerships (PDPs) seek to foster R&D and access for neglected diseases by building partnerships - based on existing capacity, expertise, and resources - in both the public and the private sector. Acting as coordinators to set a disease-specific R&D agenda and portfolio, raise funds, and manage R&D projects, PDPs work to develop the essential health tools needed by patients. Funded by public and mainly philanthropic resources, PDPs include Medicines for Malaria Venture (MMV), the Global Alliance for TB Drug Development (TB Alliance), IAVI, the Institute for One World Health (IOWH), the Foundation for Innovative Diagnostics (FIND), and DNDi. At the end of 2004, 75 percent (47 of 63) of active drug development projects for neglected diseases were conducted by PDPs, which are forecasted to bring eight to nine new drugs to market by 2010.[1] In the field of most neglected diseases, the following PDPs are active:

- Created in 2000, **IOWH** developed paromomycin for visceral leishmaniasis (VL) in India and completed registration in September 2006. Other efforts include projects on diarrhoeal disease and malaria;
- **FIND**, founded in 2003 to develop a field-adapted diagnostic for TB, is working to develop rapid, accurate, and affordable first-point-of-care diagnostic tests for poverty-related diseases that are endemic in the developing world. FIND has a specific R&D programme to develop a HAT diagnostic.

[1] Moran et al. The New Landscape of Neglected Disease Drug Development. London, UK: Pharmaceutical R&D Policy Project, London School of Economics. 2005.

Figure 4. 2007 landscape of drug R&D for kinetoplastid diseases.



Alongside the creation of PDPs, some companies in the **pharmaceutical/biotechnology sector** have recently created special R&D facilities or initiatives to develop new tools for neglected diseases (but not the most neglected). Multinationals (e.g., Novartis, GSK, Astra Zeneca, sanofi-aventis) have neglected diseases R&D units and provide their drugs on an at-cost (no profit, no loss) basis to developing countries. These commitments are motivated not purely by financial incentives, but by the desire to project a positive corporate image, to assume corporate social responsibility, and/or to secure positions in emerging, developing country markets.

- The majority of possibilities for partnerships or business relationships between pharma and PDPs are based on screening, on access to compounds or known chemical series with anti-protozoal activity, and on opportunities to build a mini-portfolio. Some companies are also involved at the production, registration, and distribution stages;
- For companies, PDPs bear the major risks of R&D, especially in clinical development, which is of particularly attractive to biotech companies;
- Small pharma, or biotechnology, companies like Advinus, Cumbre, Genzyme, Immtech, and Scynexis are participating in PDP R&D efforts in which they can play a defined role, such as screening, lead optimization, and pre-clinical development.

Many **academic & public institutes** are now players in the field of neglected disease R&D. For anti-kinetoplastid drug R&D in particular, the following groups are active:

- In 2000, the University of North Carolina (UNC) created the **Consortium to Develop New Drugs for Protozoan Disease (CDND)** to develop new drugs for HAT and leishmaniasis. In 2006, CDND expanded their mandate to include other chemical series and leads for drug discovery and development for trypanosomiasis and leishmaniasis. Currently, CDND is conducting a Phase III clinical trial on pafuramidine maleate for stage 1 HAT;
- Between 2000 and 2002, the **Sandler Center for Basic Research in Parasitic Diseases (SCBRPD)** established a consortium of core academic laboratories working in synthetic chemistry, structural biology, computational biology, biochemistry, and animal models of disease and drug metabolism, to support development of new anti-parasitic drugs. The consortium's initial work is focused on developing a drug candidate for Chagas disease;

- In 2005, Dundee University created **Drug Discovery at Dundee (DD at D)** to translate basic research discoveries into candidates ready for clinical trials. The first priority of DD at D is to generate a clinical drug candidate for stage 2 HAT, with the aim of one preclinical candidate ready for development by 2011.

A number of **emerging, developing countries,** including India, Brazil, China, Thailand, Kenya, Malaysia, and Singapore, have dedicated resources to building R&D capacity, for example: in Brazil, **Farmanguinhos** and the future Drug and Vaccine Technology Transfer Centre at the **Oswaldo Cruz Foundation**; in India, the **Centre of Drug Research Institute**; and in China, the **Shangai Institute on Materia Medica**.

New donors, but sustained financial support for the most neglected diseases is needed.

Several **donors** are now involved in funding R&D for neglected diseases, though again it is important to note that the funding is generally targeted at neglected diseases, not the most neglected diseases.

Institutional financial support for R&D for neglected diseases (mainly the Big Three of HIV, TB, and malaria) has grown, but is still far from the requisite USD 3 billion per year, as proposed by the WHO's Commission on Macroeconomics and Health in 2001.

- Only a few governments, including **France, Ireland, the Netherlands, the UK, Switzerland and the US,** have made financial commitments to R&D for the most neglected diseases;
- After public pressure from the Parliament, civil society, and NGOs, the **EU's FP7 Programme** (2007-2013) has included the most neglected diseases on the priority agenda. Moreover, in 2002, the EU's FP6 programme created the European and Developing Countries Clinical Trial Partnership (EDCTP) which focuses on facilitating clinical development of tools in sub-Saharan Africa; however, this is not applicable to most neglected diseases;
- A number of **emerging, developing countries**, for example: Brazil, has invested public funds to mobilize resources for drug R&D activities.

Philanthropic donors - most notably the Bill and Melinda Gates Foundation (BMGF), but also with the Wellcome Trust, Rockefeller Foundation, Sandler Family Foundation and other smaller foundations following their lead – have been the critical drivers for the increased R&D activity in the field for most neglected diseases.

- Since its inception in 1994 the **BMGF** alone has invested nearly USD 8 billion into global health programmes; with the recent doubling of the foundation's endowment by Warren Bufet, the annual payout is expected to double. The disease priorities of BMGF are broad, but do specifically include priorities to develop new anti-kinetoplastid drugs as shown by their full support of iOWH's VL drug development programme and by their support of CDND's HAT and VL programmes. In addition to being the largest philanthropic funder of R&D for global health issues, the BMGF has also become an influential player in international health policy.

New sustainable financial mechanisms (Global Fund, GAVI, UNITAID, IPFF) have been explored but all are currently concentrated on TB, malaria, HIV/AIDS, and vaccines.

New political environment, but a global framework for essential health R&D, including the most neglected diseases, is still needed.

The most neglected diseases are now being found on the **international agenda**.

- In 2005, the **G8** pledged that governments would increase direct investment and take forward work on market incentives, as a complement to basic research, through such mechanisms as Public Private Partnerships and Advance Purchase Commitments to encourage the development of vaccines, microbicides and drugs for AIDS, malaria, tuberculosis, and other neglected diseases.
- In September 2005, a European Parliament resolution included support for R&D on neglected diseases.
- **TDR**, has transformed its vision and strategy, which now covers three responsibilities for neglected diseases, including the most neglected: 1) provide a collaborative framework and information service for research partners; 2) empower scientists from disease-endemic countries as research leaders, and 3) support research on neglected priority needs.

- The **WHO Neglected Tropical Diseases Department** was recently created from the reorganisation of the WHO cluster of communicable diseases and focuses on diseases that include the kinetoplastid diseases, as well as helminth and nematode infections. This reorganisation, which underscores the importance of this issue on the international agenda, should facilitate and coordinate the relationship between the different partners involved in disease control and research.
- In April 2006, after two years of study, the **WHO Commission on Intellectual Property, Innovation, and Health (CIPIH),** produced a report calling for governments to set global health priorities and promote innovation to develop and deliver much-needed medicines, vaccines, and diagnostics adapted to the needs of the sick and neglected in developing countries.
- During the World Health Assembly in May 2006, **Resolution 59.24 on Public Health, Innovation, Essential Health Research and Intellectual Property Rights** was passed. Proposed by Brazil and Kenya, the resolution called for WHO member states "to make global health and medicines a priority sector, to take determined action to emphasize priorities in research and development addressed to the needs of patients, especially those in resource-poor settings, and to harness collaborative research and development initiatives involving disease-endemic countries." The WHO **Intergovernmental Working Group** was created to explore a strategy and plan of action.

3.4 OPPORTUNITIES FOR DNDi

DNDi is well-positioned to continue to play a leading role in discovery, development, and delivery of new treatments for the most neglected diseases, to advocate for greater public leadership, to catalyse new commitments from governments and philanthropic donors, and to raise awareness of the need for R&D of new drugs to treat the suffering from the most neglected diseases.

In order to ensure complementarity with research organisations like TDR and other PDPs, DNDi will seek pragmatic synergies and collaborations with others in the field. For instance, progress realised in one disease can be used to accelerate the development of a treatment for another disease: examples include DNDi's collaboration with MMV in the case of an 8-aminoquinoline project for VL, and DNDi's synergy with TDR in the case of the clinical trial examining nifurtimox-eflornithine co-administration (NECT) for HAT.

Further opportunities to work closely with other organisations could include the exchange of information, the selection of projects, shared communication and advocacy efforts, and knowledge and technology exchange in favour of patients. An excellent illustration of this collaborative potential is the involvement of FIND in the field of development of new diagnosis for HAT and in the HAT clinical research platform alongside the Swiss Tropical Institute and DNDi.

4. DNDi BUSINESS MODEL

The DNDi business model can be characterized by the following distinguishing traits:

1. **A stepwise, integrated model of drug R&D**
   - **with a primary R&D focus on the kinetoplastid diseases (HAT, VL, Chagas)**
   - **with needs-driven R&D projects that can be sourced at any stage of the R&D pipeline**
2. **A virtual organisation, managing collaborative R&D projects**
3. **A needs-driven regulatory and access strategy**
4. **R&D networks that utilise and strengthen research capacities in disease-endemic countries**
5. **International advocacy to support DNDi's R&D objectives and foster an improved global framework for essential health R&D**

4.1 A STEPWISE, INTEGRATED MODEL OF DRUG R&D

Utilizing a stepwise portfolio development approach (Figure 5), DNDi aims to discover and develop treatments to meet the medical needs of patients suffering from neglected diseases. With a strong focus on the kinetoplastid diseases (HAT, VL, and Chagas disease), DNDi has and will continue to develop, on an opportunistic basis, treatments for other neglected diseases. Current examples are the nearly completed development processes of two co-formulations for chloroquine-resistant malaria and cutaneous leishmaniasis (CL).

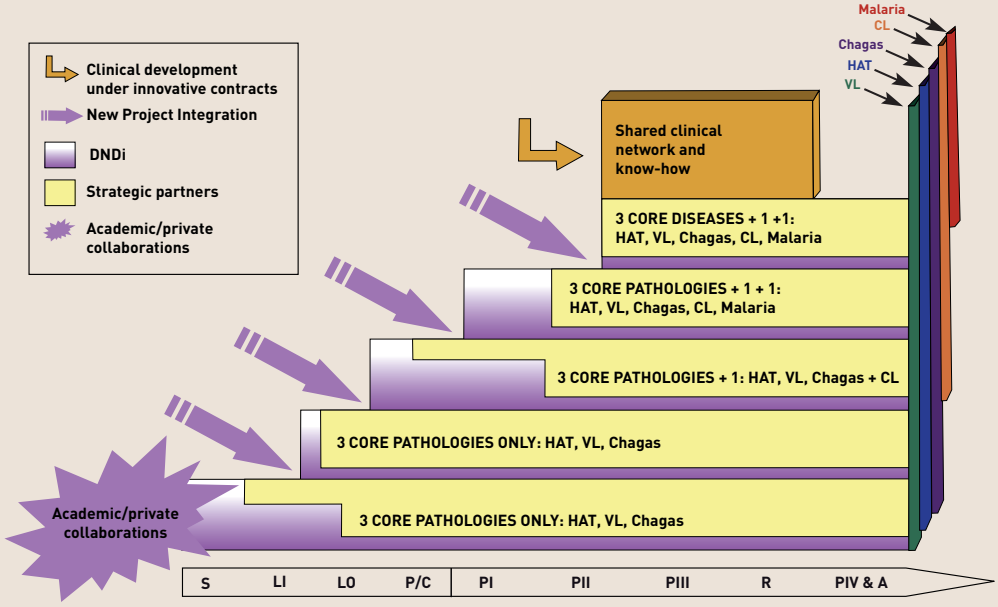
As seen in the model below, DNDi will focus on the discovery of new drug candidates for kinetoplastid diseases. For projects further downstream in development, DNDi may in-license external projects (therapeutic switching or new formulations of existing compounds) at preclinical or clinical stages for CL.

Needs-driven projects can be sourced at all stages.

As DNDi combines new drug discovery with optimisation of existing drugs and compounds, its portfolio will encompass a range of projects in-sourced at any stage of the development process, from early discovery up to late clinical development. As described in Section 5, five project categories can be distinguished by the nature of the compound/treatment under consideration and by the stage of development or expected time to reach the patients (see Figure 8, p.27).

Together with selected partners, DNDi will also ensure effective post-registration management of new treatments for these neglected kinetoplastid diseases. Mechanisms must be put into place to ensure treatment, utilisation, and access through partnership with international and national programmes and with commercial partners. Such mechanisms will also ensure the timely hand-over of projects between partners.

Figure 5. DNDi stepwise integrated model.



Needs-driven projects can be sourced at all stages.

The DNDi R&D team will proactively reach out and build a number of exploratory activities which, depending on outcomes, can be built-up to full drug development projects or maintained as backup pipeline projects. Through this approach DNDi will maintain a 'feeder' system for the pipelines of each target disease. Successful initial links with the pharma/biotech sector will be used to build further contacts and partnerships, highlighting the organisation's engagement with industry.

Systematic and opportunistic intelligence work, which will continue throughout the lifetime of the DNDi, will consist of (i) further identifying and/or monitoring unmet medical needs related to the lack of appropriate health tools for neglected diseases; (ii) closely following the scientific and technological developments in fields relevant to addressing the above identified needs in an innovative way; and (iii) matching needs and opportunities to propose new development projects.

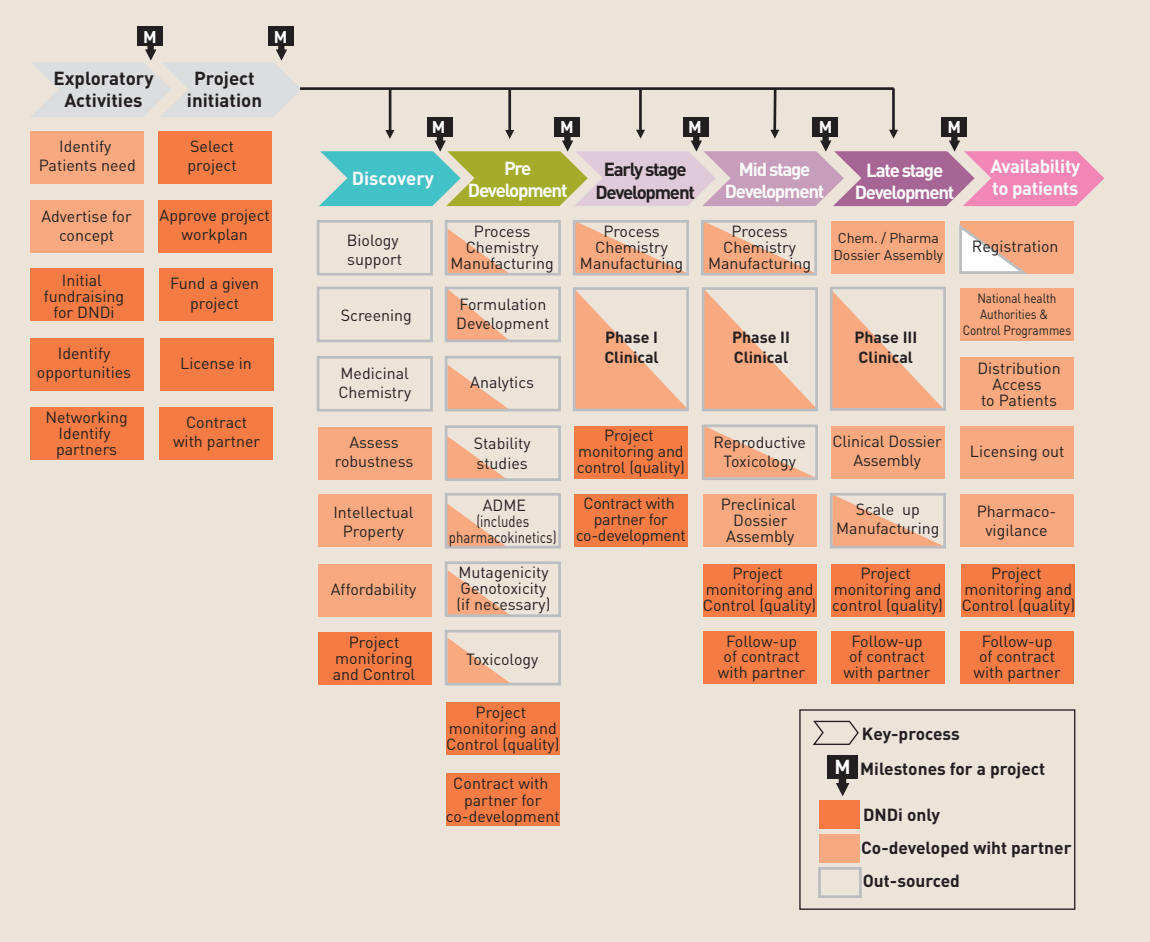
4.2 A VIRTUAL ORGANISATION MANAGING COLLABORATIVE R&D PROJECTS

DNDi does not have any research facilities and will not directly conduct R&D to develop its treatments. Instead, DNDi will follow the virtual research mode adopted by other PDPs and certain biotechnology companies whereby most research is outsourced and actively managed by DNDi personnel experienced in different aspects of pharmaceutical development. DNDi will proactively identify research opportunities that have the highest potential to translate into improved treatment options, source the research project into its portfolio, build the full development plan, identify and contract the appropriate partners for each step in the development process, and manage the efficient transition of the project throughout the pipeline.

DNDi collaborates with different types of partners in both developed and developing countries, including:

- Public and academic research institutions;
- Governments and disease control programmes of disease-endemic countries;
- Pharmaceutical and biotechnology companies, including contract research organisations (CROs) and contract manufacturing organisations (CMOs);
- NGOs, foundations and other institutions involved in R&D and/or advocacy for neglected diseases;
- Experts to advise on any and all aspects of pharmaceutical development, neglected diseases, and or business practices.

Figure 6. Breakdown of responsibilities between DNDi and its partners at different stages of the drug development process.



Source: Benchmark MMV, GATB, adapted to DNDi.

For each project, a project team, under the leadership of a DNDi project manager, is put in place to coordinate all relevant partners and expertises. The collaborations are governed by different types of contractual agreements, ranging from research funding collaborations over technical service agreements to long-term co-development partnerships with industrial partners.

DNDi and its partners share responsibilities at different stages of the drug development process (Figure7). Certain issues, such as the selection, funding, monitoring, and control of projects, will be DNDi's direct responsibility throughout the development process.

4.3 A NEEDS-DRIVEN REGULATORY AND ACCESS STRATEGY

4.3.1 International Regulatory Standards to Control and Assure Quality

DNDi operates in a highly regulated environment. From the earliest phases of the drug development process, registration requirements will be taken into account and all R&D will be performed according to international standards.

The research, development, and supply of a novel therapy invariably results in a certain level of risk. Quality is a central component associated with all of the risks: quality of the R&D activities performed, quality of the developed substances, and quality of the final product. Therefore, project-associated quality and safety from screening through clinical development and up to the implementation phase are a key success factors for DNDi.

DNDi quality control/quality assurance (QC/QA) aims to build a global set of internal and appropriate standardized operating procedures (SOPs) that will cover all stages of drug development and are based on the International Conference Harmonisation (ICH) and the Organisation for Economic Co-operation and Development (OECD) recommendations. Both GDP (Good Documentation Practice) and GRP (Good Reporting Practice) are essential.

GDP may include (but is not limited to):

- Quality assurance documents (policies, guidelines, and SOPs);
- Product specifications (sampling, regulatory specifications);
- Materials specifications (raw materials, process materials);
- Manufacturing documents (formulation/process specifications);
- Testing documents (test methods) based on risk audit processes.

GRP will be set up with subcontracting academic or private laboratories to monitor experiments and projects. Reporting done in a standard format as part of SOPs, for each stage of product development and for all subcontractors, will allow for follow-up with respect to the design, processes, and format of the reporting.

→ At the preclinical level, quality assurance will focus on appropriately interpreting OECD guidelines for GLP (Good Laboratory Practice) and on adapting GSP (Good Scientific Practice) and GDP.

→ During clinical development, translation of GCP (Good Clinical Practice) and GCLP (Good Clinical Laboratory Practice) into specific internal SOPs will be critical milestones.

→ Chemistry, manufacturing, and controls development will rely on effective and efficient GMP (Good Manufacturing Practice) SOPs to sustain a "regulatory" level of quality product development and registration.

GDP, GRP, GCP (Phase IV) and GMP will continue through the implementation period.

4.3.2 Intellectual Property

During its first years of existence, DNDi developed an intellectual property (IP) policy to guide its R&D activities and associated contractual agreements with the following objectives:

- The need to ensure that treatments are ultimately affordable to patients who need them and that access to these treatments is equitable;
- The desire to develop drugs as public goods when possible (although DNDi will not necessarily be able to control all IP for short- and mid-term projects).

The policy, which reflects the fact that DNDi outputs are likely to have negligible commercial value and that R&D agreements will often be made with public sector entities, calls for a pragmatic approach so that decisions regarding ownership of patents and of licensing terms are made on a case-by-case basis. In building its portfolio, DNDi will continue to negotiate to guarantee the best possible conditions for patients.

4.3.3 Registration

For product registration, the filing strategy for each project will be developed by performing a risk-benefit assessment in disease-endemic countries and by using a patient-oriented, needs-based rationale. In most circumstances, DNDi will file registration applications on a country-by-country basis, through industrial partners who are profit or not-for-profit. In some cases, in particular for combination treatments, it may be that individual product registration is not the most appropriate strategy and alternatives such as a WHO-recommendation and/or inclusion into the WHO essential drugs list may be the best way to make a combination treatment available in endemic countries.

4.3.4 Access

The involvement of DNDi will not end with drug registration or WHO recommendation. DNDi will take on the responsibility of ensuring that the new therapies it develops become useful treatments. Through interaction with pharmaceutical firms, international organisations, national disease control programmes, NGOs, and governments, DNDi will build a network with appropriate partners who can manufacture and distribute treatments (at affordable prices), ensure proper treatment utilisation and pharmacovigilance, and provide access to treatments. Distribution scenarios will vary depending on the disease, drugs, relevant countries, and degree of innovation: DNDi may tap into existing distribution networks or work with partners to create new channels (e.g., public or not-for-profit).

4.4 R&D NETWORKS THAT UTILISE AND STRENGTHEN RESEARCH CAPACITIES IN DISEASE-ENDEMIC COUNTRIES

As an integral part of its mission, DNDi works with R&D partners built on South-South and North-South collaborations. While using and supporting existing capacity in countries where the diseases are endemic, DNDi helps to build additional capacity in a sustainable manner through technology transfer in the field of drug research and development for neglected diseases.

DNDi will continue to work with partners in disease-endemic countries and ensure their involvement in the R&D process through technology transfer and through a global network of collaborations. This includes access to chemical diversity, establishment of discovery platforms, pharmaceutical and clinical development, and working closely with control programmes through, for example, the Leishmaniasis East Africa Platform (LEAP) and HAT platforms in Africa, Founding Partners, and other existing networks in disease-endemic countries.

DNDi balances the objective to stimulate R&D activity in the developing countries with the acute need to develop new medicines. Institutional capacity and cost structures will serve as criteria for partner selection as will the partner's ability to conduct studies that facilitate registration in endemic countries.

In addition, physical upgrading of facilities directly related to clinical trials is taking place within disease-endemic regions. DNDi has no ownership over these facilities. Such capacity building may include the building and renovation of hospital wards, clinics, and health posts; renovation and re-equipping of clinical laboratories; and training of health service personnel with particular emphasis on building expertise in clinical trial methodology, Good Clinical Practice and Ethics, patient treatment and evaluation, accurate diagnosis and follow-up by parasitology, and safety.

The Founding Partners will reinforce their role by consolidating the networks of contracted collaborators that will be managed by DNDi. This initial support from Founders has already led to the establishment of permanent regional structures such as LEAP, which provides ongoing support to DNDi and its projects.

The regional support liaison offices and regional networks will ensure the participation of endemic countries and will foster South-South collaboration.

4.5 INTERNATIONAL ADVOCACY TO SUPPORT DNDi'S OBJECTIVES

DNDi works to build awareness about the most neglected diseases in both developed and disease-endemic countries, so as to increase and to sustain support for increased public involvement. Political leadership is essential to sustaining financial support, defining priorities, creating a more favourable environment that will stimulate health R&D, and ensuring equitable access of new health tools.

DNDi will continue to ask for greater political leadership from donor and neglected diseases-endemic governments, in addition to international bodies such as the WHO and its Intergovernmental Working Group. Enabling relationships between concerned scientists, research institutes, PDPs, and NGOs is critical to accelerate the momentum that has been building since 2000.

With the objective to promote an alternative model that will enable a new environment for R&D for the most neglected diseases, DNDi will engage independent, academic experts to examine issues such as intellectual property, regulatory processes, access to knowledge, and economics in order to stimulate a new environment for R&D for neglected diseases. DNDi will continue to document experiences gained since its inception via case studies and to encourage analysis of non-traditional models of R&D (e.g., PDPs).

5. R&D STRATEGY

DNDi will use a virtual R&D model, with the aim of improving the health and quality of life of people suffering from neglected diseases. The primary R&D objective is to make six-eight new treatments available to patients by 2014 and to have a robust pipeline behind it.

Through four key processes (intelligence, project acquisition, product development, project & portfolio management), DNDi will fill the pipeline at all stages of development with a mix of short-, medium-, and long-term projects.

DNDi is proactively developing a portfolio through the identification of: 1) enduring unmet patient needs; 2) R&D opportunities such as candidate compounds and improved formulations to address such needs; 3) possible organisations to partner with in the R&D process; and 4) adequate funding to secure.

Concerted efforts that will harness discovery activities targeting all three primary diseases will be made so that the most promising anti-parasitic candidates are sourced for each disease. On a disease basis, the portfolio will be managed taking into account gap identification within the product portfolio, the pipeline projections, and strategic priorities.

By 2014, the objectives of DNDi are to:
- **Deliver four lead optimization projects in total for the three primary diseases;**
- **Deliver one new drug and one new co-administration for HAT;**
- **Deliver three new drugs and two new co-administrations for VL;**
- **Deliver one new treatment for Chagas disease.**

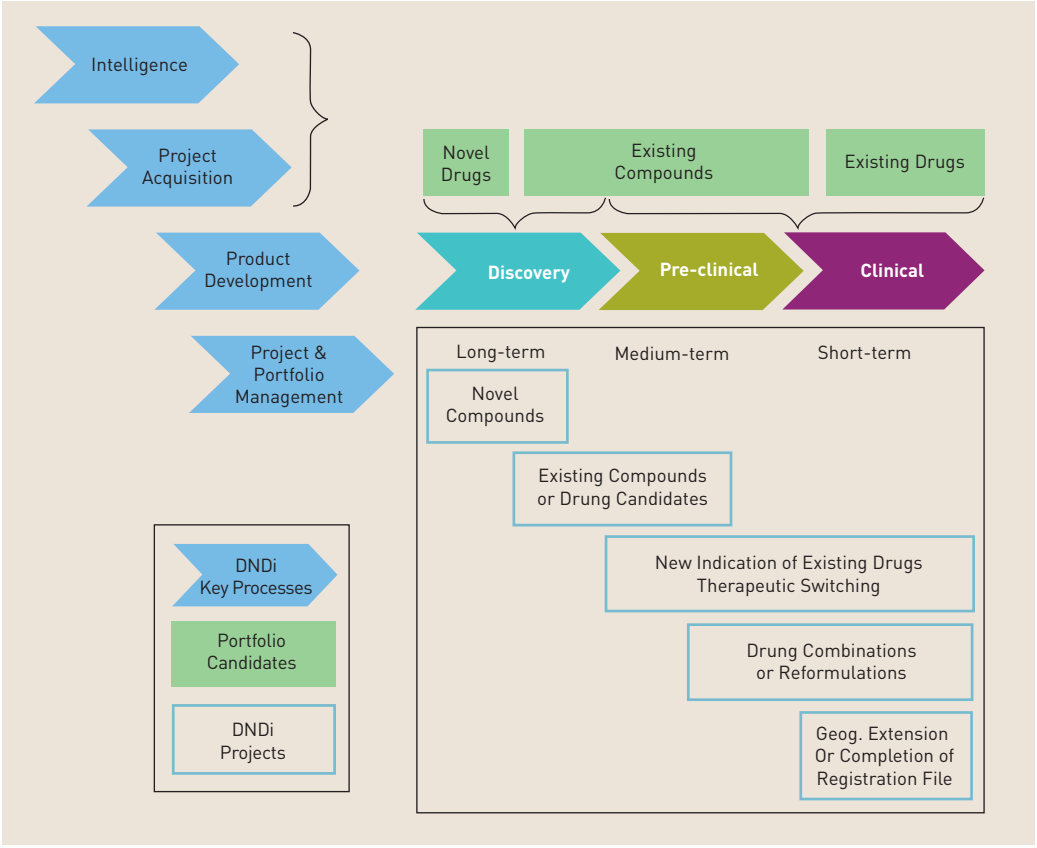
5.1 APPROACHES

Implemented through four key processes (intelligence, project acquisition, product development, project and portfolio management), DNDi will seek to fill the pipeline at all stages of development through a mix of short-, medium-, and long-term projects (Figure 7). Post-registration, mechanisms will also be leveraged to ensure treatment, utilisation and access through partnership and timely handover of projects to commercial partners, international and national programmes.

Projects will be divided into five categories:
- New drugs developed from novel compounds identified through screening and lead optimisation;

- New drugs from compounds with known antimicrobial/antiparasitic activities (could enter the pipeline at lead optimisation or pre-clinical development);
- New indications for existing medicines into the field of the most neglected diseases (therapeutic switching);
- Reformulations and combinations better adapted to field conditions (paediatric, long-acting, new route of administration; fixed-dose combinations, co-packaging, or co-administration);
- Existing drugs for target diseases (geographical extension of registration; completion of regulatory dossiers of existing drug candidates).

Figure 7. DNDi's portfolio building mechanism.



Project category 1 – New drugs developed from novel compounds

Radical improvement of therapies for the leishmaniases and the trypanosomiases requires the identification, evaluation, and development of novel compounds that are significantly better than current therapies. The approach to screen (libraries of) compounds *in vitro* against both molecular targets (crucial enzymes, receptors) and whole organisms to identify novel compounds is well-established in industry and academia. Recognising the established expertise in High Throughput Screening (HTS) on specific target enzymes in academic institutes and industry, DNDi will seek to work in partnership with these groups to help select and progress hits and leads according to DNDi's target product profiles (TPPs) and decision matrices. Access to the partner's chemical diversity and drug-like compound libraries is critical to the success of this approach.

In addition, DNDi will:

- Establish natural product screens against target organisms and build networks of screening laboratories with supporting compound evaluation centres (disease models and ADME);
- Screen focussed synthetic product libraries with groups that have knowledge of drug-like molecules and network these groups with compound evaluation centres and medicinal chemistry teams;
- Facilitate the partnering of organisations, such as other PDPs or TDR to extend the screening process to include pathogens for other neglected diseases.

Lead compounds identified through these processes will progress into focused lead-optimisation programmes, which will be implemented by experienced medicinal chemistry groups. Optimised leads can then enter the classical drug development process of pre-clinical and clinical development.

Project category 2 New drugs developed from compounds with known antimicrobial/antiparasitic activities

Past and ongoing research efforts in industry, public institutes, and academic groups have identified or generated compound series with documented anti-protozoal activities. DNDi has established contacts or partnerships with the major research groups active in this field and supports collaborative research efforts to identify and optimise promising leads for leishmaniasis or trypanosomiasis through medicinal chemistry and/or target-related, structure-activity relationships.

In parallel, DNDi is actively screening the scientific literature, including patent and pharmaceutical industry databases, to identify new and old antimicrobial compounds and drug candidates that may show promise for the kinetoplatid diseases. Compounds and drug candidates identified and accessed in this way are evaluated in the target disease models and could enter into the DNDi portfolio at any stage, from lead-optimisation to late clinical development. As this approach may identify drug candidates that have already gone through some stage of development, rapid progress may be expected in the R&D process. A successful example of this approach is the ongoing nitroimidazoles project.

Lead compounds or drug candidates identified within this category will be developed through lead-optimisation programmes and pre-clinical and clinical development as required. Critical in this approach will be to conclude innovative agreements to in-source the compounds or drug candidates and put in place R&D partnerships that ensure the successful development and delivery of the products to neglected patients.

Project category 3 New indications for existing medicines (therapeutic switching)

Therapeutic switching, in which existing drugs developed or in clinical development for other indications are re-oriented or co-developed as anti-kinetoplastids has already proved a successful approach to generate new drugs for leishmaniasis and trypanosomiasis. In particular, the therapeutic areas of anti-fungals, anti-bacterials, anti-malarials, and anti-cancer drugs may provide promising sources for therapeutic switching.

DNDi will continuously monitor developments in these areas with aims to either co-develop such drugs with partners (pharma, biotech, or PDP) or in-licence them and to develop them internally for the specific target disease indications.

Project category 4 Re-formulations or combinations better adapted to field conditions

Needs and opportunities exist for extension or improvement of existing drugs through re-formulation to better adapt to patient needs. In general, this process involves new pre-clinical and clinical studies, and the development or extension of a regulatory dossier. A successful example of this approach is the development by DNDi of two fixed dose combinations for malaria (artesunate-amodiaquine and artesunate-mefloquine). Other opportunities exist in relation to:

- Combinations better adapted to field conditions (long-acting formulations or route of administration, i.e., topical formulations for cutaneous leishmaniasis);
- Paediatric formulations, especially for diseases (like leishmaniasis and Chagas disease) with considerable infant target populations;
- Co-formulations of oral drugs to prevent development of resistance or to significantly improve treatment regimens (especially for chronic disease stages/manifestations).

Project category 5 Existing drugs for target diseases

There are several instances in which existing drugs for target diseases fail to reach patients or are underutilised because they are not registered in the endemic countries, are too difficult to use, or have not been demonstrated to be effective in specific manifestations of the disease. In addition, in the absence of highly effective and easy-to-use drugs, combination treatments offer the potential to improve efficacy, reduce treatment duration and possibly prevent resistance.

Based upon patient needs and a clear understanding of the limitations and constraints of currently available treatments, opportunities exist to:

- Extend the registration and use of existing drugs to other geographical regions (possibly involving different disease manifestations). An example is paromomycin for visceral leishmaniasis in Africa and Latin-America;
- Validate a co-administration protocol of existing drugs to significantly improve the treatment regimen and/or prevent the development of resistance. This can involve co-packaging in the case of oral drugs. An example is the eflornithine-nifurtimox combination for stage 2 HAT;
- Validate a co-administration schedule of known chemotherapeutics with therapeutic vaccines or immunomodulators to improve efficacy. An example is imiquimod as adjunct therapy for CL treatment.

5.2 THE DNDi PORTFOLIO

5.2.1 Current Portfolio, January 2007

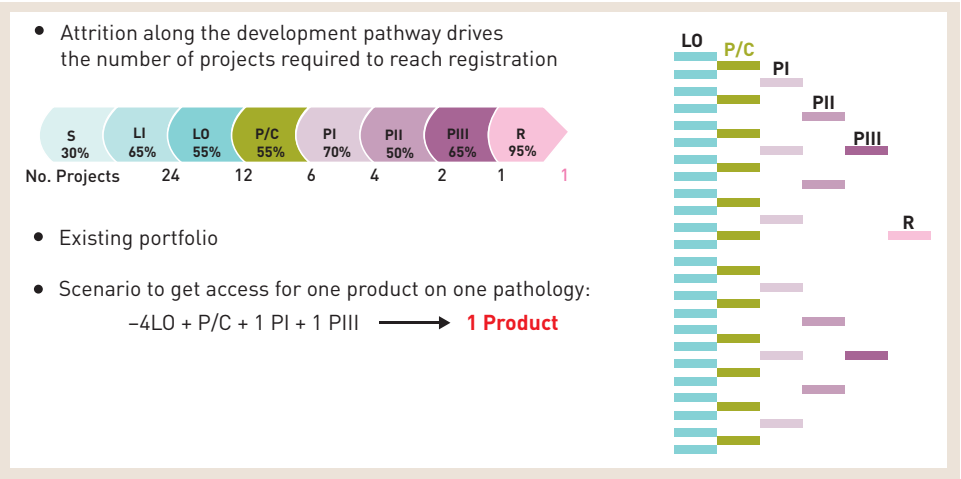
The portfolio of DNDi has grown to 22 projects (six clinical, four preclinical and twelve discovery projects) from the four projects described in the original Business Plan written in 2003 (Section 2.3).

5.2.2 Portfolio Development

The main R&D focus is to successfully manage and progress ongoing R&D projects to deliver new treatments to neglected patients in the shortest possible time. To ensure that the full discovery and development process flows without interruption, DNDi will use a decision matrix, a core model that is adaptable for each disease manifestation and class of compounds, along with review by internal and external experts relevant to the development stage and therapeutic area.

In addition, the DNDi R&D team continues to build the portfolio of projects for HAT, VL and Chagas through exploratory activities which focus on the pharma and biotech sectors, as well as established academic and public sector groups with expertise in the field. These exploratory activities are essential to fully exploit new opportunities, replace projects in the portfolio due to the attrition rate associated with drug development, and give the DNDi team the ability to choose the strongest and most appropriate activity.

Figure 8. Structuring the DNDi portfolio based on attrition rate.



Source: Nwaka, Ridley. Nat Rev Drug Discov. 2003; 2:919-928.

The probability of a given project leading to registration of a drug and the speed of the development programme varies widely according to the disease, the nature of the compound, and the stage of discovery or development at which DNDi becomes involved. The risk of 'compound failure' or 'drop-out' is intrinsic to drug development and is estimated by attributing theoretical attrition rates that predict the chance that a project will fail at any specific stage in the process.

For each target disease, DNDi has built baseline pipeline projections upon:

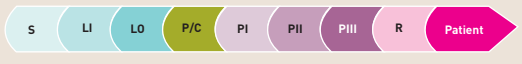
- theoretical attrition rates appropriate to not-for-profit drug development;
- the number and the status of ongoing projects (see existing portfolio, Figure 1, p.8);
- the potential for addition of new projects at different stages;
- the public health need (related to the Target Product Profile [TPP]).

If the project attrition rates adhere to the pattern illustrated above, it follows that in order to register one new product, DNDi must initiate or in-source four projects at lead-optimisation, two in preclinical development, one in Phase I clinical trials, and one in Phase III clinical trials. Massive, concerted efforts focused on discovery must and will be undertaken in order to achieve these objectives. Per disease, the portfolio will be managed taking into account gap identification within the product portfolio, the pipeline projections and strategic priorities, thereby highlighting the type and number of projects to in-license for each disease.

The figures below (Figures 9 through 14) show by disease, a projection of the progression of the ongoing projects, of the number of new project entries needed at each stage, and of their progression over the 2007-2014 period. It uses both attrition rate and project phase duration estimates described above (Figure 8). These projections have also formed the basis for the calculation of the financial and human resource required.

Legend for Figure 9 through 14.

STEP	COLOR	TYPE OF NEW TREATMENT
Screening		▲ New Drug
Lead Identification		◆ New Co-administration
Lead Optimization		
Safety & Toxicity		
Phase I		
Phase II		
Phase III		
Registration		
Patient availability, Implementation, Supply chain etc.		



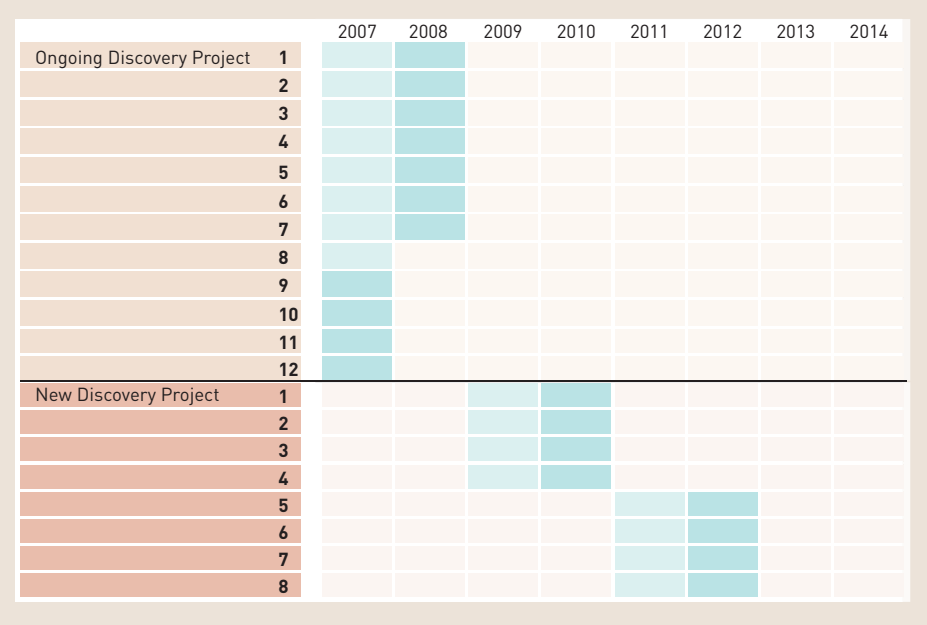
5.2.3 Discovery Projects

Portfolio Objective:
To deliver four lead optimization projects in total for the three primary diseases

Compounds in discovery projects are initially tested against all kinetoplastids. Based on the data at this stage, a decision is then made to focus the project on a specific disease. Discovery includes (a) screening of compounds against pathogens that cause the target disease, (b) hit expansion, where chemical series similar to hits are explored for selectivity, and (c) lead identification, where further *in vitro, in vivo*, and ADME studies identify a small series of compounds for lead optimisation.

The high number of projects required in this discovery phase is based upon both the established attrition rate and the requirement to 'feed' three different disease portfolios.

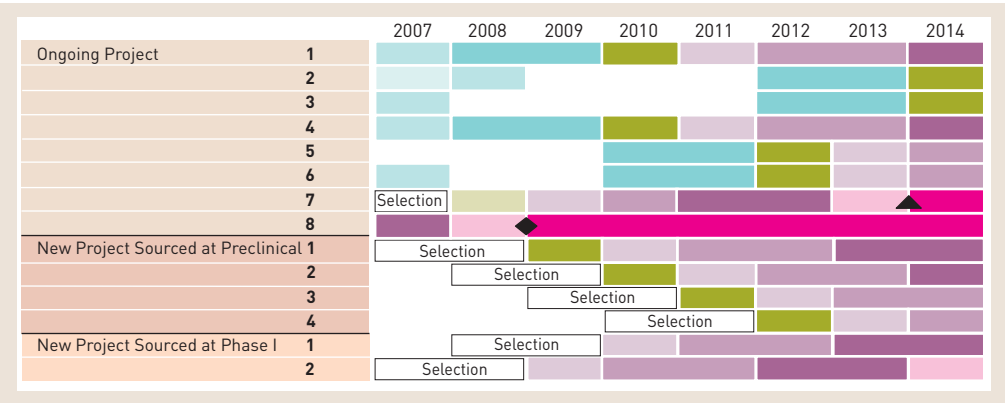
Figure 9. DNDi discovery pipeline.



5.2.4 Human African Trypanosomiasis (HAT)

Portfolio Objective for 2014:
To deliver one new drug and one new co-administration (Figure 10)

Figure 10. Human African Trypanosomiasis (HAT).



DNDi has two TPPs for HAT:

1. **The priority is to develop a safe, effective, and practical stage 2 HAT drug** to replace current first-line treatments, and to improve and simplify the current case management. The aim is to develop one drug that is effective against both stages 1 and 2 of HAT.
2. **A simple stage 1 treatment,** to be used at the local health centre level, could also represent a great improvement by increasing access to treatment and coverage of HAT. Depending on the availability of a simple diagnostic, such a drug would allow for mass screening and treatment campaigns in endemic areas, and thus prevent disease progression to stage 2 and reduce disease transmission.

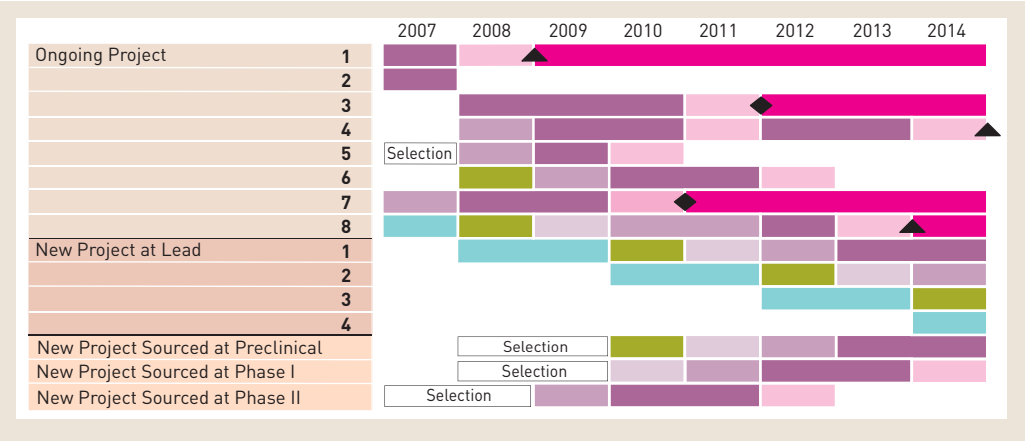
The hypothesis presented in the model illustrates a number of necessary components in order for the HAT portfolio to meet its 2014 objective:

- Two projects per year in lead optimisation: i.e., Scynexis;
- Selection of candidates from existing drug candidates: i.e., nitroimidazoles;
- Co-administration that will complete Phase III clinical trials in 2007/8 and be ready for WHO recommendation by the end of 2008: i.e., nifurtimox-eflornithine combination trial (NECT);
- In-sourcing of four projects at preclinical stage and two projects at Phase I, with strong efforts needed to identify projects for in-licence at later stages of development.

5.2.5 Visceral Leishmaniasis (VL)

Portfolio Objective for 2014:
To deliver three new drugs and two co-administrations (Figure 11)

Figure 11. Visceral Leishmaniasis (VL).



DNDi has defined a TPP for VL:

The priority is an oral, safe, effective, low-cost, and short-course (10-day) treatment that could replace current treatments, improve and simplify current case management. Ideally, this treatment will be effective against all forms of disease and adapted for use in health centres.

For VL, recent clinical development of new drugs performed by organisations other than DNDi provided both the opportunity and the need to 1) improve treatment through geographic extension to other endemic regions outside India, and 2) explore the potential of combinations and new formulations for VL. Therefore, DNDi aims to develop one new drug, to deliver two co-administrations, and to obtain the extension of two registered drugs for the treatment of VL in endemic regions outside India by 2014. The geographic extensions are especially important for VL because the cure rates of known drugs are different in the main endemic regions, and all endemic regions should have a choice of treatment.

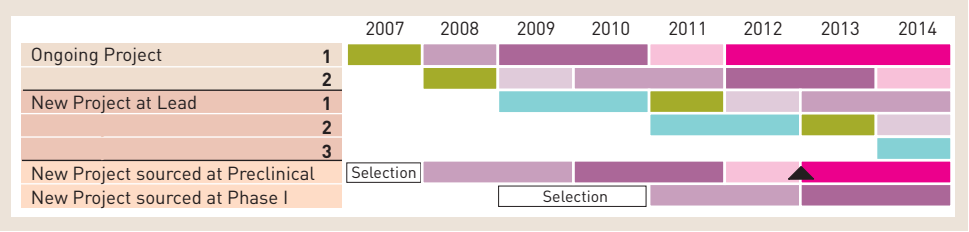
A number of components are needed in order for the VL portfolio to meet its 2014 objective:

- One project per year in lead optimisation: i.e., Advinus;
- Co-administration: i.e., VL drug combinations in India;
- Therapeutic switching: i.e., NPC1161B;
- Complete development of existing drugs: e.g., paromomycin, AmBisome;
- In-sourcing of numerous projects: three at lead optimization stage, one at preclinical stage, one project at Phase I, and one project at Phase II. Strong efforts are needed to identify projects for in-licence at later stages of development.

5.2.6 Chagas disease

Portfolio Objective for 2014:
To deliver one new treatment (Figure 12)

Figure 12. Chagas disease.



For Chagas disease, the current pipeline is limited, so greater effort and focus are required to develop a well-balanced portfolio. New drugs are required for all three phases of the disease (acute, indeterminate, and early chronic).

The priority is for DNDi to deliver an effective, non-toxic, inexpensive treatment for acute, indeterminate and early chronic phases, by 2014. Analysis has also shown that a reformulation, specifically a paediatric formulation of a drug known to be effective in the acute phase, could also represent a great improvement in treatment.

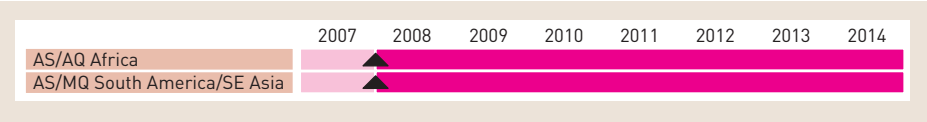
A number of components are needed in order for the Chagas portfolio to meet its 2014 objective:

- One project per year in lead optimisation: i.e., Advinus;
- Development of a new treatment for indeterminate/early chronic disease through the discovery-to-clinic process or therapeutic switching: i.e., ravuconazole (Eisai);
- Focused efforts on reformulations: i.e., paediatric benznidazole (known to be effective in children in acute phase);
- In-sourcing of numerous projects: three at lead optimization stage, and two projects at Phase I.

5.2.7 Other disease projects

Malaria Objective:
To register two new drugs by the end of 2007 (Figure 13).

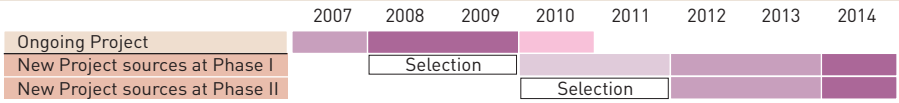
Figure 13. Malaria.



The two fixed dose co-formulations, artesunate/amodiaquine and artesunate/mefloquine, are being registered in 2007. The success in bringing these new drugs to registration within four years will be followed by studies to ensure utilisation and access.

DNDi does not plan to be involved in the development of further anti-malarial agents.

Figure 14. Cutaneous Leishmaniasis (CL).



DNDi's development approach for CL will be pragmatic and opportunistic as no discovery research will be conducted. Because CL is a complex drug target and presents less of a disease burden than DNDi's primary kinetoplastid diseases, CL will remain a secondary disease target. New drugs and treatments will be developed either through (a) in-licence or co-development of formulations with proven activity against some form of leishmaniasis, or (b) in-house, from compounds in pre-clinical development for VL where re-formulation for topical use or oral treatment present a clear potential benefit. Evaluation against parasite species that cause CL will then have to take place.

Other disease projects

Similar to the selection process described with CL, other disease projects will be considered based on needs and opportunities.

5.3 SUMMARY OF OBJECTIVES

Based on the hypotheses developed in Section 5.3, DNDi will meet its objective of developing six to eight new treatments by 2014 for patients with neglected diseases through a mixture of new drugs and new treatments for each of its primary diseases. Figure 15 below presents a range of possibilities to achieve this objective.

Figure 15. Summary of portfolio objectives by chronology and by disease.

Summary 2003 - 2014		
	5 to 7	New drugs registered (induding geographical extensions)
	1 to 3	Co-administrations will be recommended by international organisations (i.e., WHO)
Objective	**6 to 8**	**New treatments for neglected patients**

Summary of objectives by disease			
HAT	**VL**	**Chagas**	**Malaria**
1 new drug registered	1 new drug registered	1 new drug registered	2 new drugs registered
1 co - administration	2 geographical extensions		
	2 co - administrations		

Scheduling over the period		
2007	**2008-2009**	**2010-2014**
2 new drugs registered in malaria	1 new drug registered in VL	4 new drugs registered
	1 co - administration in HAT	2 co - administrations

In 2014 : a well - balanced portfolio

A robust pipeline delivering :

- Networked discovery efforts targeting all 3 primary diseases & delivering 4 lead optimization projects per annum as of 2008
- Several clinical candidates corresponding to target product profile

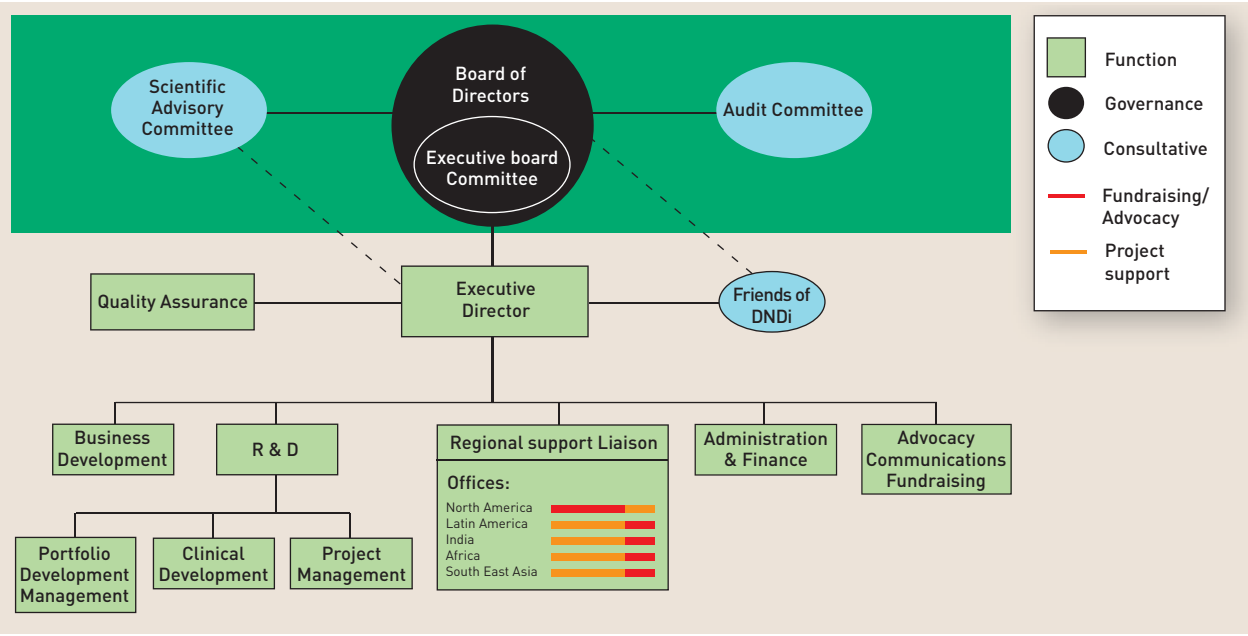
6. ORGANISATION & GOVERNANCE

Governed by the Board of Directors with the Scientific Advisory Committee, Audit Committee and Executive Board Committee providing key scientific and management guidance for decision making, the DNDi Executive Team implements the R&D strategy, manages the global portfolio, allocates resources, fundraises, and advocates.

6.1 ORGANISATION, MANAGEMENT OVERSIGHT

DNDi is composed of three bodies: 1. The Board, 2. The Management, 3. The Auditor.

Figure 16. Functional chart of DNDi by end of 2007.



DNDi is governed by the Board of Directors. The Scientific Advisory Committee, Audit Committee and Executive Board Committee provide key scientific and management guidance for decision making. The primary functions of the Board of Directors are to exercise ultimate authority over DNDi activities according to the charter and organisational by-laws (available upon request).

The Board of Directors delegates the coordination and implementation of DNDi's objectives and actions and the day to day oversight to the Management, i.e., the Executive Team.

Controls are assumed by the Auditor who is independent and external to DNDi operations and management. He monitors compliance to DNDi's statutory provisions and legal standards. He reports to the Board and to the Swiss Supervisory Board for Foundation any irregularities noted during his audit.

6.2 GOVERNANCE

The **Board of Directors** is made up of ten to thirteen members including a patient advocate, with each of six Founding Partners nominating one board member. In principle, Board members serve for a term of four years. At the end of this 4-year period, Founding Partners are responsible for either proposing to renew the existing board member's term or proposing another person to be appointed as their representative. The Board of Directors elects the Chair, the Secretary and the Treasurer among its members. The Board of Directors is then free to appoint up to five additional board members that fill skill areas not represented by the board members appointed by the Founding Partners or the patient advocate. Currently three additional Board members have been nominated and are presently active. In 2007, The Board is composed of ten members, plus a permanent observer from TDR. The Chair of SAC and the Executive Director are permanent invitees.

Both Founding Partners' representatives and additional board members are experts in their fields and have been chosen for their commitment to the public interest, technical credibility to oversee executive activity and integrity and skill in ensuring adherence to the DNDi vision and mission.

Procedures to organize Board of Directors meetings, as well as a Board of Directors' list of duties and powers are defined in the charter and organisational by-laws (available upon request).

The Board created three committees for the implementation of the purposes, programmes, and projects of DNDi.

- The **Scientific Advisory Committee (SAC)**, composed of not less than five (17 in 2007) prominent scientists with expertise in various scientific disciplines relating to drug discovery and development, and/or to the specific reality of neglected diseases and patients. The committee operates independently of the Board of Directors and the Executive Team. The Board of Directors approves the selection of SAC members. The SAC has the mission to advise the Board of Directors on matters related to research and development and choice of projects as well as quality of the scientific production. Both Executive and Scientific Directors can consult with the SAC.
- The **Audit Committee** is responsible for selecting the Auditors, overseeing their work, recommending financial policies, reviewing financial statements, and supervising the investments of DNDi funds;
- The **Executive Board Committee** oversees all DNDi activities and makes recommendations to the Board of Directors when decisions have to be made. The committee interfaces between the Board and the Management, and supports the Executive Team in implementing DNDi's strategy.

The **Executive Team** encompasses the Executive Directors and Staff members. The Executive Team is responsible for: executing Board decisions, managing human and financial resources of DNDi, preparing and implementing the annual work plan and budget, establishing protocols and procedures for management, reporting on a regular basis to the Board of Directors on the action plan and performing such other tasks as assigned by the Board.

DNDi operational policy framework includes its Charter and Bylaws, the Code of Practice of the Scientific Advisory Committee (SAC), the R&D guideline, the Intellectual Property Policy, the Human Resources Policy, the Fundraising Policy, a Travel and Reimbursement Guideline and Financial and Management procedures.

6.3 COORDINATION & IMPLEMENTATION

Remaining small and leveraging external expertise, the DNDi Executive team in Geneva is led by the Executive Director. The team includes the R&D Director, the Director of Advocacy and fundraising, the Director of Administration and Finance, and the Director of Business Development. It also includes the Directors of Regional support offices.

The Executive team is responsible for:

- Managing the implementation of the R&D strategy, notably by coordinating the scientific and technical activities of the partners, monitoring the progress of projects, managing the sourcing activities, negotiating intellectual property rights and contract agreements, deciding upon and implementing appropriate drug strategy, managing and controlling quality, supervising manufacturing processes, and securing access delivery and use;
- Allocating and controlling resources for all aspects related to cost, timing, data quality, and protocols;
- Coordinating and overseeing Regional support offices' activities;
- Implementing DNDi advocacy and communication strategy and building relationships with national and international organisations and media;
- Implementing fundraising strategy and cultivating relationships with donors;
- Providing sufficient information flow within the organisation, notably to the governing body on project progress.

The **Executive Director** reports to the Board of Directors. The Executive Director is a permanent invitee to Board meetings. S(he) does not hold voting rights on the Board. S(he) supervises all operations within DNDi and maintains an effective, motivated, competent and legislation-compliant organisation to achieve business goals. S(he) is responsible for ensuring that a quality control system is implemented. S(he) works with the Board to develop and execute corporate strategy. S(he) has also a critical function as a representative of DNDi's vision and mission.

The **R&D Director's** first priority is to maintain a well-balanced project portfolio. While s(he) remains responsible for overall scientific and clinical development, s(he) is in charge of building all necessary project management tools, such as databases and performance indicators.

S(he) engages the R&D team to support the identification of sourcing opportunities. S(he) provides scientific advice to the Business Development Director to assess technical feasibility of business opportunities.

The R&D Director leads the implementation of projects selected for the portfolio. S(he) appoints the R&D team, coordinates their activities, and ensures optimum involvement of regional collaborators based in Asia, Africa, and Latin America.

She/he should assemble a team comprising of:

- **Project Managers** are in charge of monitoring and coordinating the progress of projects. They are responsible for devising development plans and ensuring that projects advance in a timely manner. Project Managers are closely linked to regional support offices from which they receive support.
- A **Project-Portfolio Manager** will be recruited in 2008 to assist the R&D Director and Director of Business Development to build and manage a portfolio.
- The **Head of Clinical Development** will be recruited by January 2008. (S)he will supervise all clinical activities from Phase I to regulatory approval. (S)he will be responsible for advising the R&D Director on decision making for all clinical activities and building relationships with pharmaceutical partners and regulatory authorities .

The **Advocacy and Fundraising Director** is responsible for designing and implementing communication and fundraising strategies. (S)he will oversee wide dissemination of information on DNDi and research in the field of most neglected diseases. Target audiences include national and international political leaders, the scientific community, Founders and Friends of DNDi, the pharmaceutical industry, the media, and the public at large.

The **Friends of DNDi** will comprise individuals, representatives around the world. They will be leaders in fields relevant to DNDi's work and beliefs. This group will contribute by supporting DNDi's innovative model, vision and mission, thereby acting as DNDi's Ambassadors by providing facilitated access to private and public high level decision makers. This group is managed by the Executive Director, has no decision making power, and must be approved by the Board.

The **Director of Administration & Finance** oversees accounting, finance, and relationships with auditors and controllers. (S)he supports the Executive Director on governance, tax and legal issues and requirements. (S)he is responsible for all Human Resources issues, and is in charge of setting up and maintaining an efficient IT infrastructure.

The **Director of Business Development** will be recruited by January 2008. (S)he will prepare the business development plan. (S)he will facilitate partnerships and negotiate terms of agreements. (S)he conducts landscape analysis to identify and prioritize business opportunities. (S)he prepares business development tools. (S)he develops objectives and operational guidelines for business development. (S)he measures the effectiveness of on-going contracts (especially milestones and respect for timelines).

The **Regional Office Director(s)** are an integral part of the coordination team. They are located in the Regional Support Offices, in South America (Brazil), Asia (India and Malaysia), and Africa (Kenya).

The responsibilities of the Regional Support Office Director include: identifying potential new projects and regional partners; undertaking regional advocacy and fundraising work for DNDi; and supporting project management and implementation.

A fifth Regional Support Office will be set up in North America (New York, USA) during the course of 2007. The main responsibility of this office will be to support fundraising activity. In addition, DNDi North America will also support the R&D and advocacy strategy in facilitating contacts and problem solving with North American partners.

6.4 ACCOUNTABILITY, TRANSPARENCY AND ETHICAL PRINCIPLES

DNDi will constantly strive to hold itself to the highest standards of accountability, transparency, and ethics.

There are numerous stakeholders to which DNDi is accountable: patients living in countries where neglected diseases are endemic, the Founding Partners, national disease programmes in endemic countries, public and private donors, public and private research institutions, international medical organisations and NGOs, scientific groups that contribute to R&D activities, and the wider public.

The charter and the organisational by-laws oblige the Board, the SAC, and staff members to disclose conflict-of-interest issues to the Chair of the Board when such issues emerge between decision-makers and the recipients of DNDi resources.

It is DNDi's aim to share timely, accurate, and relevant information that enables stakeholders to be aware of our current operations, including critical scientific and financial information. Regular communications *via* newsletter, website, publications, targeted advocacy, and scientific meetings will be maintained.

DNDi is vigilant regarding ethical issues related to its activities, for instance the choice of research programmes and projects, and the best use of its resources in a manner that favours patients' needs. When activities involve human subjects or patients in clinical pharmacology or clinical trials, international standards are followed. These include protecting the interests of volunteer subjects and patients' by ensuring informed consent, ethical trial design and implementation, and making sure that study subjects receive follow-up care once trials are completed.

Specifically, as per the R&D Guideline, all clinical programmes are guided by international, regional, and local regulations and standards: Good Clinical Practice guidelines (GCP/ICH) and the 2000 Helsinki Declaration, following the basic principles for medical research involving human beings, and according to the local and external institutions review boards and local rules and regulations of the countries.

7. EXPENDITURES

7.1 TOTAL EXPENDITURE

The global budget over the period from 2004 to 2014 is estimated to be a minimum of EUR 274 million, with the desired outcome to be six-to-eight new treatments for neglected diseases and the creation of a robust, well-balanced portfolio containing 28 projects in the development pipeline. Total expenditure will steadily grow until 2010 when DNDi will have a full pipeline (Figure 17).

Figure 17. Total expenditure, 2004-2014, summary table.

In million €	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total	in %
Total R&D costs	1.95	3.67	6.86	11.46	19.90	24.78	32.24	27.44	35.76	34.75	31.05	**229.86**	83%
Strengthening Capacities	0.16	0.45	0.80	1.04	1.07	1.21	1.26	1.28	1.31	1.33	1.35	**11.26**	4%
Advocacy	0.49	0.54	0.72	0.88	0.89	0.94	0.99	1.01	1.02	1.04	1.06	**9.58**	4%
Fundraising	0.08	0.21	0.27	0.68	0.85	1.09	1.37	1.38	1.40	1.42	1.43	**10.19**	4%
General management	1.28	0.85	0.99	1.18	1.26	1.25	1.29	1.28	1.32	1.31	1.35	**13.37**	5%
Total	**3.96**	**5.72**	**9.64**	**15.23**	**23.97**	**29.27**	**37.15**	**32.40**	**40.81**	**39.86**	**36.25**	**274.25**	**100%**

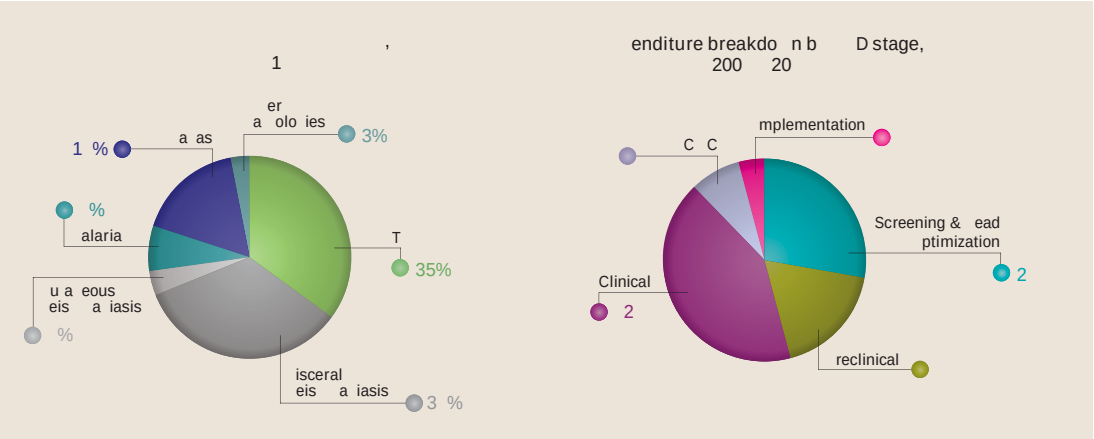
Figure 18. Total expenditure, 2004-2014, per disease.

COSTS PER YEAR *In million €*	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
Discovery*	223	307	902	960	972	246	497	252	509	0	0	4,868
HAT	470	742	1,463	1,790	5,738	6,452	10,261	9,073	13,693	10,688	11,469	71,838
VL	484	825	1,545	3,550	6,021	8,500	11,504	7,552	9,182	8,486	7,392	65,042
Chagas	0	109	200	1,500	2,125	3,943	4,975	5,716	4,193	6,767	4,294	33,823
Cutaneous Leish.	0	0	0	300	1,265	1,280	415	315	1,645	1,665	1,468	8,352
Malaria	775	1,126	2,189	2,700	2,125	1,075	829	734	637	430	380	13,001
Other Pathologies	0	0	0	0	0	0	311	315	1,645	1,665	1,468	5,403
CMC	0	0	0	0	501	1,966	2,114	2,129	2,887	3,663	3,174	16,435
R&D Additional	0	556	561	660	941	952	964	975	987	999	1,011	8,607
Business Development	0	0	0	0	213	369	373	378	382	387	391	2,492
Total R&D costs	1,952	3,665	6,860	11,460	19,901	24,784	32,243	27,438	25,760	34,750	31,047	**229,862**
Strengthening Capacities	157	448	795	1,040	1,073	1,208	1,261	1,284	1,307	1,330	1,353	**11,256**
Advocacy	492	537	720	875	891	942	990	1,007	1,024	1,042	1,060	**9,580**
Fundraising	81	213	270	680	850	1,086	1,368	1,385	1,401	1,418	1,435	**10,186**
General Management	1,275	853	993	1,175	1,259	1,254	1,289	1,284	1,320	1,315	1,352	**13,369**
Grand Total	**3,957**	**5,716**	**9,638**	**15,230**	**23,973**	**29,274**	**37,152**	**32,398**	**40,813**	**39,855**	**36,248**	**274,254**

*Discovery costs here cover only those costs which are inclusive of all three primary diseases, whereas other discovery efforts targeted specifically to a disease are included in the R&D costs per disease.

The expenditure per disease (Figures 18 and 19) highlights the commitment of DNDi to VL and HAT, both diseases in which DNDi will invest one-third of its resources.

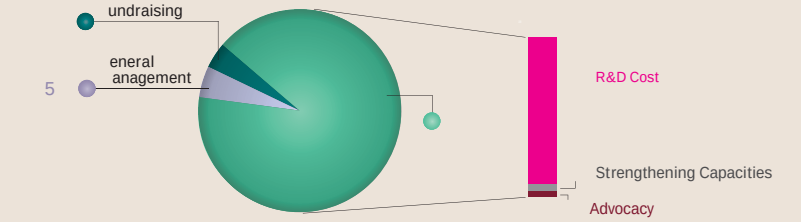
Figure 19. Expenditure breakdown by disease and by R&D stage, 2004-2014.



As Figure 20 shows, 91% of DNDi expenses are dedicated to its social mission, with 84% of total expenditure (EUR 230 million) allocated for R&D.

Figure 20. Social Mission apportionment.

Cost apportionment DNDi 2004-2014	*(in '000 €)*
R&D Costs	230 (84%)
Strengthening Capacities	11 (4%)
Advocacy	10 (3%)
Fundraising	10 (4%)
General Magagement	13 (5%)
Total 2004-2014	**274 (100%)**



7.2 METHODOLOGY OF COSTING

Costs were established according to: 1) the operational model defined in this business plan; 2) previous studies carried out by DNDi; and 3) benchmarking analyses of similar initiatives, such as the Medicines for Malaria Venture (MMV) and the Global Alliance for TB Drug Development (GATB).

Using a full-cost, activity-based calculation, DNDi considered all costs associated with projects, including project management costs. DNDi's approach reflects true costs which are influenced by project origin, type of partners, and contract conditions of the projects entering the portfolio. However, through in-kind contribution from partners, some outsourcing costs may be performed. For instance, in the DNDi partnership with sanofi-aventis on the FACT ASAQ project, part of the CMC costs were not charged to DNDi, but were considered as in-kind contribution from the partner.

Social mission costs and supporting costs are based on the number of staff employed by DNDi. DNDi evaluates the cost of its staff as follows:

- Executive management: EUR 200K per annum
- Middle management: EUR 140K per annum
- Support staff: EUR 80K per annum
- Regional liaison support: EUR 100K-200K per annum depending on their geographical location

These cost estimates consist of gross salary, social charges and benefits, consumables, IT and other office costs, as well as an estimate of position-related travel costs. Given that DNDi hires highly skilled and motivated individuals who share the organisation's mission and vision. Salary assumptions have been made accordingly. DNDi uses a balance sheet approach to remuneration, where salaries and compensation are adjusted to guarantee equivalent standard of living (whether in the Geneva office or in regional liaison support offices).

7.3 RESEARCH & DRUG DEVELOPMENT ESTIMATE OF COSTS

Estimated discovery costs

Discovery costs, which can vary widely, are difficult to estimate across the board. DNDi has based its cost estimates on previous studies carried out by the organisation and its partners. The cost of EUR 2 million/year per single project in Lead Optimization includes five to six chemists, one to two support pharmacologists, and one project manager (EUR 250K is the estimated full-time employee cost of a medicinal chemist at a CRO.)

Figure 21. Expenditure breakdown by R&D stage, 2004-2014

DISCOVERY	COST PER PROJECT
Costs per year	*(in '000 €)*
Screening	60
Lead Identification	120
Lead Optimization	2,000

Estimated preclinical and safety package costs

The estimates here, which are based on DNDi analysis and standard estimates of preclinical regulatory packages, incorporate the cost and duration of preclinical safety studies required for a 4-week administration in humans.

Figure 22. Annual preclinical costs.

PRECLINICAL	COST PER PROJECT
Total cost	*(in '000 €)*
Preclinical	1,500

Estimated clinical development costs

Estimates of clinical development costs necessary to obtain drug regulatory approval, from Phase I to Phase III, are based on DNDi's previous experience in clinical research on the targeted diseases. PDPs, such as MMV and DNDi, are currently evaluating the true costs of clinical trials for PDPs working in neglected diseases.

The cost estimates here were based on unique features related to the strategic objectives of DNDi:

- Statistical demonstration of superiority and/or non-inferiority does not require large samples of patients because current standards of treatments for the three diseases are not optimal in terms of efficacy and tolerance.
- The epidemiology of the three primary diseases (in terms of geography and morbidity) – there is not a large geographic distribution (with the exception of VL).
- The use and strengthening of existing trial capacities in target disease-endemic countries (i.e., LEAP, HAT Platform, and Indian and Latin American clinical trial networks).

Figure 23. Annual clinical costs.

CLINICAL DEVELOPMENT PHASE	AVERAGE NUMBER OF PATIENTS	COST PER PATIENT PER YEAR	TIME DURATION*
Costs per year		*(in '000 €)*	
Phase I	30	10,0 / patient / year	1 year
Phase II	120	2,5 / patient / year	2 years**
Phase III	500	2,5 / patient / year	2 years

* Time duration, based on DNDi operational expertise and benchmarking of similar initiatives, is inclusive of DNDi's primary target diseases as well as CL (unless otherwise noted).
**Estimated time duration for a Phase II clinical trial for VL is estimate to be only 1 year.

For example, the per-patient costs to complete a Phase III clinical trial for HAT would be EUR 5,000.

Estimated CMC Costs

The overall costs for the chemistry, manufacturing, and controls (CMC) are influenced by a number of factors such as the developed chemical entity, the industrial partner for the co-development, etc. Usual CMC development steps include: chemistry evaluation, lab-to-pilot optimization, process development, preparation of pilot batches, analytical development, analytical chemistry, analytical technology transfer to the commercial manufacturing site, and manufacturing of clinical supplies. CMC costs can be estimated as a proportion (20%) of clinical development costs.

Figure 24. Basis of CMC cost estimates.

CMC
CMC = 20% of (Phase I + Phase II + Phase III costs) as from 2009

Estimated registration or recommendation costs

Drug candidates, such as New Chemical Entities (NCE), are developed primarily through partnerships. Registration costs for DNDi are estimated around EUR 100K because the industrial partner will be primarily responsible.

Figure 25. Annual registration or recommendation costs.

DRUG CANDIDATE	COST
Costs per year	*(in '000 €)*
Drug registration	100
Co-Administration, recommendation	50

Estimated implementation costs within the DNDi model

Given that the role of DNDi in the implementation phase is to facilitate the process with its partners, DNDi will remain involved for a minimum period of 7 years (duration of contract with industrial partner).

Figure 26. Annual implementation costs and duration.

IMPLEMENTATION	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Type of treatment *(in '000 €)*							
New drugs	400	400	200	200	200	100	100
Co-administration	200	200	100	100	0	0	0

Estimated additional management costs

Additional costs for R&D and portfolio management exist and are expected to increase in the future, notably for quality control purposes and for development of the portfolio. As of the end of 2007, business development will be a new activity used to reinforce and develop the DNDi portfolio by improving agreements with industry and academic groups.

Figure 27. Additional R&D management costs.

ADDITIONAL R&D MANAGEMENT COSTS	2007	2008	2009	2010	2011	2012	2013	2014
Costs per year *(in '000 €)*								
Scientific Dir + SAC	530	597	604	611	619	626	634	641
Portfolio Management	70	142	143	145	147	149	150	152
Business Development	210	364	369	373	378	382	387	391
Quality Control	60	202	205	207	210	212	215	217

7.4 OTHER SOCIAL MISSION ESTIMATE OF COSTS: STRENGTHENING CAPACITIES & ADVOCACY

Other social mission costs, estimated on an annual basis, are made by utilizing a full-cost activity-based method. All associated costs (salary costs, social charges, logistics, meetings, travel, office rental, depreciation and IT, etc.) are included in the two following expenditure categories: **Strengthening Capacities and Advocacy.**

Together with **Research & Development, Strengthening Capacities**, and **Advocacy** are part of the social mission of DNDi, as defined by DNDi's Charter. These cost categories include:

Strengthening Capacities: improving capacities for scientists, research institutes, and/or companies from developing countries

Costs, estimated at EUR 1,040K in 2007 up to EUR 1,353K in 2014, comprise:

- Four regional liaison support offices in Nairobi, Rio de Janeiro, New Delhi and Penang;
- Two platforms for VL and HAT, with other platforms foreseen;
- Construction and equipment costs depending on clinical development needs in the field.

Figure 28. Strengthening existing capacities costs.

	2007	2008	2009	2010	2011	2012	2013	2014
Costs per year *(in '000 €)*								
Regional liaison support offices	325	329	384	389	393	398	403	408
Platforms: training & meeting	545	572	599	593	607	622	637	652
Rehabilitation, equipment	70	71	72	73	73	74	75	76
Total	**1,040**	**1,073**	**1,208**	**1,261**	**1,284**	**1,307**	**1,330**	**1,353**

Advocacy and Communication costs include staff and activities such as external communication, document production and event organisation. Costs are estimated from EUR 875K in 2007 to EUR 1,060K in 2014.

Figure 29. Advocacy costs.

	2007	2008	2009	2010	2011	2012	2013	2014
Costs per year *(in '000 €)*								
Advocacy	875	891	942	990	1,007	1,024	1,042	1,060

7.5 ESTIMATE OF SUPPORT COSTS: FUNDRAISING & GENERAL MANAGEMENT

Support costs, estimated on an annual basis, are made by utilizing a full-cost activity-based method. All associated costs (salary costs, social charges, logistics, meetings, travel, office rental, depreciation and IT, etc.) are included in the two following expenditure categories: Fundraising and General Management.

Fundraising includes activities to target public and private donors in Switzerland, the United States, and other countries. Costs, which are estimated at EUR 680K in 2007 up to EUR 1,435K in 2014, do not cover expenses related to fundraising campaigns aimed at the general public (Chapter 8). Such campaigns could have a major impact on the budget (over EUR 1 million a year in the case of direct fundraising to the general public).

General management includes corporate affairs (Board and Audit Committee), executive coordination and administration and financial services. Costs are estimated at EUR 1,175K in 2007 up to EUR 1,352K in 2014.

The costs presented here are discounted at an inflation rate of 1.2% per annum.

Figure 30. Support costs.

	2007	2008	2009	2010	2011	2012	2013	2014
Costs per year *(in '000 €)*								
Fundraising	680	850	1,086	1,368	1,385	1,401	1,418	1,435
General management	1,175	1,259	1,254	1,289	1,284	1,320	1,315	1,352

7.6 FIXED COSTS VERSUS PROJECT VARIABLE COSTS

Fixed costs, estimated on an annual basis, include:

- General management (staff, logistic, communication & meetings);
- Corporate affairs (Board, Scientific Advisory Committee);
- Finance & Administration (staff, office costs, audit, IT & some legal costs);
- Fundraising (staff and prospecting activities);
- Advocacy (staff and communication activities);
- Business development (staff, logistics, communication & meetings);
- Quality Control (staff, logistics, communication & meetings);
- R&D coordination activities (staff and portfolio management);
- Four Regional Support Offices (administrative costs, five offices as per 2007).

Project variable costs comprise of all costs allocated to a project including its management costs.

Figure 31. Fixed and variable costs.

(in '000 €)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total (%)
Fixed costs	1,848	1,603	2,759	3,715	4,270	4,618	5,000	5,044	5,131	5,177	5,266	44,430 (16%)
Project variable costs	2,109	4,113	6,879	11,515	19,704	24,656	32,152	27,354	35,682	34,678	30,982	229,824 (84%)
Total	**3,957**	**5,716**	**9,638**	**15,230**	**23,973**	**29,274**	**37,152**	**32,398**	**40,813**	**39,855**	**36,248**	**274,254 (100%)**

8. RESOURCES

8.1 HUMAN RESOURCES EVOLUTION

At the start of 2007, the DNDi team included 22 full-time staff throughout the world. In order to achieve its objectives, DNDi will recruit a maximum of 18 additional staff by 2011 and will have a total staff of 40.

In order to have greater proximity to project implementation, 30% of DNDi team members will work from regional liaison support offices by 2011.

Figure 32. Evolution of DNDi staff and recruitment planning.

DEPARTMENTS	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number of FTE											
R&D in HQ*	4	7	8	10	11	12	14	14	14	14	14
R&D in RSO***	0.5	1.5	2	3	4	5	6	8	8	8	8
Advocacy	1.5	2.5	3.5	3.5	3.5	4	4	4	4	4	4
Fundraising**	1.5	1.5	1.5	2.5	4	5	6	6	6	6	6
General management	4	5	5	6	6	6	6	6	6	6	6
Management of RSO***	1	1.5	2	2	2	2	2	2	2	2	2
Total Staff (FTE)	**12.5**	**19**	**22**	**27**	**30.5**	**34**	**38**	**40**	**40**	**40**	**40**

* R&D at headquarters is comprised of Business Development and Quality Control.
** Fundraising staff are located in several places: i.e., Geneva, New York.
*** 80% of staff in Regional Support Offices are involved in R&D (project support, project management, project coordination, or medical coordination for clinical trials).

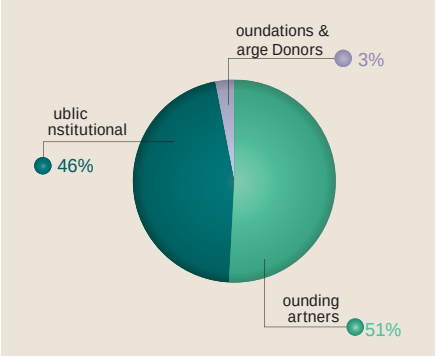
8.2 FUNDING STRATEGY & INCOME PLAN

To date: 2003-2006

In addition to the initial contribution of EUR 25M from Médecins Sans Frontières, DNDi had successfully raised EUR 24M as of the end of 2006.

This result was achieved with a primary focus on public institutional donors in line with the DNDi objective of encouraging public responsibility and in line with the initial objective of obtaining substantial public institutional funds. This has not been easy as few institutions have mechanisms to support research and development for neglected diseases and even fewer via product development partnerships such as DNDi. During this period, the UK's Department for International Development (DFID), the Netherlands' DGIS (Ministry of Foreign Affairs-Development Cooperation), and the USA's National Institute of Health (NIH) created new mechanisms for supporting Product Development Partnerships developing drugs for neglected diseases, and France's Agence Française de Développement (AFD) gave its first PDP commitment to DNDi.

Figure 33. Funding commitments 2002-2009 = 49M€



This has only been achieved with targeted advocacy to brief policy makers about the needs and how DNDi works. It is still rare to get commitments outside of the big three neglected diseases – malaria, TB and HIV/AIDS, so there is much work yet to do to convince policy makers to fund neglected disease R&D and DNDi specifically. Momentum must be maintained to leverage the investments of these pioneers in funding neglected disease R&D.

Though only opportunistic efforts have been made to obtain private foundation funds, DNDi has obtained several grants from private foundations in Switzerland and hopes to maintain those relationships in the future. DNDi is investing human and financial resources toward obtaining private foundation and major donor funds primarily from the USA and Switzerland. In addition, DNDi Regional Liaison Support Offices have begun to explore fundraising potential in their regions that offer growth potential for the future.

Supporting the R&D Strategy

The DNDi fundraising strategy should follow and support the R&D strategy and donors should be sought in alignment with the R&D strategy as well as the vision and mission of DNDi. For the initial period, R&D strategy was still being defined, making this difficult. Now, with well-defined R&D strategies, projects, project partners worldwide and the strengthening of the liaison offices, the DNDi fundraising strategy can align itself with the R&D strategy, supporting DNDi to achieve its objectives.

Independence

DNDi's independence remains a cornerstone of its strategy. Every effort will therefore be made to create a pool of funds from diverse sources without any one donor contributing more than 25% of annual revenue and with an attempt to minimize earmarked donations. In general, the Governing Board will define funding parameters that ensure the initiative's independence.

Core funding supplemented by project approach

To allow for the greatest flexibility in decision making needed for the R&D portfolio management strategy and to allow greater independence in its operations, the DNDi priority is to raise unrestricted core funding versus project specific or earmarked funding. In cases where this is not possible, DNDi will pursue project specific or earmarked funding without requirements that may interfere with the objectives of the project.

Fundraising Policy

To develop its activities and achieve its objectives, DNDi seeks different sources of funding – cash contributions, in kind contributions, grants, sponsorships, and legacies – from individuals, governments, public institutions, companies, foundations, NGO's, and alternative mechanisms who share a commitment to the DNDi vision and mission.

- DNDi's independence is a cornerstone of its development, so diversified sources of funding are necessary in order to prevent dependence upon contributions from a specific donor;
- The contributions will support the initiative, specific projects for research and development and all activities pursued to achieve DNDi's mission;
- DNDi will transparently provide activity and financial information on the use of donor contributions. An annual financial audit will be done on DNDi accounts which will be made publicly available;
- DNDi reserves the independence to pursue its mission and research and development projects based upon patient needs and scientific merit.

According to the goals of DNDi to ensure the quality of life of neglected populations and the DNDi's humanitarian values, DNDi will not accept contributions from:

→ Corporations (which includes companies and corporate foundations) that derive their income from the production and /or sales of tobacco, alcohol, and arms manufacturing industries,

→ Groups and individuals who encourage racism and intolerance,

- DNDi will provide appropriate recognition of donor support except when the donor would prefer to remain anonymous;
- Before accepting an anonymous contribution, the Board of Directors will seek the advice of lawyers or national authorities in certain cases;
- The Board of Directors may refuse a contribution if the proposed support could negatively affect the image or the social mission of DNDi;
- The terms for use of DNDi's logo and brand by the donor and the use of the donor's logo and brand by DNDi will be agreed by mutual consent at the time of the contract.

Sources of Funding

Four different sources of funding have been identified and are being pursued by DNDi.

1. Governments and International Organisations

DNDi aims to stimulate increased involvement and responsibility of national governments and international organisations in R&D for neglected diseases. In accordance with its vision, DNDi will strive, as much as possible, to obtain, on a cumulative basis over time, a majority of its funding from public sources. DNDi can achieve this objective with a mix of 6 public institutional donor commitments of EUR 2-3M per year or national and regional governmental project support of EUR 2-3M per year total.

Donor prospects for governments and international organisations include:

- Governments that have a clear track record in supporting overseas aid development. DNDi has already obtained funding from the governments of the United Kingdom, France, Switzerland, and the Netherlands, so will seek to maintain and/or increase sustainable funding from these countries while pursuing support from Canada, USA, Spain, Ireland, Germany, Japan, Italy, Brazil, India, Belgium, Malaysia, the Nordic countries, and others opportunistically;
- Regional blocks, such as the European Union which has already funded two DNDi projects, will continue to be pursued. Others, such as MERCOSUR, ASEAN and OAU will be approached by the liaison offices;
- UN agencies (especially WHO, UNICEF; UNDP), the Global Fund to Fight AIDS, Malaria and TB, and the World Bank, though not likely to fund DNDi directly, should be regularly briefed on DNDi activities due to their influence in recommending, purchasing and funding developing country purchases of drugs for neglected diseases;
- Alternative R&D funding mechanisms and drug purchasing facilities, such as the Global Fund, IFF, UNITAID, Global Subsidy, IRFF, SecureAid, should be continually explored and encouraged when deemed to be relevant for increasing funding for neglected disease research and development.

2. Private foundations and large private donors

DNDi will also secure a significant part of its budget from foundations or individual philanthropists based in North America, Europe, Asia, Latin America, and the Middle East who have been traditionally active in global health, international development, medical research, and related fields. Specific attention will be given to developing private donor prospects in the USA, Switzerland, and through regional liaison networks in Asia, Latin America, and Africa. Prospects will be identified through existing networks and especially via the global "Friends of DNDi" network (see below).

Specifically, large private foundations, like The Bill & Melinda Gates Foundation, Rockefeller Foundation, the Wellcome Trust, all recognised leaders in the field of neglected disease funding, will be pursued as funding partners during this period.

Friends of DNDi

The creation of "Friends of DNDi," a group of individuals from around the world committed to DNDi's vision and mission, will equip DNDi with an additional tool to strengthen and support the implementation of its fundraising strategy as well as raise awareness of the need for R&D for neglected diseases. It is envisaged that the "Friends of DNDi" will contribute to DNDi as individuals to support DNDi's vision and mission and to open doors and provide access to private foundations, wealthy individuals, and high-level decision makers in government.

DNDi estimates that 30 – 35% of funding will come from private foundations and large private donors.

3. General Public

Giving the general public and opportunity to support DNDi's activities is another way to engage them in the issue, in DNDi, and to illustrate the new R&D model. However, DNDi is not well-suited for mass general public fundraising campaigns. DNDi will seek limited general public support through very targeted direct mailings and more passive means, such as web fundraising. DNDi will seek to obtain part of its general public resources through mailings or other actions of well known founding partners on behalf of DNDi.

DNDi estimates 3 – 5% of the total annual income will come from the general public.

4. Founding Partners

During the launch period of the initiative (2003-2008), MSF channelled funds from the general public to DNDi to a total of EUR 25M. DNDi will seek continued core support from MSF, though at a lower level.

To date, other Founding Partners have provided some in-kind support of office space, administrative staff, and meeting organisation. For the next period, DNDi will value this support and seek an increased commitment of financial and/or in-kind support for project implementation.

The targeted founding partner support is approximately 10% of the total income per year.

Income plan: towards maturity 2007-2014

DNDi's funding mix will change slightly from year to year but should move in the next years to a decreasing dependence on Founding Partner contributions due to a significant increase in private funding primarily from foundations and major donors, some general public funding and a steady increase of public funding.

Figure 34. Projected Commitments 2003 – 2014 = 276M€.

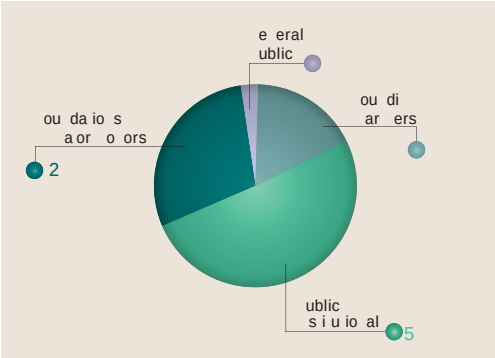


Figure 35. Total income projection 2006-2014 (in '000 €, w/actuals for 2003-6).

DONORS	PROJECT	2003/ 2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total	Ratio
Founding Partners		**9,200**	**5,000**	**5,900**	**5,500**	**3,500**	**3,500**	**3,500**	**3,500**	**3,500**	**3,500**	**46,600**	**17%**
MSF	initiative	9,200	5,000	5,800	5,000							25,000	
Founding Partners	initiative			100	500	3,500	3,500	3,500	3,500	3,500	3,500	21,600	
Public		**1,330**	**5,447**	**9,465**	**14,950**	**15,700**	**17,500**	**18,000**	**18,500**	**19,000**	**19,500**	**139,392**	**51%**
UK	initiative	0	3,598	3,000	3,000							9,598	
France	project	0	1,100	2,400	2,000	2,000						7,500	
Netherlands	project	0	125	1,500	650	700						2,975	
European Union	project	1,200	84	165	100							1,533	
Regional/ Institutional/ New Mechanisms / Endemic Countries	mix		130	540	200	200						1,070	
Governments Objectives	initiative	0	0	2,200	8,000	13,000	17,500	18,000	18,500	19,000	19,500	116,716	
Private		**372**	**417**	**1,900**	**7,650**	**8,700**	**10,650**	**12,300**	**14,100**	**16,000**	**17,500**	**89,589**	**32%**
CH Private	mix	202	330	330								862	
US Private	mix	170	0									170	
Other Countries Private	mix			87	87	87							
US Objectives	mix			1,300	6,500	7,000	8,000	8,500	9,500	10,000	11,000	61,800	
CH Objectives	mix			100	750	1,000	1,500	2,000	2,000	2,500	2,500	12,350	
Private Objectives (Others...)	mix	0	0	83	313	700	1,150	1,800	2,600	3,500	4,000	14,146	
Grand Total		**10,902**	**10,864**	**17,265**	**28,100**	**27,900**	**31,650**	**33,800**	**36,100**	**38,500**	**40,500**	**275,581**	**100%**

In conclusion, the funding opportunities and outlook are good. DNDi is well positioned to obtain the funds necessary to sufficiently support its mission, vision, and objectives, and to maintain independence. The income and fundraising expense projections in this business plan are realistic and based upon the implementation of the strategy and policy described above.

Designed and artworked by BRIEF, Paris
Printer: SRO-Kundig
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Best Science
for the Most Neglected

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