

2011.2018

Business Plan



DNDi

Drugs for Neglected Diseases *initiative*

PROCESS

The revision of the Business Plan, with methodological support and coaching by Adviseo, was prepared over a period of eight months with extensive internal and external consultation and workshops. The plan was approved by the Board of Directors in June 2011.

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01.

EXECUTIVE SUMMARY

DNDi has updated its Business Plan to outline how the organization will make significant progress between now and 2018 toward accomplishing its mission to develop new treatments for patients suffering from the most neglected communicable 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 and biotechnology industries, and other relevant partners.

1.1 | DNDi OVERVIEW

Founded in 2003, DNDi is a collaborative, patients' needs-driven, not-for-profit drug R&D organization that operates with an alternative R&D model.

DNDi's primary objective is to deliver 11 to 13 new treatments by 2018 for leishmaniasis, human African trypanosomiasis (sleeping sickness), Chagas disease, malaria, paediatric HIV, and specific helminth infections and to establish a strong R&D portfolio that addresses patients' treatment needs.

In 2011, DNDi's portfolio has grown to 24 projects, including six projects⁽¹⁾ in the implementation phase and several partnerships in the discovery phase. Through continuous collaboration and exchange with academia, pharma, biotech, and other product development partnerships (PDPs), DNDi is building a portfolio that proactively identifies critical R&D challenges and opportunities.

Operating in some 40 countries, DNDi has six Regional Offices that will be increasingly empowered in the coming years to reinforce its business model and better seize opportunities. DNDi operates with a small, dedicated core team, leveraging expertise and partnerships to deliver upon the vision and mission set by its Founding Partners.

DNDi is recognized as a trusted partner in the field of neglected diseases. Its on-going advocacy efforts aim to stimulate the set-up of a global framework for essential health R&D.

DNDi has invested EUR 94 million between 2003 and 2010 and has secured an additional 76 EUR million to fund approximately 25% of its estimated needs by 2018.

1.2 | AN IMPROVING LANDSCAPE FOR NEGLECTED DISEASE R&D

Since 2000, the R&D landscape for neglected tropical diseases (NTDs) – including the most neglected – has improved, although these communicable diseases continue to cause significant morbidity and mortality in endemic countries. The need for new, field-adapted treatments remains urgent and largely unmet.

The critical mass of players now involved in NTD R&D is encouraging, and has led to a replenished pipeline for these diseases. Involvement of pharmaceutical companies is also increasing, enabling novel alliances

(1) Registration of the paediatric dosage form of benznidazole is foreseen for Q4 2011.

between not-for-profit organizations and private companies to form a new paradigm, with opportunities for new pathways for innovation.

Having said this, funding remains a critical issue to sustain these R&D efforts. Philanthropic organizations continue to play an instrumental role in the increased R&D activities. New funding mechanisms are needed to complement existing government funding, which has tapered during the period of protracted financial crisis and economic slowdown. Additional opportunities are coming from emerging economies, which are showing a new focus and growing investments to build capacity for neglected diseases.

1.3 | DNDi'S ALTERNATIVE MODEL

DNDi builds its disease portfolio through its R&D projects. The business model can be characterized by certain distinguishing traits including its not-for-profit and needs-driven approach, empowerment of endemic country partners, dynamic disease portfolio, diversity of partnerships, international advocacy in support of a global framework for essential health, diversity and balance of public and private donors, and delivery of health tools as public goods.

1.4 | FROM R&D TO ACCESS

The primary R&D objective for DNDi is to deliver a total of 11 to 13 new treatments to patients by 2018 (five to seven more than the six already in implementation phase in 2011) backed by a robust pipeline to support long-term objectives.

DNDi will fill the pipeline at all stages of development through a mix of short- to long-term projects. To do so, DNDi proactively identifies: significant unmet medical needs; R&D opportunities such as candidate compounds and improved formulations to address the needs; possible organizations to partner with in the R&D process; and adequate funding sources.

Concerted efforts will be exerted to harness discovery activities targeting the three primary diseases (leishmaniasis, Chagas disease, and human African trypanosomiasis) so that the most promising anti-parasitic candidates are sourced for each disease. On a disease basis, the portfolio will be managed by taking into account gap identification within the product portfolio, the pipeline projections, and strategic priorities. DNDi will complete its malaria activities and launch two 'mini-portfolios': paediatric HIV and specific helminth infections.

With its pipeline maturing, DNDi's 'advocacy for access' efforts range from development to implementation, from global health policy to specific treatment uptake activities. These efforts are tailored to diseases and geographical areas, with the ultimate aim of facilitating maximum impact via appropriate use of treatments, assuring their effective transition to relevant access partners and implementers, and leveraging success for future steps.

DNDi will assess the outcomes and impact of its model and operations on a continuing basis.

1.5 | AN EVOLVING ORGANIZATION, EMPOWERING REGIONAL OFFICES

A critical component of this updated strategy is the further empowerment of Regional Offices, aiming at their transition from a support role to a more active contribution to all DNDi activities. Two-thirds of the human resource growth needed to implement this Business Plan will thus be allocated to Regional Offices. Their operations will be embedded in the overall organization, with significant autonomy to deliver within the scope of the DNDi Action Plan.

Such a strategic shift, given the addition of new disease areas and their corresponding projects, as well as the maturation of the portfolio with several projects advanced to the implementation phase, necessitates organizational adaptation and adjustment. With this in view, an Operations department will be set up to coordinate international operations and develop transversal approaches to streamline the organization.

1.6 | FINANCE – DIVERSIFIED AND SUSTAINED

The annual budget is expected to grow from EUR 29 million in 2011 to EUR 40 million in 2014 and onwards. The overall expenses during the 2011-2018 period are estimated at EUR 301 million, with the targeted outcome of an additional five to seven new treatments and a robust portfolio.

On average, the majority of expenses are dedicated to R&D, and DNDi's social mission ratio reaches 89%. From a disease perspective, DNDi will allocate 36% of its planned investments to the development of treatments for leishmaniasis, 22% for HAT, 22% for Chagas disease, and 8% for the paediatric HIV and helminth infection mini-portfolios.

DNDi seeks to diversify its funding sources and maintain a balance of public and private donors including: established government and international organizations; governments of emerging countries; DNDi Founding Partners; and large foundations. DNDi will also continue to advocate for new funding mechanisms. In addition to the resources already secured, EUR 245 million still needs to be raised, with priority given to unrestricted core funding (and with the objective of securing six months of reserves).

02.

ORGANIZATION OVERVIEW

Founded in 2003 to address the needs of patients with the most neglected diseases, DNDi is a collaborative, patients' needs-driven, not-for-profit drug R&D organization that operates with an alternative and virtual R&D model.

2.1 | VISION, MISSION & OBJECTIVES

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 has been the development of drugs for the most neglected diseases, such as human African trypanosomiasis (HAT, or sleeping sickness), visceral leishmaniasis (kala-azar), and Chagas disease, while considering engagement in R&D projects for other neglected diseases or development of diagnostics and/or vaccines to address unmet needs that others are unable or unwilling to address.

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 R&D for neglected diseases.

In December 2010, the Board of Directors decided that while maintaining its full commitment to neglected diseases such as sleeping sickness, leishmaniasis, and Chagas disease, DNDi will conclude its malaria activities by 2014, maintaining emphasis on technology transfer and sustained access, and take on new activities in the fields of paediatric HIV and specific helminth infections.

DNDi's objectives:

The primary objective of DNDi is to deliver a total of 11 to 13 new treatments by 2018 for leishmaniasis, sleeping sickness, Chagas disease, malaria, paediatric HIV, and specific helminth infections and to establish a strong R&D portfolio that addresses patient needs. Expanding upon R&D networks built on South-South and North-South collaborations, DNDi aims to bring medical innovation to neglected patients by developing field-adapted treatments (categories are described in Section 5.2).

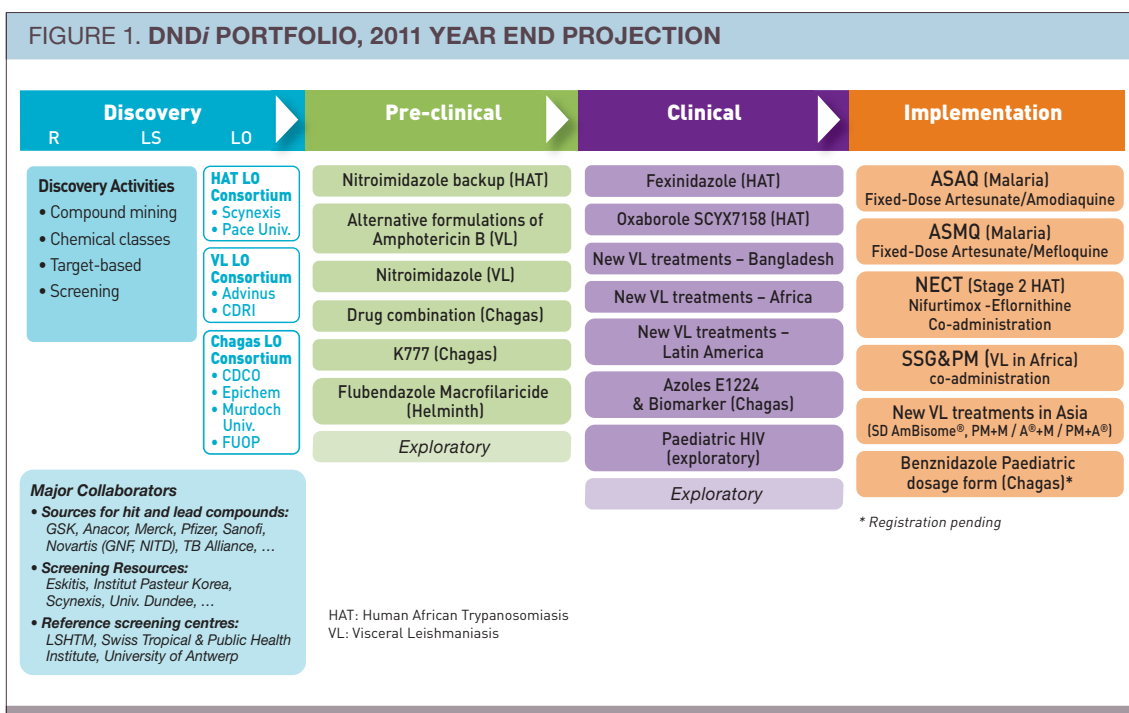
In doing this, DNDi has two further objectives:

- Use and strengthen existing capacities in disease-endemic countries via project implementation
- Raise awareness about the need to develop new drugs for neglected diseases and advocate for increased public responsibility.

2.2 | EVOLUTION OF THE PORTFOLIO

In 2011, the portfolio of DNDi has grown to 24 projects from the four described in the original Business Plan in 2003. The current portfolio primarily focuses on the three kinetoplastid diseases (human African trypanosomiasis, leishmaniasis, and Chagas disease), and includes malaria at the phasing-out stage and the initiation of 'mini-portfolios' for paediatric HIV and specific helminth infections. Six projects are at the implementation phase (including four products delivered and two in Registration/Recommendation phase), with eight clinical and seven pre-clinical projects, in addition to the partnerships and consortia at discovery level. Through continuous collaboration and exchange with academia, pharmaceutical and biotechnology companies, and other PDPs, DNDi is building a portfolio that proactively addresses critical R&D challenges and opportunities (see Section 4).

FIGURE 1. DNDi PORTFOLIO, 2011 YEAR END PROJECTION



2.3 | DNDi TODAY

DNDi today consists of a team of committed people dedicated to maintaining the momentum achieved since the launch of the initiative in 2003. With an ambitious vision, the small team of permanent staff at Headquarters and Regional Offices, together with a group of expert consultants, has made significant headway in achieving DNDi's mission.

Under the leadership of the Executive Director, the **DNDi Executive Team** oversees the implementation of the R&D strategy, manages the global portfolio, identifies opportunities and manages partners and service providers, allocates resources, and leads fundraising and advocacy. **Heads of Programmes**, with experience in different aspects of pharmaceutical development, drive the strategy and oversee the implementation of selected projects by managing a worldwide network of scientists.

The **Regional Offices** play an increasingly important role in all DNDi operations, shifting from a role of 'support' to one of extended responsibility, with activities ranging from patient needs assessment and treatment implementation to business development. Advocacy and fundraising activities have also increased in Regional Offices, more efficiently addressing local challenges and opportunities.

With expertise in all aspects of NTD R&D, the **Founding Partners** continue to play a critical role in the overall development of DNDi, in addition to their financial and in-kind contributions.

DNDi'S FOUNDING PARTNERS

- Oswaldo Cruz Foundation (Fiocruz), Brazil
- Indian Council for Medical Research (ICMR), India
- Kenya Medical Research Institute (KEMRI), Kenya
- Ministry of Health of Malaysia
- Médecins Sans Frontières
- Institut Pasteur, France
- UNICEF-UNDP-World Bank-WHO's Special Programme for Research and Training in Tropical Diseases (WHO/TDR) as special observer

2.4 | KEY ACCOMPLISHMENTS AND CHALLENGES

A number of milestones, ranging from the portfolio to policy, have been reached in a relatively short period of time. The following are particularly noteworthy:

■ Regional Disease-Specific Platforms Enabling Access to Research Capacity

For human African trypanosomiasis (HAT) and visceral leishmaniasis (VL) in Africa, and Chagas disease in Latin America, DNDi has helped to establish disease-specific platforms that utilize and develop clinical research capacity in endemic regions by involving key scientists, clinicians, research organizations, international organizations, NGOs, National Control Programmes, health ministries, regulatory authorities, and private-sector actors. These platforms have allowed for clinical research to be conducted in extremely difficult, resource-poor, rural settings in endemic countries and play a key role in facilitating patient access to the treatments developed.

■ Products

Since 2007, DNDi has delivered one new treatment per year: for malaria (ASAQ – 2007; ASMQ – 2008), for sleeping sickness (NECT – 2009), and for visceral leishmaniasis (SSG&PM – 2010). In addition, in 2011, DNDi has taken on implementation projects for new treatments for visceral leishmaniasis in Asia and is currently awaiting registration of a paediatric dosage form of benznidazole for Chagas disease. These treatments, developed in partnership with public and private institutions, have been made available as non-patented products to facilitate access and uptake in national programmes.

It is important to note that some **key challenges** lie ahead for DNDi, including:

- **Effective delivery of new chemical entities**
- Securing **sustained funding** in a particularly challenging period of protracted financial **crisis and economic slowdown**
- Management of growth associated with **expansion of the disease portfolio**
- Efficient management of **empowering Regional Offices**
- Further opening DNDi's alternative model to create additional opportunities with partners, while **maintaining core values** and organizational culture.

03.

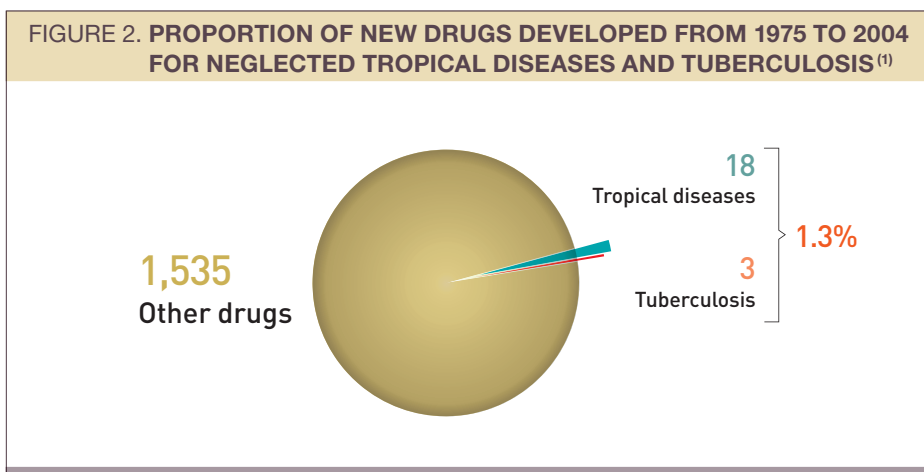
R&D LANDSCAPE FOR NEGLECTED DISEASES

Since 2000, the R&D landscape for neglected tropical diseases (NTDs) – including the most neglected – has improved, although they continue to cause significant morbidity and mortality in endemic countries. The need for new, field-adapted treatments remains urgent and largely unmet.

3.1 | INTRODUCTION

Despite phenomenal advances in medicine over the past half-century, with many millions of lives being saved, adequate drugs are not sufficiently available for diseases afflicting the poorest, most neglected populations in low-income settings. While millions continue to die from preventable and treatable diseases, such as HIV/AIDS, malaria, and tuberculosis, those succumbing to other tropical diseases are all but forgotten.

Of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases including malaria and tuberculosis, although they account for 11.4% of the global disease burden (Figure 2).⁽¹⁾ **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.**



With progress made in advancing the fundamental knowledge of many tropical diseases, drug R&D for such diseases has significantly improved in early discovery phase, but has yet to lead to sufficient development of new drugs. Most drugs currently used to treat kinetoplastid diseases (human African trypanosomiasis, leishmaniasis, Chagas disease) have unacceptable toxicity, are not adapted to the settings in which they are administered, or are too expensive. Today, there are clear signs that the R&D pipeline for neglected diseases is being replenished, with estimates by the Bill and Melinda Gates Foundation showing that in 2009, PDPs were managing nearly 150 projects (including vaccines, diagnostics, and drugs) in pre-clinical and clinical development.

(1) Chirac P, Torrele E. *The Lancet*. 2006 May 12; 1560-1561.

3.2 | SHORT- AND LONG-TERM NEEDS OF PATIENTS SUFFERING FROM NEGLECTED DISEASES

3.2.1 Overview

Most of the 17 neglected tropical diseases (NTDs), as defined by WHO, do have health tools available, but in certain cases they are far from being implemented. For NTDs that can be effectively diagnosed and treated with existing tools, enormous challenges remain in getting the treatments to those who need them. Furthermore, for many NTDs, the available diagnostics, treatments, and implementation strategies are suboptimal, incomplete, or inadequate to sustain elimination efforts. Consequently, substantial R&D investments are urgently needed to develop new-generation control tools as well as the strategies for their improved use and implementation.

DNDi's R&D strategy addresses **immediate patient needs** in the short term, through **improvement of existing treatment regimens and drug formulations**. These treatments improve safety and efficacy, and can potentially reduce treatment duration and cost, as well as lowering the risk of resistance development. While these treatments form a substantial improvement with respect to their predecessors, currently they are not all fully adapted to supporting elimination programmes as they necessitate administration in specialized treatment centres (as opposed to simple oral treatments which can be administered in the most remote settings).

In the longer term, DNDi's objective is to **deliver innovative medicines** by developing new chemical entities (NCEs). These should correspond to the target drug profiles that support elimination strategies, for example, for HAT and VL, and optimal case management for Chagas disease. The treatments should be safe, effective, short-course, affordable, and orally administered – ideally at the primary healthcare level in combination with a simple diagnostic tool. As such, these innovative medicines can have a much greater impact on public health in disease-endemic countries.

3.2.2 DNDi's NTD Focus

Since its inception, DNDi has focused on the kinetoplastid (the most fatal of the vector-borne parasitic protozoan) diseases, a brief overview of which is provided below.

Human African Trypanosomiasis (HAT)

HAT, known as sleeping sickness, is caused by two sub-species of *Trypanosoma* parasites, which are transmitted to humans by the tsetse fly. Sleeping sickness, occurring only in sub-Saharan Africa, takes one of two forms, depending on the parasite sub-species (either *T. b. gambiense* or *T. b. rhodesiense*). In 2010, the estimated number of cases was 30,000, with over 36 African countries at risk, the seven most affected of which represent 97% of reported cases.

Sleeping sickness has two stages. The first 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.

Today, DNDi and FIND (Foundation for Innovative New Diagnostics) are developing **new oral treatments** and **simplified diagnostic technologies**, respectively, for HAT, with the objective that they be used together in primary healthcare centres (PHCs) rather than in hospitals where late stage HAT patients are currently treated. Once available, and with the support of an effective access strategy, these innovative tools will enable a **substantial paradigm shift in the existing management of HAT**, thus potentially contributing to sustainable elimination of the disease.

Leishmaniasis

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, with over 350 million people at risk (200 million of which for VL alone) in 98 countries.

VL is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, progressive anaemia, and is complicated by co-infection with other infectious diseases, such as HIV or malaria. Fatal if untreated, an estimated 500,000 new cases of VL occur each year. A significant proportion of clinical cases occurs in children.

DNDi and its partners are strongly focused on contributing to control and elimination strategies for VL. Long-term projects focus on **discovery and development of an easy-to-use, efficacious, oral drug**. Shorter-term projects aim at **development and implementation of monotherapy regimens and combination therapies**, as well as geographical extensions of existing treatments.

Chagas Disease

Chagas disease occurs almost exclusively in the Americas. Chagas disease affects an estimated 8 million people, with 100 million people at risk in 21 countries across Latin America. Transmitted to humans by a triatomine insect containing the *T. cruzi* parasite, the disease is contracted through the bite of insects widely known as 'kissing bugs'.

There are two clinical phases of the disease: acute and chronic. The latter can be divided into two stages: the chronic, asymptomatic 'indeterminate' stage, and the chronic symptomatic stage. In the acute phase (fatal for 2-8% of infected children), 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 the chronic, asymptomatic 'indeterminate' phase that can last anywhere from 10 years to life. The symptomatic chronic stage of Chagas disease develops in up to 30% of infected persons and most commonly affects the heart. Death usually results from cardiac arrhythmia or congestive heart failure.

DNDi and its partners aim at developing a **safe, easy-to-use, oral drug effective for both stages of the disease**, in addition to improving existing treatments such as the paediatric dosage form of benznidazole. To complete its strategy for Chagas disease, DNDi is also evaluating **selected biomarkers, which could shorten the patient follow-up for test of cure**.

3.2.3 Portfolio Expansion and New 'Mini-Portfolios'

While its core focus will remain on the most neglected diseases, notably kinetoplastids, DNDi has responded to a call by various international organizations and partners to address other urgent patient needs, notably for paediatric HIV and specific helminth infections. After in-depth needs assessments conducted by expert working groups, focusing on unmet medical needs, existing R&D opportunities, absence of actors, potential partners, and required resources, DNDi decided to extend its portfolio by addressing the two following specific unmet needs:

Paediatric HIV

According to the WHO, currently more than 2.5 million children under the age of 15 are living with HIV – 2.3 million of whom (92%) live in sub-Saharan Africa.^[2] Each day, more than 1,000 children are newly infected with HIV, and each day, an alarming 700 die from AIDS-related complications. In southern Africa, the epicentre of the pandemic, HIV/AIDS is the leading cause of under-five mortality, accounting for more than half of all child deaths in this age group in several of the highest prevalence countries, including South Africa (57%), Lesotho (56%), Botswana (54%), and Namibia (53%).^[3] According to UNAIDS, only 355,000 children with HIV/AIDS have access to antiretroviral therapy (ART). **Without treatment, one-third of children born with HIV will die before their first birthday; 50% will die before they turn two.**

Despite progress, access to ART in a **formulation adapted for young children in low-resource settings is still lacking**. DNDi will focus on opportunities for developing appropriate first-line treatments for children under the age of three.

Helminth Infections

Filarial diseases (onchocerciasis, lymphatic filariasis, and loiasis), caused by filarial nematode worms, have a low associated mortality rate but cause chronic diseases and life-long disabilities, in addition to their very high prevalence (128 million for lymphatic filariasis (LF); 47 million for onchocerciasis; unknown for loiasis). Onchocerciasis and LF can be controlled by mass drug administration (MDA; treatment duration up to 15 years). In Africa, effective treatment with the microfilaricidal drug ivermectin, exists. However,

[2] *Treatment of children living with HIV/AIDS*. WHO, 2011. Available at <http://www.who.int/hiv/topics/paediatric/en/index.html> (accessed 23 May 2011).

[3] Leeper S, Reddi A. 'United States global health policy: HIV/AIDS, maternal and child health, and The President's Emergency Plan for AIDS Relief (PEPFAR)', *AIDS*. 2010 Sep 10;24(14):2145-9.

people living in *Loa loa* co-endemic areas may be co-infected and in their case, **the standard prevention treatment with ivermectin for onchocerciasis or LF can result in very severe neurological reactions, which can be fatal or debilitating**. DNDi will focus on developing a **macrofilaricide** that could be used as an alternative preventive treatment and in case management. Additionally, a macrofilaricidal drug will reduce the number of MDA cycles needed for onchocerciasis and LF control in all areas. Opportunities for partnerships have been found in the animal health field and laboratory work on one new drug candidate has been initiated.

3.3 | LANDSCAPE EVOLUTION FOR NEGLECTED DISEASE R&D

3.3.1 Overview

Prior to 2000, there were few players in the field of the most neglected diseases. The Special Programme for Research and Training in Tropical Diseases (TDR), GlaxoSmithKline (GSK), and the Walter Reed Army Institute of Research (WRAIR) had specific project-related activities.

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 produce needs-adapted health tools. The first product development partnerships (PDPs) for neglected disease R&D were established in the 1990s (e.g. International AIDS Vaccine Initiative (IAVI) and Medicines for Malaria Venture (MMV)).

During this period, market push and pull mechanisms, which included various financial and economic incentives, were designed to encourage the R&D-based pharmaceutical industry to develop drugs for neglected diseases. 'Push' mechanisms, such as R&D grants, lower the costs and risks for companies' R&D efforts; while 'pull' mechanisms, such as market exclusivity and patent extension, secure the profitability of the market (see Figure 3).

The past decade has seen a steady increase in resources given to global health and the development of new essential health tools. Today, several new actors, new donors, new financial mechanisms, and a new political environment have contributed to an increasingly active field of R&D for neglected diseases. However, greater investment – along with new and adapted funding mechanisms – is needed from both governments and the private sector to ensure that the efforts of the past two decades are strengthened and sustained.

3.3.2 Key Actors

The role of the **World Health Organization (WHO)** in the fight against neglected tropical diseases and particularly in the implementation of all new health tools currently emerging from the drug development pipeline will be critical. In 2006, WHO created a Neglected Tropical Diseases Department to facilitate and coordinate the relationships between the different partners involved in NTD disease control. This department recently released its first NTD report, which presented evidence that activities undertaken to prevent and control neglected tropical diseases were producing results, including innovative tools developed for some of these diseases.

As set forth in the Global Strategy and Plan of Action (GSPA) on Public Health, Innovation and Intellectual Property, adopted by the 2008 World Health Assembly, WHO's role is vital in working with Member States to define the global R&D agenda, and in creating adapted and sustainable policy instruments to secure essential innovation and access to lifesaving tools for neglected diseases.

Product Development Partnerships (PDPs) seek to foster R&D and treatment access for neglected diseases by building partnerships based on existing capacity, expertise, and resources in both the public and private sectors. They fill a gap by focusing on essential health tools that would not otherwise be developed due to lack of profitable markets.

Currently, there are over 17 PDPs developing drugs, vaccines, microbicides, diagnostics, and devices. To date, they have developed and licensed 14 products to combat **malaria, sleeping sickness, cholera, Japanese encephalitis, meningitis, VL, and TB** in low- and middle-income countries, with many more tools in the pipeline.

The PDP model shows how crucial it is to build new collaborative business models through partnerships, alliances, and consortia amongst those whose objectives are driven by needs, not profit. The not-for-profit model demonstrates innovative ways to share knowledge and avoid duplication in research, thereby saving costs and speeding up the R&D process for the benefit of patients. In the past few years, **DNDi has established synergies with other PDPs**, for example, MMV, FIND, and CPDD. In 2010, DNDi and The Global Alliance for TB Drug Development (TB Alliance) signed the first-ever royalty-free license agreement between two not-for-profit drug developers, speeding up progress towards markedly improved therapies for multiple neglected diseases.

In past few years, DNDi has formalized strong relationships with several **pharmaceutical and biotechnology companies committed to R&D for NTDs**. These business relationships, at all stages of the R&D pipeline, include screening of compound libraries, access to compounds or chemical series with known anti-protozoal activity, clinical development, production, registration, and risk management plans. Such relationships illustrate the **growing involvement** of large pharmaceutical and biotechnology companies, as well as service providers and generic companies, from both high-income and emerging economies.

Many **academic and public institutions** are now players in the field of neglected disease R&D. For anti-kinetoplastid drug R&D, a number of **low-income and emerging countries** have dedicated resources to building R&D capacity (e.g. Farmanguinhos and the forthcoming Centre for Technological Development in Health at the Oswaldo Cruz Foundation – Brazil; Central Drug Research Institute – India; and Institut Pasteur Korea – South Korea).

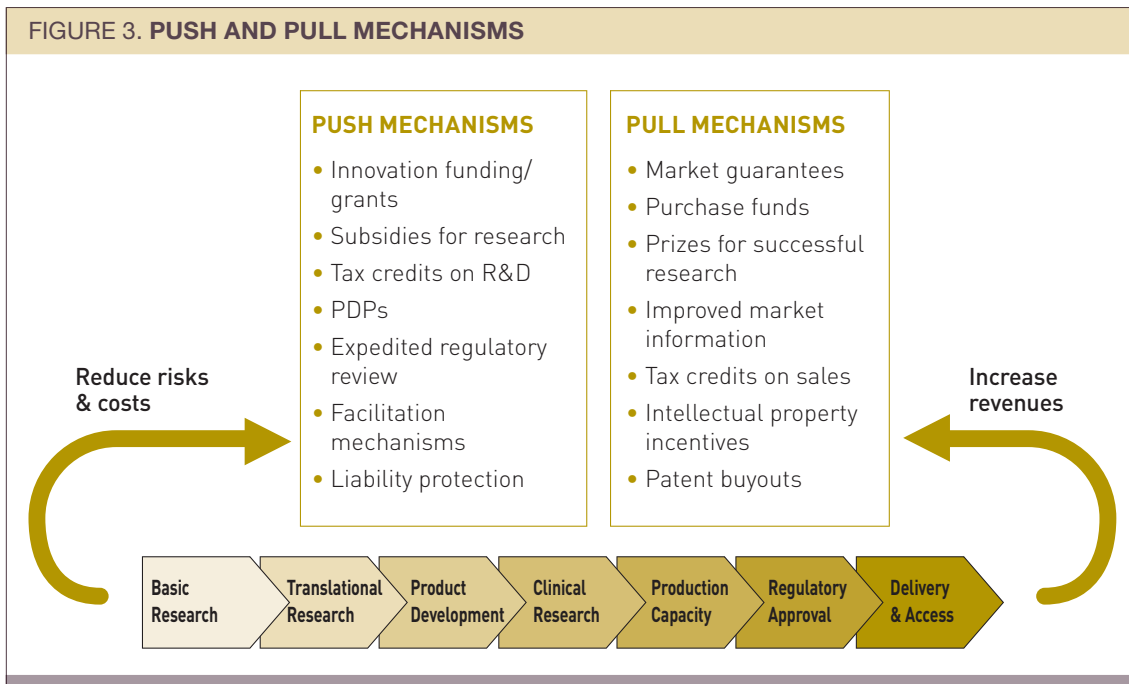
3.3.3 Sustainable Financing

To support these initiatives, sustainable funding is needed. Global neglected disease R&D funding in 2009 totalled USD 3.2 billion (including malaria, tuberculosis, and HIV/AIDS),^[4] which is still largely insufficient to support development efforts. Furthermore, of this amount, only USD 162 million – slightly over 5% – was spent on kinetoplastid diseases.

Within the public sector, a few governments (UK, The Netherlands, Spain, Switzerland, and France) have made significant financial commitments to support innovation and implementation programmes for neglected diseases, despite financial crises. Interest in supporting NTDs has been indicated by other governments such as Germany and Australia, as well as by emerging economies. While such signs are hopeful, far too few governments are firmly engaged and commitments from major research funding sources such as the FP7 (EU) and NIH (USA) are inadequate to support PDP portfolio management.

[4] G-Finder 2010, *Neglected Disease Research and Development: Is the Global Financial Crisis Changing R&D?*, by M. Moran et al. Policy Cures, Sydney and London, 2011.

FIGURE 3. PUSH AND PULL MECHANISMS



Source: 'Financing neglected disease R&D: Principles and options', DNDi study based on an analysis by Paul Wilson, 2010.

Within the group of philanthropic donors, the Bill and Melinda Gates Foundation (BMGF) covers almost 60% of total funding for PDPs, while the Wellcome Trust and the Rockefeller Foundation have also been important drivers. In particular for DNDi, Médecins Sans Frontières is a major financial supporter.

From its inception, DNDi has advocated for increased resources for innovation for neglected diseases and for new and sustainable mechanisms to ensure flexibility in management of portfolios. DNDi and other PDPs are examples of new forms of push mechanisms that have successfully attracted public and private funding.

Other new mechanisms, including the advance market commitment for pneumococcal vaccines and the US FDA's Priority Review Voucher, have been launched recently by donor governments, but it is too soon to evaluate their impact. New incentives such as Milestone Prizes to stimulate early-stage discovery of promising compounds for neglected diseases should be developed.

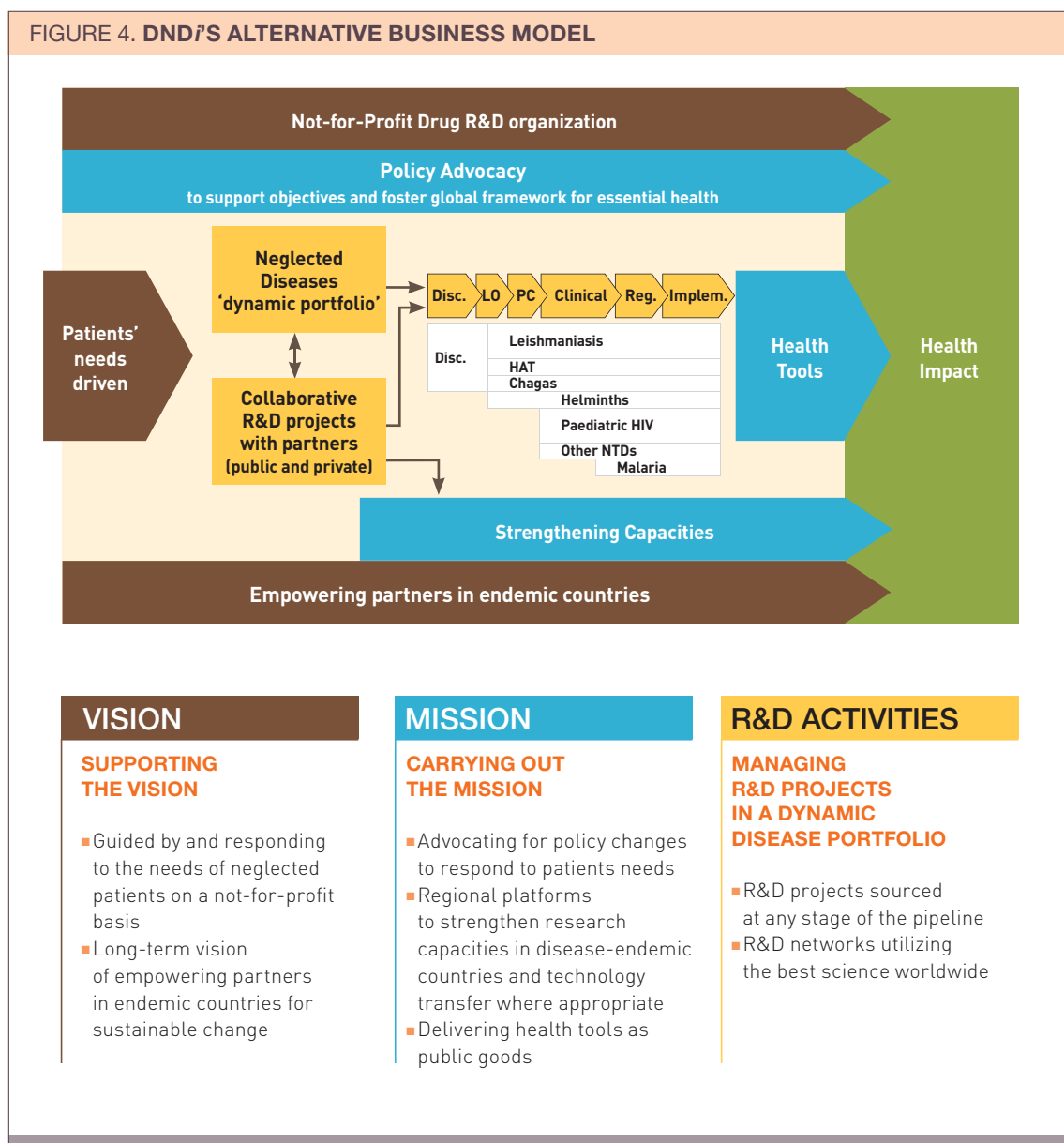
While it can be said that there is a new political environment, a global framework for essential health R&D is still needed. Currently, WHO Member States are examining financing, coordination, and proposals for new and innovative sources of funding to stimulate R&D for neglected diseases through the implementation of the Global Strategy and Plan of Action (GSPA) on Public Health, Innovation and Intellectual Property adopted by the 2008 World Health Assembly. It is also vital that public leadership contribute to innovative needs-based measures such as IP management policies, to encourage needs-driven R&D, technology transfer, and strengthening of research and regulatory capacities in endemic countries.

As PDPs have now advanced several compounds to clinical development, additional **sustainable funding to ensure late-stage development of, and access to, promising compounds is also urgently needed.** Clearly, the successes of existing international organizations and mechanisms that have addressed market and public policy failures, such as UNITAID, should be considered as a model to be emulated.

04.

DNDI'S ALTERNATIVE BUSINESS MODEL

A not-for-profit R&D organization, DNDi builds its disease portfolio through its R&D projects. The business model can be characterized by certain distinguishing traits.



4.1 | A NOT-FOR-PROFIT R&D ORGANIZATION DEVELOPING HEALTH TOOLS AS PUBLIC GOODS

4.1.1 Public Goods for Health

DNDi aims to develop treatments that meet neglected patient needs, without seeking to generate profit from its R&D efforts. As such, the products, compounds, or technologies resulting from its partnerships are conceived as public goods⁽¹⁾, adhering to the principles of global access to healthcare (see also Section 4.6). The resources obtained from partners and co-funders are generated through various financing mechanisms, including in-kind contributions (see Section 9 for fundraising information).

Whereas DNDi does not seek to finance any portion of its activities through revenue linked to the commercialization of its products by third parties, it will consider – on a case-by-case basis – acquiring resources through royalty mechanisms from commercial revenues from its partners (such as ASAQ royalties from Sanofi) in a way that will not impact its vision and independence, or patients' access to the product in question. Such resources are re-injected into research projects.

4.1.2 Intellectual Property Policy

DNDi's intellectual property (IP) policy guides its R&D activities and associated contractual agreements with the following guiding principles:

- Treatments should be affordable to patients who need them and **access to these treatments should be equitable**
- **Drugs should be developed as public goods** whenever possible.

Although DNDi will not necessarily be able to control all IP related to each project, the appropriate licensing rights ensuring equitable access for any treatment it develops are secured in its agreements.

In practice, freedom to operate for DNDi is obtained through non-exclusive and sub-licensable licensing rights allowing for the execution of all R&D activities necessary to deliver products to patients, including royalty-free distribution in the public sector of disease-endemic countries. DNDi promotes open source models at all stages of R&D.

4.1.3 New Funding Sources and Mechanisms

Despite the growing attention from public and private donors described in the previous section, funding gaps still remain. DNDi advocates for additional funding and new mechanisms to address neglected disease R&D challenges, including:

- Funding from emerging economies;
- New funding mechanisms similar to that of the UNITAID model;
- Access to in-kind resources from pharmaceutical and drug development partners to reduce overall development and access costs;
- Creation of Milestone Prizes;
- Seeking synergy with other partners, such as PDPs, to lower overhead, share experiences and resources, and further improve cost effectiveness.

(1) In other words, no individual can be excluded from their use, and use by one person or group does not reduce their availability for another.

4.2 | BUILDING AND MANAGING A DYNAMIC DISEASE PORTFOLIO

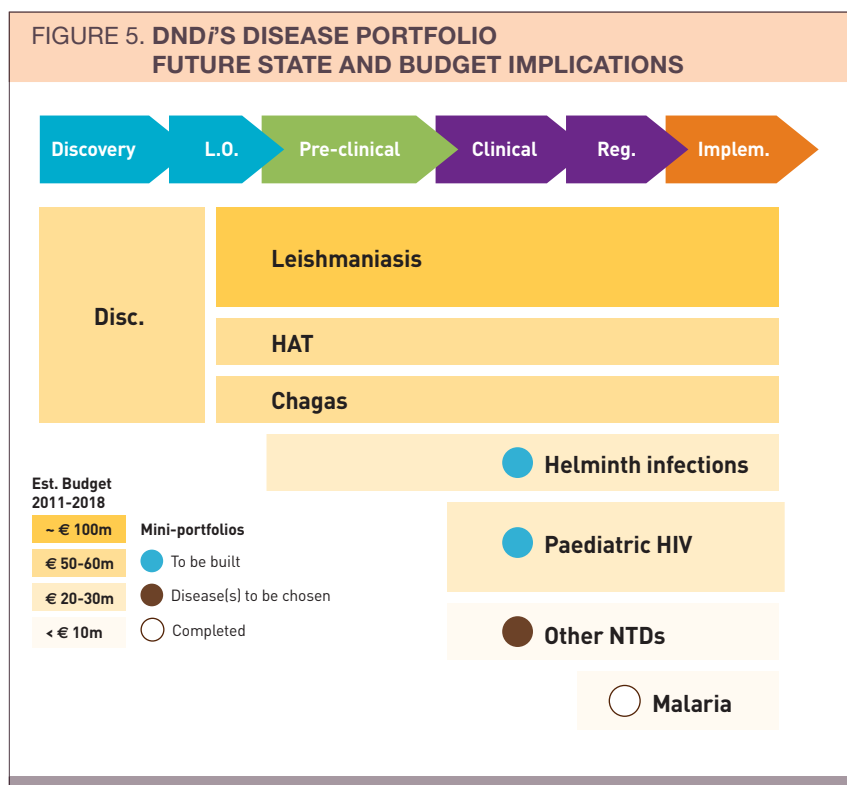
DNDi's disease portfolio has primarily focused on **kinetoplastid** diseases (HAT, leishmaniasis, and Chagas disease) and malaria. Two new disease areas have been added in response to calls by international organizations and partners.

By 2018, the portfolio-related objectives are to:

- Further develop the kinetoplastid disease portfolio, including ongoing discovery activities to feed long-term objectives
- Complete the **malaria** activities and hand these over to partners by 2014
- Develop **mini-portfolios** for **paediatric HIV** and helminth infections
- Consider specific activities or mini-portfolios for other neglected diseases, should a clear need, demand, or opportunity arise, and based on DNDi's comparative advantage.

Unlike traditional portfolios fed with projects that span from discovery to late development stages with respect to disease-wide objectives and attrition, **mini-portfolios** are more targeted in their objectives and focus on later stage opportunities with a high potential for success.

For each disease area, DNDi has a specific strategy, which is updated annually (for key elements of the R&D strategy, see Section 5).

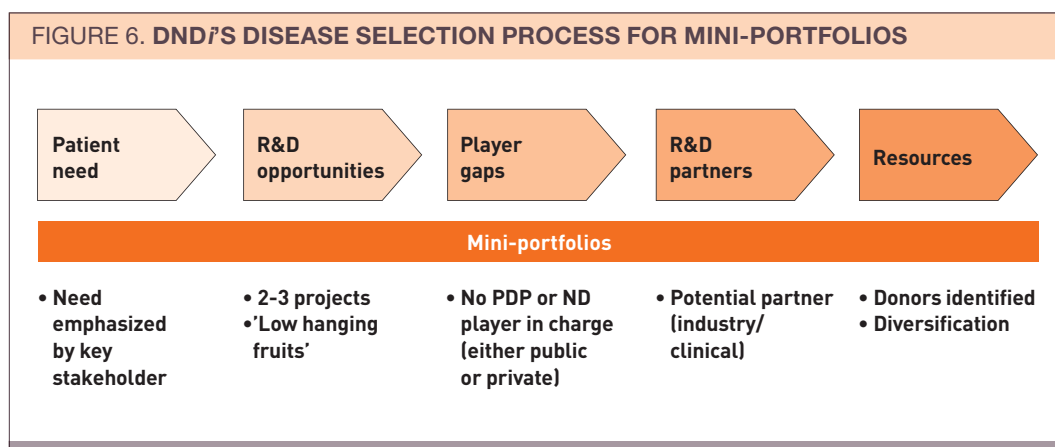


An increasingly systematized approach to decision-making, measuring outcomes, and responsiveness to patient needs will include two main areas of focus:

- Building on experience from its malaria portfolio, DNDi will elaborate on **metrics for success** and **conditions for concluding activities** in a given disease area.
- **Systematic intelligence work** will be integrated with identification and/or monitoring of:
 - Unmet medical needs
 - Deficiencies in appropriate health tools to address these needs
 - Relevant scientific innovation and technological developments.

By doing so, DNDi will be able to initiate new R&D projects appropriate for the needs and opportunities.

To manage its dynamic portfolio, DNDi has developed guiding principles to select new diseases (Figure 6). New disease areas are considered on an opportunistic basis: key stakeholders and internal analyses may emphasize a specific patient need to be considered by the Executive Team. Should R&D opportunities be identified, DNDi verifies that no other organization can take leadership before considering its own investment. The selection of potential R&D partners and funders complete the case study, which is then submitted to the Board of Directors. Risk analyses are undertaken to support the decision-making process.



4.3 | MANAGING COLLABORATIVE R&D PROJECTS SOURCED AT ANY STAGE OF DEVELOPMENT

4.3.1 A Collaborative Model

DNDi does not operate its own research facilities to develop new treatments. It functions based on a collaborative research model, also adopted by other PDPs and certain biotechnology companies, whereby research is outsourced but actively managed and directed by DNDi personnel, highly experienced in pharmaceutical R&D. DNDi proactively and continuously identifies research opportunities that have the highest potential to translate into improved treatment options. DNDi management encompasses integration of research projects into its portfolio, building a full development plan, identification and contracting of appropriate partners, and management of the efficient progression of projects throughout the pipeline.

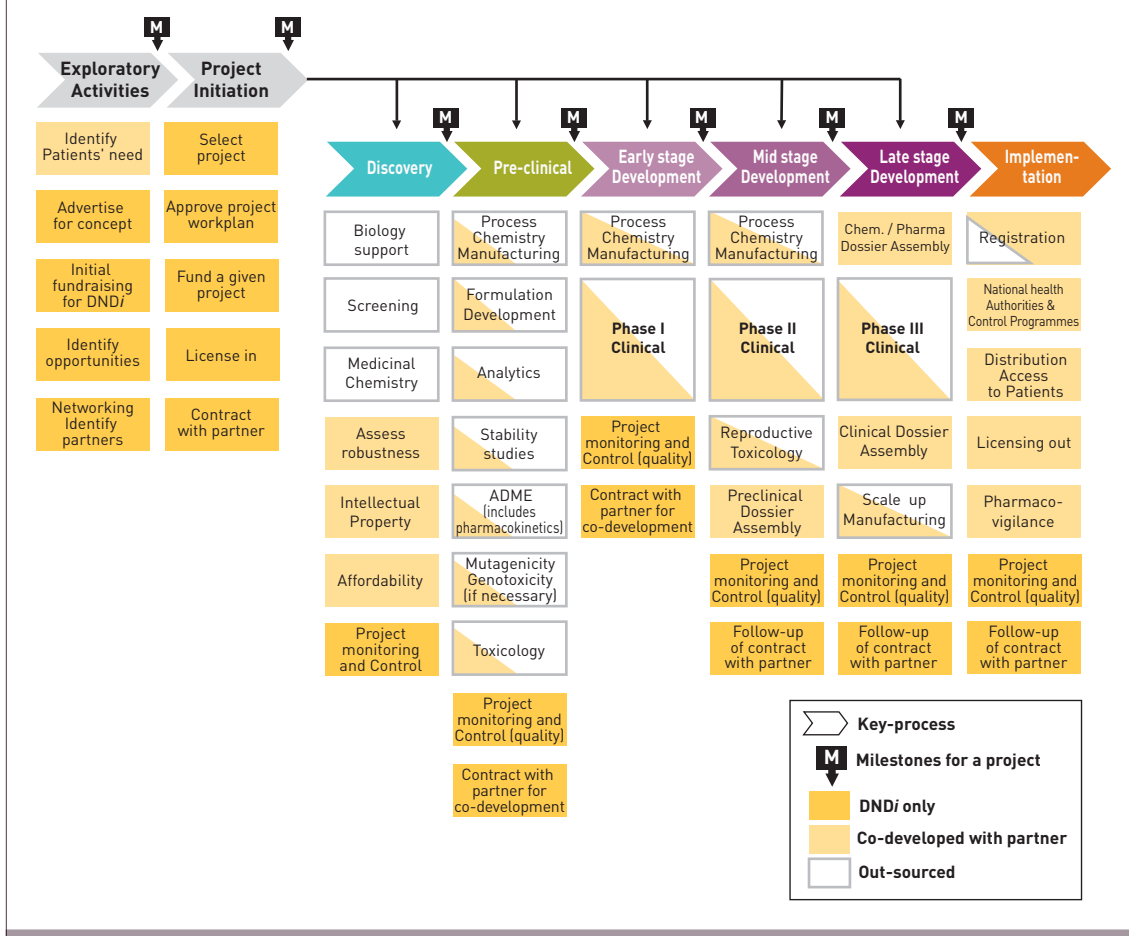
In doing so, DNDi collaborates with a wide range of partners and contractors in both endemic and non-endemic countries, including:

- Public and academic research institutions and associated institutions;
- Governments and National Control Programmes of disease-endemic countries;
- Pharmaceutical and biotechnology companies, including contract research organizations (CROs) and contract manufacturing organizations (CMOs);
- NGOs, foundations, and other institutions involved in R&D and/or advocacy for neglected diseases;
- Individual experts on any given aspect of pharmaceutical development, neglected diseases, and business practices, in addition to patient representatives.

A team is set up for each project, under the leadership of a DNDi Head of Programme, to coordinate all relevant partners and expertise. Such collaboration is governed by various types of contractual agreements, ranging from research funding collaborations, to 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 (Figure 7), whereas selection, funding, monitoring, and control of projects are DNDi's direct responsibility throughout the development process.

FIGURE 7. BREAKDOWN OF RESPONSIBILITIES BETWEEN DNDi AND ITS PARTNERS AT DIFFERENT STAGES OF THE DRUG DEVELOPMENT PROCESS



4.3.2 Needs-Driven Projects Sourced at All Stages of Development

DNDi's portfolio comprises projects in-sourced at any stage of the development process, from early discovery to 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 patients.

The DNDi R&D team conducts a number of exploratory activities which can be built up to full drug development projects or maintained as backup pipeline projects. Through this approach, DNDi will continue to feed the pipeline of each target disease.

For the selection of new chemical entities, DNDi focuses on compound libraries from pharmaceutical and biotech companies and will continue to engage partners in the industry. It will also maintain an opportunistic approach with respect to other sources (e.g. PDPs, academia) and build strategies for the future, including greater involvement from emerging economies.

4.3.3 Technology Transfer

In addition to in-sourcing, DNDi will continue to transfer technologies in fulfilment of its objectives. Transfers can apply to compounds, technologies, or knowledge at all stages of development and implementation.

When possible, contracts with partners (public or private) will include options for technology transfer (e.g. IPK on High Throughput Screening). Examples of such transfer may include drug screening tools through to manufacture of drugs for distribution. Transfer may be implemented within South-South or North-South frameworks (e.g. for ASMQ, Fiocruz/Farmanguinhos – Brazil and Cipla – India; and for ASAQ, a recently signed contract to transfer technology to Zenufa, a manufacturing partner in Tanzania).

In the future, DNDi will also consider out-sourcing compounds or technologies for others to further conduct research and development, with the possibility of in-licensing at later stages.

4.4 | R&D NETWORKS: UTILIZING AND STRENGTHENING RESEARCH CAPACITIES IN DISEASE-ENDEMIC COUNTRIES

4.4.1 Building upon DNDi's Vision and Founding Partners

Starting with its unique governance model, which includes Founding Partners from endemic countries (see Section 7), empowerment of partners in disease-endemic countries is a critical component of DNDi's vision and a recognized differentiating factor from other neglected disease R&D ventures. The Founding Partners will continue to reinforce their role by consolidating the networks of regionally contracted collaborators that will be managed by DNDi.

As an integral part of its mission, DNDi works with all its R&D partners to build on South-South and North-South collaborations. While capitalizing upon and supporting existing capacity in countries where the diseases are endemic, DNDi helps to build additional capacity in a sustainable manner through technology transfer, clinical research, pharmacovigilance training, and strengthening of infrastructure.

4.4.2 A Facilitating Role in the Development of Platforms and Other Capacities

DNDi will continue working with partners in disease-endemic countries, ensuring their close involvement in the entire R&D process, starting from needs identification, via a global network of collaborations and technology transfer. This includes access to chemical diversity, discovery platforms, pharmaceutical and clinical development, and collaboration with National Control Programmes. Such collaboration is exemplified by the HAT Platform and the Leishmaniasis East Africa Platform (LEAP) in Africa, the more recent Chagas Clinical Research Platform in Latin America, and other existing networks in disease-endemic countries.

DNDi balances the objective of stimulating R&D activity in disease-endemic countries with the urgent need to develop new medicines and carefully assess each potential partner's ability to deliver in a sustainable manner (e.g. effective delivery of study results; active contribution to the registration process). Selection of partners is done case-by-case, taking into account the probability of success given adequate investment. The latter may imply, for example, modestly delaying the start of a trial to ensure sustainable patient access as well as a new research and treatment facility.

Capacity building may include the building or renovation of hospital wards, clinics, and health posts; renovation and re-equipment of clinical laboratories; and training of health service personnel with particular emphasis on providing expertise in clinical trial methodology, Good Clinical Practices and Ethics, patient treatment and evaluation, accurate diagnosis, and follow-up, to name a few.

DNDi's role is that of facilitator, with the objective of **empowering local partners** with contributions such as needs assessments, seed or core funding, knowledge transfer, administrative support, and business development support.

4.4.3 Role of Regional Offices

Implementing DNDi's vision of empowering regional partners from disease-endemic countries will be made possible, in particular, through a more reinforced role of Regional Offices. These DNDi resource centres play a key role in supporting projects, in advocating for access and awareness, and in generating and/or sustaining local and regional initiatives (e.g. Chagas Clinical Research Platform in Latin America). They will increasingly manage R&D programmes from endemic countries under the supervision of R&D management. Delegation of responsibilities from DNDi Headquarters to the Regional Offices will depend on whether the critical size is present or on partners' capacity. The nature, structure, roles, and responsibilities of each Regional Office are tailored to the local/regional situation and will develop accordingly.

A 'one organization, one strategy' principle will guide DNDi in this process and, while allowing for maximum flexibility and a pragmatic approach to empowering Regional Offices and partners, it guarantees institutional integrity. DNDi will not implement a regionalization model whereby each Regional Office would develop its own agenda and manage all operations for DNDi in a given geographical area. Rather, each Regional Office will develop mid- to long-term strategic plans fully in line and harmonized with the overall organizational objectives, Business Plan, processes, and organization, upon different empowering schemes, which can include activities that are either:

- Initiated and led locally.
- A contribution to DNDi's global programmes;
- Run from the Regional Offices on behalf of the whole organization;
- Under direct supervision of Headquarters, especially when partners or local means do not meet the critical needs.

See Section 7 for more information on these and other organizational issues.

4.5 | DEMONSTRATING FEASIBILITY AND IMPACT THROUGH A PORTFOLIO OF BUSINESS MODELS

The magnitude of R&D needs for neglected diseases and the diversity of potential partners are such that DNDi cannot operate according to a single model. Considering its mission, DNDi needs to have the institutional agility and flexibility to provide appropriate responses to neglected patients' needs, making no compromises on ethics and the quality of the science required to do so. This is what is meant by the motto 'best science for the most neglected'. As a developing and learning institution, DNDi is willing to engage in original approaches to the target diseases, portfolio size, product categories, health tools, or access models.

For each activity, DNDi can utilize different partner categories, collaboration schemes, funding mechanisms, or advocacy activities, and adjust the intensity of its contribution – from light support to leadership.

As part of its ongoing programme management, DNDi will continue to explore different partnership and business models to assess their feasibility and impact. Its will and capacity to explore innovative approaches – the risks of which are always carefully assessed – makes DNDi an incubator of R&D solutions for neglected diseases.

A key element of DNDi's current and future work is the economic **appraisal of its model and impact** in terms of:

- Cost tracking and evaluation for **comparative assessments**
- Cost effectiveness and **cost benefit analyses** which will help to further validate and improve the R&D model pursued.

FIGURE 8. DNDi'S DIVERSITY OF PARTNERSHIPS & MODELS



4.6 | NEEDS-DRIVEN REGULATORY AND ACCESS STRATEGIES

4.6.1 International Regulatory Standards to Control and Assure Quality

Operating in a highly regulated environment, DNDi fully adheres to international quality, ethical, and regulatory standards of drug R&D. From the earliest phases of the drug development process, registration requirements are taken into account and all R&D is performed in accordance with international standards.

The research, development, and delivery of a novel drug therapy invariably involve a certain level of risk. Quality is a central component associated with all of the risks: quality of the R&D activities performed and quality of the final product.

To support quality control and quality assurance (QC/QA), DNDi has built internal and appropriate standardized operating procedures (SOPs) based on the International Conference Harmonization (ICH) and OECD recommendations.

While continuing to 'play by the rules', DNDi will also continue to advocate for adapted regulatory and registration strategies for neglected diseases (e.g. pushing for regional harmonization).

4.6.2 Registration

DNDi does not intend to hold market authorization. Building on its experience, it will look for industrial partners to register treatments (e.g. Sanofi for ASAQ) and, on a case-by-case basis, will consider playing a more active role if a given partner is not in a position to lead the registration/recommendation process (e.g. NECT).

With its industrial partners, DNDi will seek the best-adapted regulatory route to facilitate rapid, field appropriate, and quality-based assessment of each regulatory dossier. Currently, outside of the EU, registration is country-based and not all countries possess the full resources to assess registration files. For diseases that affect entire regions, this time-consuming country-by-country process may delay patient access to treatments in areas where a number of agencies are concerned.

Several options already exist, such as a twinned review between a 'stringent' regulatory agency and a less resourced one (e.g. EMA article 58). Coupled with WHO pre-qualification, these approaches could impact the speed of patient access to new treatments in each country, whilst maintaining the essential standards of quality and contributing to the capacity strengthening of some regulatory agencies, thus promoting South-South exchanges.

Registration, however, is not sufficient. In most cases, adoption of international (e.g. WHO, PAHO) and national treatment guidelines (such as for HAT, VL, and Chagas disease) is also required for the treatments to be recommended, and therefore purchased and used, in the public sector. The case will be made that the new treatment options are indeed safe and effective, but also affordable, field-adapted, and coherent with public health strategies. The latter parameters are not examined by regulatory agencies but are essential for sustainable use. Inclusion of treatments in the WHO Essential Medicines List will also be targeted as an appropriate mechanism to facilitate multi-country uptake of treatments in national programmes.

DNDi, as part of its mandate to facilitate patient access to treatments, will explore and support, with its regional partners, the most suitable means to facilitate adoption of new treatments delivered.

4.6.3 Enabling Access

DNDi's involvement will not end with drug registration or WHO recommendation, even more so now that its portfolio is maturing and the number of products in the implementation phase is growing. DNDi will take on the responsibility of ensuring that the new tools it develops become useful, accepted, and accessible. Consistent with its collaborative model and the objective to develop public responsibility for neglected diseases, DNDi will primarily engage in partnerships to ensure appropriate access to treatments, thus not taking or claiming sole ownership for access programmes.

Distribution and overall access scenarios will vary depending on the disease, drugs, relevant countries, and degree of innovation. See Section 6 for more detailed information on DNDi's access model.

4.7 | INTERNATIONAL ADVOCACY TO SUPPORT DNDI'S OBJECTIVES

Working to build awareness about the most neglected diseases in both non-endemic and endemic countries, DNDi aims to increase and sustain its advocacy efforts for greater public responsibility to address neglected diseases. Political leadership is essential for continued financial support, definition of priorities, the creation of a more favourable environment to stimulate health R&D, and guaranteeing equitable access to new health tools.

DNDi will continue to ask for greater political leadership from governments of both donor and disease-endemic countries, in addition to international bodies such as the WHO and its Intergovernmental Working Group. Fostering relationships between concerned scientists, research institutes, PDPs, and NGOs is also critical to accelerating the momentum that has been building up since 2000.

DNDi will do the following to advocate for a more effective neglected disease R&D environment:

- Continue to **engage independent experts** to examine intellectual property, regulatory processes, access to knowledge, and conduct economic appraisals to stimulate the environment;
- Continue to **document experience** gained since its inception via case studies or comparative and transparent appraisals of the business model with regards to R&D effectiveness and costs;
- Encourage the comparative **analyses of non-traditional R&D models** (e.g. PDPs).

05.

R&D STRATEGY

DNDi's primary R&D objective is to deliver a total of 11 to 13 new treatments to patients by 2018 (five to seven more than the six in implementation phase in 2011) and to maintain a robust pipeline to support long-term objectives.

DNDi will fill its pipeline at all stages of development through a mix of short-, medium-, and long-term projects, managed via its collaborative R&D model.

DNDi is proactively developing its portfolio through the identification of:

- Significant unmet medical needs;
- R&D opportunities such as candidate compounds and improved formulations;
- Potential partner organizations for R&D;
- Adequate funding sources.

Concerted efforts to harness discovery activities targeting the three core kinetoplastid diseases are focused on sourcing the most promising anti-parasitic drug candidates. On a disease basis, the portfolio is managed by taking into account the gaps identified within the product portfolio, pipeline projections, and strategic priorities.

DNDi will complete its malaria strategy and launch two mini-portfolios in the areas of paediatric HIV and specific helminth infections.

FIGURE 9. DNDi'S OBJECTIVES

2003-2011 implementation	Diseases	2012-2018	Beyond
NECT	HAT	Kinetoplastids: 1 or 2 NCEs	+ Strong clinical pipeline (Phase II & III)
Paed. Benznidazole	Chagas		Combo with 2 NCEs Combo incl. NCE
2 VL Combos	Leishmaniasis		VL - 1 treatment (Geographical extension) CL - 1 treatment PKDL - 1 treatment
	Helminths	1 new treatment for filariasis	TBD
	Paediatric HIV	1 new treatment	TBD
ASAQ + ASMQ	Malaria	Completion by 2014	
	New NTD		Treatments
6 new treatments	5 to 7 new treatments including at least one NCE (+ geo. extensions) + strong pipeline (Ph II and III) to deliver additional treatments with NCEs + stimulate 2 to 3 critical technologies (e.g. Biomarker, test) to sustain R&D + Diseases exit strategies		

5.1 | SYNTHESIS OF OBJECTIVES PER DISEASE AREA

In addition to the six treatments in implementation phase in 2011, DNDi is committed to:

- Providing five to seven new treatments, including at least one new chemical entity (NCE) and potential geographical extensions
- Developing a strong pipeline of projects in Phase II and Phase III that could deliver additional treatments with NCEs beyond 2018;

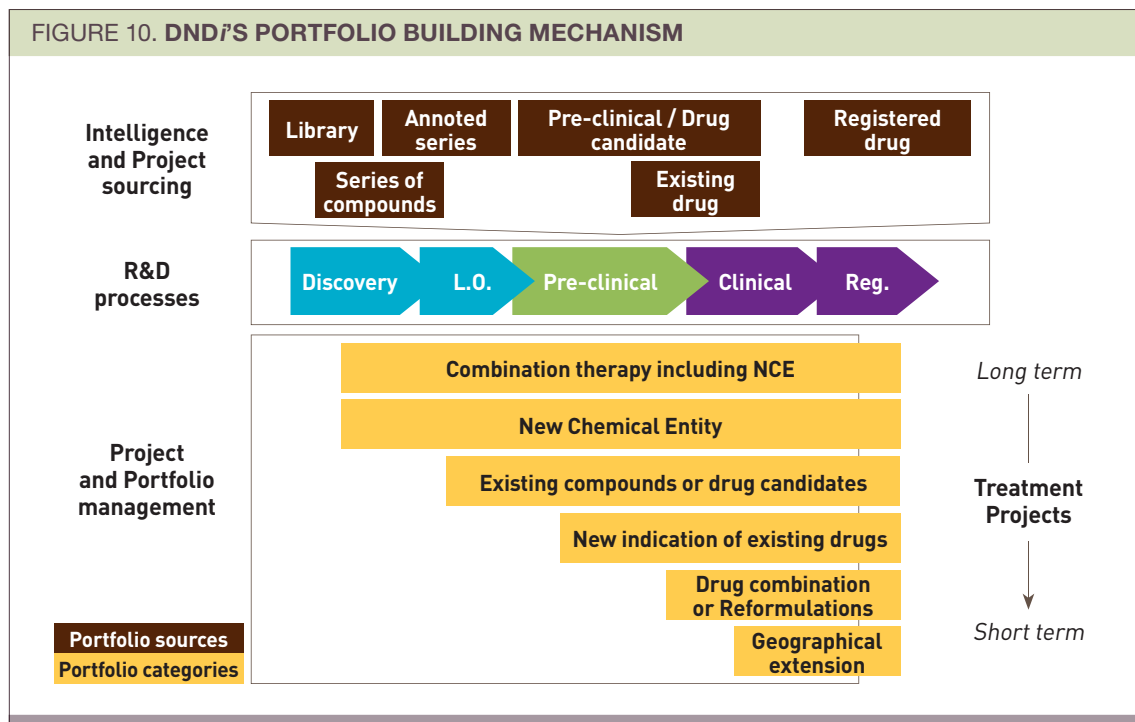
- Stimulating the development of two to three technologies to support R&D (e.g. biomarkers, diagnostic tools);
- Developing clear disease completion strategies for its disease portfolio, and a smooth hand-over of its malaria portfolio by 2014.

5.2 | PORTFOLIO BUILDING APPROACHES

The three key processes – **intelligence and project sourcing, R&D, and project & portfolio management** – will be further implemented by DNDi to fill the pipeline by seeking leads and drug candidates at all stages of development (Figure 10). At the post-registration stage, existing and new mechanisms will be leveraged to ensure patient access to treatments through partnerships with industrial partners, international organizations, and national programmes.

Projects will be divided into five categories:

- New treatments (involving NCEs) developed from novel compounds identified through screening, lead optimization, or licensing. These drugs must meet target product profiles (TPPs) and may be used in monotherapy or as part of combination therapies when appropriate;
- New treatments developed from compounds with known antimicrobial/antiparasitic activities (could start at lead optimization or pre-clinical development);
- New indications for existing treatments (therapeutic switching);
- Combinations or new formulations of existing drugs that are better adapted to field conditions and patient needs (paediatric dosage forms, long-acting, new route of administration, fixed-dose combinations, co-packaging, or co-administration);
- Geographical extension of existing treatments, including completion of regulatory dossiers in new countries.



5.2.1 Sourcing

Building on its experience of sourcing projects since 2003, DNDi has refined its sourcing approach, aiming to:

- Proactively manage access to pharmaceutical companies' annotated series to accelerate identification of drug candidates;
- Source projects from partners in the public sector;
- Explore new business models for DNDi to co-develop compounds with partners;
- Continuously advocate for investment (public and private) in neglected disease research to secure sources of innovation;
- Stimulate innovation in targeted disease areas via advocacy for public research in emerging economies.

5.2.2 Discovery

Radical improvement of therapies for leishmaniasis, human African trypanosomiasis, and Chagas disease requires the **identification, evaluation, and development of novel compounds that are better than current therapies**. The screening of (libraries of) compounds *in vitro* against both molecular targets (crucial enzymes, receptors) and whole organisms to identify novel compounds is a well-established approach in industry and academia. From 2007 to 2010, DNDi built and refined a virtual model of drug discovery capable of producing drug candidates. However, the lack of high quality hits and leads, and the high attrition rate at the hit-to-lead stage necessitates continued adjustment of drug discovery approaches to ensure continued success.

As some chemical classes have a broad spectrum of activities against parasites causing the target diseases, DNDi will further seek access to **compound series** with proven drug-like characteristics from **pharmaceutical and biotechnology partners**. Access to partners' chemical diversity as well as drug-like and annotated compound series is critical to the success of this approach. Several agreements have been entered into with major companies such as Sanofi to screen their compound libraries. DNDi also seeks access to **knowledge and know-how** associated with such classes to ensure efficient drug development.

DNDi continues to encourage **open exchange of information** related to drug R&D in the field of neglected diseases. By collaborating with other laboratories/institutions to promote rapid development of new treatments for patients in need, **unnecessary duplication of effort is avoided** and synergies between research groups created.

For example, DNDi has developed a partnership with the Institut Pasteur Korea (IPK) for High Throughput Screening (HTS) on specific target parasites to help select and progress hits and leads according to its target product profiles and decision matrices. The outcome of this work with IPK (funded by DNDi) is made public for others willing to pursue R&D for neglected diseases.

The virtual drug discovery research framework is operational and has yielded promising candidate compounds. DNDi will continue to streamline its model for more rapid advancement of drug candidates.

One of the challenges for 2011 onwards is to effectively continue to **organize and manage alliances, especially with pharmaceutical and biotechnology partners**.

Lead compounds identified within this framework will progress into focused lead optimization programmes, which in turn will be implemented by experienced medicinal chemistry groups. Optimized leads will then enter the drug development process of pre-clinical and clinical development.

5.2.3 Lead Optimization

Building upon its Lead Optimization Consortium framework developed in 2008, DNDi will further **leverage key competencies of its partners, and continue to strive for cost effective delivery**.

Within its lead optimization activities, DNDi will emphasize the strengthening of its internal competencies in medicinal chemistry and CMC (chemical manufacturing control) to better manage its work with partners and CROs (contract research organizations). Outsourcing technical operations to **cost-effective providers** will be augmented with supervision of and advice from consortium partners.

In addition, value-added **partnerships in endemic countries** will be pursued with the objective of strengthening capacities where and when appropriate.

DNDi counts an increasing number of projects at the late lead optimization stage. Therefore, in order to ensure smooth transition to early development, DNDi's translational research strategies will be refined and strengthened.

5.2.4 Pre-Clinical and Clinical Development

DNDi will continue to explore the **repurposing of existing drugs** (such as the antifungal drug E1224 for Chagas). Therapeutic switching – re-orienting drugs that exist or are in clinical development for other indications – has already proven successful in generating promising new drugs for leishmaniasis and trypanosomiasis. Anti-fungal, anti-bacterial, and anti-malarial drugs are particularly promising drug sources for therapeutic switching. DNDi is closely monitoring developments in these areas, with the aim of co-developing such drugs with partners (including with other PDPs) or in-licensing them to be developed for the specific target disease indications.

For helminth infections (see below), partnerships will be sought with animal health companies.

A ‘pre-competitive approach’ to collaboration will also be pursued, by which DNDi and its partners share approaches and knowledge before launching their own initiatives or projects. DNDi will explore appropriate models accordingly.

DNDi will continue to develop **combinations of existing drugs** to address immediate patient needs. In the absence of new, highly effective, easier-to-use drugs, combination treatments offer the potential to improve efficacy, reduce treatment duration, and reduce costs, in addition to lowering the risk of drug resistance. Similarly, developing **improved formulations** that are better adapted to field conditions comprises another approach to address immediate patient needs. This involves short pre-clinical studies followed by clinical studies, and the development or extension of a regulatory dossier. Examples of successful improvement of formulations include the two fixed-dose combinations for malaria (ASAQ and ASMQ), and the paediatric dosage form of benznidazole.

In some cases, existing drugs for target diseases are available in certain countries of endemic regions, but fail to reach patients or are underutilized because they are not registered in other endemic countries. Thus **geographical extension of existing drugs** represents another approach to delivering near-term benefits to patients in need.

In support of its approach to clinical development, DNDi will:

- Maintain the capacity to conduct 10 to 12 ongoing trials;
- Further explore critical pathways for developing improved therapies, including NCEs;
- Grow its operations in resource-limited locations and sustain capacity strengthening objectives to serve its clinical development and implementation needs;
- Manage studies according to geographical differences of diseases (e.g. VL);
- Aim for partners to take full implementation responsibility, yet assess needs for pharmacovigilance and develop/support capabilities accordingly (including implementation of risk management plans and Phase IV studies);
- Continue to implement QA/QC procedures and comply with ethical and regulatory frameworks;
- Bridge development and implementation objectives by further empowerment of DNDi Regional Offices;
- Advocate for increased regulatory capabilities in endemic regions to prepare decision-makers (Ministries of Health, National Control Programmes) and healthcare providers to adopt DNDi treatments.

One of the main challenges for DNDi's R&D is the ability to advance the increasing number of new drugs through the clinical development, registration, and implementation processes.

5.2.5 Disease Strategies

To guide all components of DNDi approaches (R&D, policy, access, partnerships) leading to the delivery of new treatments, disease strategies are developed for each of the target diseases, and are reviewed and updated on a regular basis. Beyond the critical role of the Scientific Advisory Committee, ad hoc **disease committees** will be set up to challenge internal approaches, gather input from various stakeholders, and provide insight and guidance (see Section 7).

Full disease strategies are available on the DNDi website.

5.3 | DNDi'S PORTFOLIO

5.3.1 Current Portfolio, October 2011

DNDi's portfolio has grown to 24 projects (with six treatments in implementation phase – four available and two in registration/recommendation phase) from its initial four projects in 2003. DNDi continues to substantially increase the number of clinical research projects and has developed an integrated strategy for drug discovery, which includes risk management strategies to deal with attrition rate associated with drug discovery and development.

5.3.2 Portfolio Development

The main R&D focus is on successfully managing and progressing on-going R&D projects to sustainably 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 and class of compounds – along with review by internal and external experts specialized in the given development stage and therapeutic area.

In addition, the DNDi R&D team continues to build the portfolio of projects for HAT, VL, and Chagas disease through exploratory activities which focus on the pharmaceutical and biotechnology 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 and replace projects in the portfolio when appropriate, allowing the DNDi team to selectively focus on the strongest and most promising activity.

The probability that a given project will lead to eventual drug registration, and the speed of the development processes vary according to the disease, the nature of the compound, the project category, and the stage of discovery or development at which DNDi becomes involved. The risk of compound 'failure' or 'drop-out' is intrinsic to drug R&D and is based on estimated attrition rates.

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

- Objectives by disease;
- Number and status of ongoing projects (see Figure 1);
- Theoretical attrition rates appropriate for not-for-profit drug development⁽¹⁾;
- Potential for addition of new projects at different stages.

Per disease, the portfolio is managed by taking into account the gaps identified within the existing product portfolio and the pipeline projections and objectives (see Section 5.1). For each disease, a hypothetical targeted portfolio has been built – based upon DNDi's experience and adjusted assumptions from its previous Business Plan – and the corresponding financial and human resources estimated (see Section 8).

5.3.3 Discovery Projects

DNDi's objective is to maintain four series of compounds to feed the pipeline for the three kinetoplastid diseases: Human African Trypanosomiasis, Leishmaniasis, and Chagas Disease.

Compounds in discovery projects are initially tested against all kinetoplastids. Based on the data at this stage, a decision is taken 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 the hits are explored for selectivity, and (c) lead identification, where further *in vitro*, *in vivo*, and ADME (absorption, distribution, metabolism, and excretion) studies identify a small series of compounds for lead optimization.

Should DNDi sufficiently feed its kinetoplastid pipeline by 2015, it may envisage a decrease in the number of compound series to be maintained in 2016. However, additional discovery efforts may be pursued should there be a need to support the potential addition of new disease areas.

(1) Based on Nwaka S, Ridley RG. Virtual drug discovery and development for neglected diseases through public-private partnerships. *Nat Rev Drug Discov.* 2003 Nov;2(11):919-28.

5.3.4 Human African Trypanosomiasis (HAT)

DNDi has two target product profiles (TPP) for HAT (*T. b. gambiense* and *T. b. rhodesiense*). **Priority is given to the development of an oral, safe, effective stage 2 HAT treatment to improve current case management, but ideally to be used with the same regimen for stage 1 HAT** – this would avoid spinal taps that are currently needed to determine the disease stage in patients. Treatment strategies would then be adapted accordingly.

Ultimately, when coupled with new field-adapted diagnostic tools, such a treatment would efficiently contribute to the control and elimination strategies for HAT, even in the most remote areas.

Alternatively, should an NCE developed up to Phase II or Phase III not show sufficient levels of efficacy in stage 2, its development for the stage 1 indication may be considered to offer a short-term alternative to the current parenteral treatment options.

5.3.5 Leishmaniasis

DNDi has one TPP for an NCE for **visceral leishmaniasis**. **The priority is to develop an oral, safe, effective, low-cost, and short-course (≤10-day) treatment** that could replace current treatments, improving and simplifying current case management. Ideally, this treatment would be effective against all forms of disease and adapted for use in peripheral health centres.

Unless the NCE demonstrates very short treatment duration (≤3 days), low potential risk for resistance development, and high ease of use, the objective will be to develop a co-administration of two drugs that are field adapted, therefore easy to deploy by the national programmes, and useful in preventing the development of resistance to each of its components.

Although the ideal TPP is to develop one NCE that would show similar efficacy in all VL-endemic regions, data tend to show that geographical differences of the pathogens exist. It may thus be necessary to adjust the treatment strategies accordingly, a factor that will be assessed throughout the course of development.

For **PKDL** (post-kala-azar dermal leishmaniasis), DNDi's objective is to develop a treatment that is shorter course and better tolerated than the currently used long-course antimonial, using existing medications but potentially combining them with an immune stimulant.

For **HIV-VL** co-infected patients, the minimum objective will be to find treatment options that would limit VL recurrences.

TPPs for PKDL and HIV-VL co-infection will be developed in 2011 and the respective strategies refined.

DNDi's development approach for **cutaneous leishmaniasis (CL)** will be pragmatic and opportunistic, and no discovery stage project will be initiated. As CL is a complex disease, with a number of clinical forms of varying severity, the focus will be on those causing the highest public health burden. Once successful treatments have been developed for the latter, their potential for treatment of other forms of the disease will be assessed.

DNDi's objective will be to develop a treatment for patients with CL caused by *L. tropica* and *L. braziliensis*, looking essentially at 'low hanging fruit' approaches based on existing treatments or drugs in development. The treatment should be of shorter duration (<21 days for oral), safe, and effective, with no need for close medical supervision.

The CL strategy will be further refined in 2011.

5.3.6 Chagas Disease

For Chagas disease, DNDi has one TPP for **an effective and safer oral treatment for the chronic form of Chagas disease**, ideally effective also against the acute form of the disease.

Depending on the efficacy and safety results, a combination treatment may be considered to optimize the use of each component, reducing the treatment duration and possibly improving the tolerability of each.

DNDi will also support the development of **biomarkers** to gain understanding of the disease pathology, ease the development of diagnostic tools, and support drug development (see Figure 8).

5.3.7 Malaria

Two fixed-dose combinations were developed by DNDi with its partners.

The first – ASAQ, artesunate + amodiaquine – has now been successfully developed, prequalified by WHO, registered in 30 African countries and India (with over 80 million treatments distributed by the end of 2010). Technology transfer to Zenupa is underway for ASAQ.

The second – ASMQ, artesunate + mefloquine – was registered in Brazil in 2008 and is now in the process of being registered in other Latin America countries as well as Southeast Asia and India. DNDi's objective will be to complete the current clinical activities on ASMQ in Africa and support the ongoing access issues until adoption and implementation is in place.

DNDi will not be involved in further development of anti-malarial agents and plans to transfer its portfolio to partners by 2014. DNDi will apply lessons learned from its malaria mini-portfolio to the management of other disease portfolios.

5.3.8 Other Neglected Disease Projects

DNDi will continue to advocate for neglected disease R&D and play a pivotal role among stakeholders. Fulfilling its role as an 'incubator' for neglected disease R&D solutions (see Section 4.5), DNDi will maintain an opportunistic approach for other neglected diseases, developing specific strategies when appropriate. However, considering the significant investments in the new helminth and paediatric HIV mini-portfolios, DNDi will finalize the pilot phases of these before launching new R&D initiatives.

5.4 | PAEDIATRIC HIV

To meet the specific needs of paediatric HIV patients (see Section 3.2.3), DNDi's objective is to develop an improved first-line treatment for infants and young children under three years of age that is low cost, easier to use, and better adapted for this age group.

5.4.1 Opportunities for Consideration

The scope of the paediatric HIV mini-portfolio is dedicated to the needs of children with HIV under three years of age in need of first-line therapy, regardless of prior ARV exposure. DNDi convened, in April 2011, a panel of paediatric HIV experts to define the TPP and identify the gaps and opportunities.

The current TPP includes: appropriate dosage forms usable across WHO weight bands, high genetic barrier to resistance, no cold chain needed, well tolerated, no lab monitoring required, and affordable. Ideally, the treatment will also be compatible with TB medicines. Exploratory activities have been initiated. The TPP is available on DNDi's website, and a detailed strategy will be developed in 2011.

5.4.2 Project Implementation

DNDi will partner with organizations with demonstrated experience in HIV R&D. Potential development partners will likely include generic and pharmaceutical companies, academic groups in African countries, NIH, MRC, ANRS, as well as implementation partners such as the UNITAID Medicines Patent Pool, the Clinton Health Access Initiative (CHAI), MSF, and National Control Programmes.

DNDi's approach consists of the following phases:

- **Pilot phase:** full assessment of opportunities, feasibility (including laboratory work), and adjustment of the strategy, with an estimated budget of approximately EUR 2 million (by end of 2012);
- **Development phase:** two to three projects to be developed by DNDi, with an estimated budget of EUR 10 to 15 million (2013-2015);
- **Adjustment phase:** adjustment of approaches taken, according to needs and impact, and potentially stop, grow, or spin off the activity (after 2015).

5.5 | HELMINTH INFECTIONS

To meet the specific need introduced in Section 3.2, DNDi's objective is to develop a new treatment that can be used by Mass Drug Administration (MDA) programmes devoted to the control and elimination of onchocerciasis and lymphatic filariasis (LF) in *Loa loa* co-endemic regions. A drug with **macrofilaricidal** activities has the potential for broader treatment with greatly reduced treatment cycles (still within MDA programmes) for onchocerciasis and LF in other regions, thereby reducing drastically the length and number of MDA campaigns. The TPP will be defined in 2011.

5.5.1 Opportunities for Consideration

Flubendazole has been identified as the immediate opportunity. Additional opportunities will be assessed through a landscape analysis, with the intention of selecting one or two candidates emanating from the animal health industry or leads in development in biotechnology and academic labs.

5.5.2 Project Implementation

Potential partners have been identified, including Michigan State University and McGill University. Additional potential partners will be sought in 2011, and will include pharmaceutical and biotechnology industry and academic collaborators.

DNDi will adopt a phased approach (2011-2012: approximately EUR 4.5 million; 2013-2015: approximately EUR 10 to 15 million) to managing a well-focused mini-portfolio.

06.

ACCESS STRATEGY

The objectives of DNDi's Access Strategy can be summarized as follows:

- Facilitate maximum impact via appropriate use of treatments
- Assure effective transition of treatments to relevant access partners and implementers, including National Control Programmes, WHO, and NGOs
- Demonstrate success and secure funding for follow-up R&D programmes.

6.1 | DNDi APPROACH TO ACCESS

6.1.1 DNDi's Access Guiding Principles

The Board of Directors approved in 2009 the *DNDi Access Guiding Principles* that bring further clarity to the organization's role in and approach to access. This policy, which has been an effective tool to guide actions at global policy and treatment levels, will be revised on a regular basis.

As DNDi and its partners will be bringing more treatments to patients, analysing successes and challenges will enable the organization to further elaborate its access strategy, taking into account the evolution of the neglected disease landscape (see Section 3) and associated gaps.

6.1.2 Bridging Global Health Concerns and Product-Specific Issues

Access-related issues can be analysed by means of two different approaches, which are not antagonistic, but meet different expectations:

- The **public health approach** (e.g. Harvard analytical framework⁽¹⁾ – architecture, availability, affordability, adoption) allows for addressing macro-level challenges and structuring thinking around critical access gaps, and adequately supporting implementation of essential medicine policy at WHO level;
- The **product development approach** (i.e. pharmaceutical operations) supports operations at treatment level with processes and skill sets that are also more familiar to industrial partners.

These approaches will sustain DNDi's ability to organize its operations and communication – internally and with third parties.

At treatment level, DNDi will develop a more segmented approach, given the diversity of operations involved: operational components (needs assessments, regulatory affairs, uptake in national protocols, manufacturing and supply, economic affairs, distribution) will be addressed according to each professional practice – with some impact on the organization and skill set of DNDi.

(1) Frost, Laura J., and Reich, M. 'How Do Good Health Technologies Get to Poor People in Poor Countries?' Cambridge, Harvard Center for Population and Development Studies, March 2009.

6.1.3 Building on Lessons Learned from Products in Implementation Phase

Lessons learned from the first years of DNDi have highlighted several key success factors to build upon:

- The **early set up of the TPP** in close collaboration with stakeholders is vital;
- The **choice of industrial partner(s)** is critical and terms of reference for implementation phase should be defined and agreed upon as early as possible;
- R&D alone is not sufficient: Even in the context of DNDi's collaborative model, **additional skills** and operations are needed to prepare and deploy the implementation phase, such as policy-making, manufacturing, distribution, and supply;
- **Importance of anticipation:** Planning ahead, with a view of the critical issues that will arise in later stages, is needed especially to select and manage partners, adjust DNDi's own contribution, design effective transitioning phases, and eventually ensure timely delivery to patients;
- Relevance of the ability to **operate locally:** Regional Offices have been instrumental and have demonstrated impact. It is vital for DNDi to further grow its local capabilities to understand regional policies and orientations, analyse markets, and implement treatments;
- **Capacity strengthening is not a 'nice to have'** mission: It is a key component to prepare uptake and ensure sustainability through platforms, networks, pharmacovigilance training, and technology transfer;
- **Adaptability and flexibility** to best fit the local situation are required to complement DNDi's guiding principles.

Experience has also confirmed that there is **no single access model**. As mentioned in Section 4, according to projects and countries, DNDi will continue to adjust its approach as needs demand. The objective remains to choose sustainable partners, to have limited post-registration activities, and to ensure timely hand-over of projects.

For each disease and project, DNDi will define **access plans** that will synthesize all components of access, including advocacy. In particular, each plan will define 'when to stop' (usually uptake in national programmes in key endemic countries) and metrics for success.

DNDi will develop a more detailed access approach to guide its action, stimulate its response, and better engineer and control partnerships. **Additional guidelines** will be developed (including checklists, roadmaps, SOPs) to help Heads of Programmes and Regional Office Directors or Heads to get prepared for implementation.

6.2 | ACCESS PHASES

DNDi's initial access strategy was to develop products to registration and then rely on implementation partners to ensure effective availability to patients. Experience has shown that access does not only relate to post-registration activities, but encompasses at least three different phases in which DNDi's role will differ according to specific needs. In the base case, DNDi's role at each access phase can be summarized as follows:

- **R&D:** DNDi will address access issues through the process that includes needs assessments, design of the TPP with key stakeholders, selection of partners, organization of clinical operations, design of networks that can support uptake, etc;
- **Implementation** (registration, recommendation, and early adoption): DNDi's role is one of facilitator, relying as much as possible on the partners contracted upstream. DNDi will collaborate with WHO and National Control Programmes to influence health policies, benefitting from its position as a trusted partner to support uptake of treatments. DNDi can also be involved in implementation studies that will document patient benefits in a specific geographical setting;
- **Sustainability** (ability to serve patients in the long term): DNDi's action will be limited. Upstream contributions (such as capacity strengthening or promoting IP-free agreements) will produce their effect during this phase. DNDi may contribute to pharmacovigilance and best use of treatments. It will contribute to assessing outcomes (see below), controlling partners' engagements, and enabling technology transfer when appropriate.

6.3 | EMBEDDING ACCESS INTO DNDi OPERATIONS

Based on analysis of needs and lessons learned from its treatments and pipeline, rather than establishing an 'access department', DNDi has chosen to embed access into each component of its operations, combining activities from Regional Offices and Headquarters. **DNDi's vision on access is to grow operational leadership in endemic regions.**

As reflected by the organization as described in the next section, access will be transversal, and will be developed throughout the three following areas of the organization:

- R&D and medical affairs;
- Policy and advocacy;
- Operations, including Regional Offices, partner relations, supply chain management, market analyses (i.e. all access-related operations not directly linked to R&D or policy-making).

In addition to contributions from each department, an Access Committee will be set up to ensure strategic coherence of access-related activities (at product, country, or policy level) and overcome obstacles. Led by DNDi's Executive Director and composed of the Executive Team, the Access Committee will also involve, depending on topics addressed, Regional Offices and Heads of Programmes. An annual work plan will be set up and reviewed regularly.

Heads of Programmes (part of R&D) will act as coordinators of access plans at product and disease levels. They will support the other two pillars of access plans (policy and operations).

The role of **Regional Offices** will be reinforced, especially with the development of **policy, uptake, and communication capabilities**. They will also play a key role to leverage platforms and networks (and Founding Partners when appropriate) to make the case and ensure timely adoption of treatments and advocate for adapted frameworks for neglected diseases.

In addition to Heads of Programmes and Regional Offices, DNDi will grow its internal capability to develop contracts and **manage partners with in-house expertise in market analyses, supply, and distribution**. As part of the DNDi Business Development team, a new manager will act as internal consultant for the development of access plans (project and regions) or business cases. The team will also lead specific processes or studies on an ad hoc basis (e.g. technology transfer). The manager will also serve as secretary to the Access Committee. This internal expertise will be complemented with local experts in endemic regions as well as global technical experts in relevant fields.

6.4 | ASSESSING OUTCOMES AND IMPACTS

DNDi's success has largely been measured by the number of treatments made available. The objective of delivering 11 to 13 treatments in 15 years remains the cornerstone of its mission. It is now necessary to develop methodologies and tools to better document outcomes of its model, resource investments, and activities.

Building on current practice, DNDi will systematically include clauses in contracts with its partners that enable the organization to access information to assess partners' engagements.

Bearing in mind the complexity and costs of such assessments, DNDi will have a balanced approach to its resources allocated to such analyses, including specific audits and case studies, growing toward a more systematic approach over time, with the following objectives:

- Assess the health impact of each treatment;
- Enable risk/benefit ratio assessment post-implementation (directly or more often via partners);
- Feed understanding of disease epidemiology;
- Evaluate partners' impacts – from contracting phase onwards – and isolate DNDi-specific contribution;
- Ensure DNDi is implementing relevant access models;
- Learn lessons and adjust partnerships or models.

In addition to improving access outcomes, DNDi will use the outcome of these assessments to support fundraising and to nurture advocacy on the relevance and effectiveness of its model.

07.

ORGANIZATION & GOVERNANCE

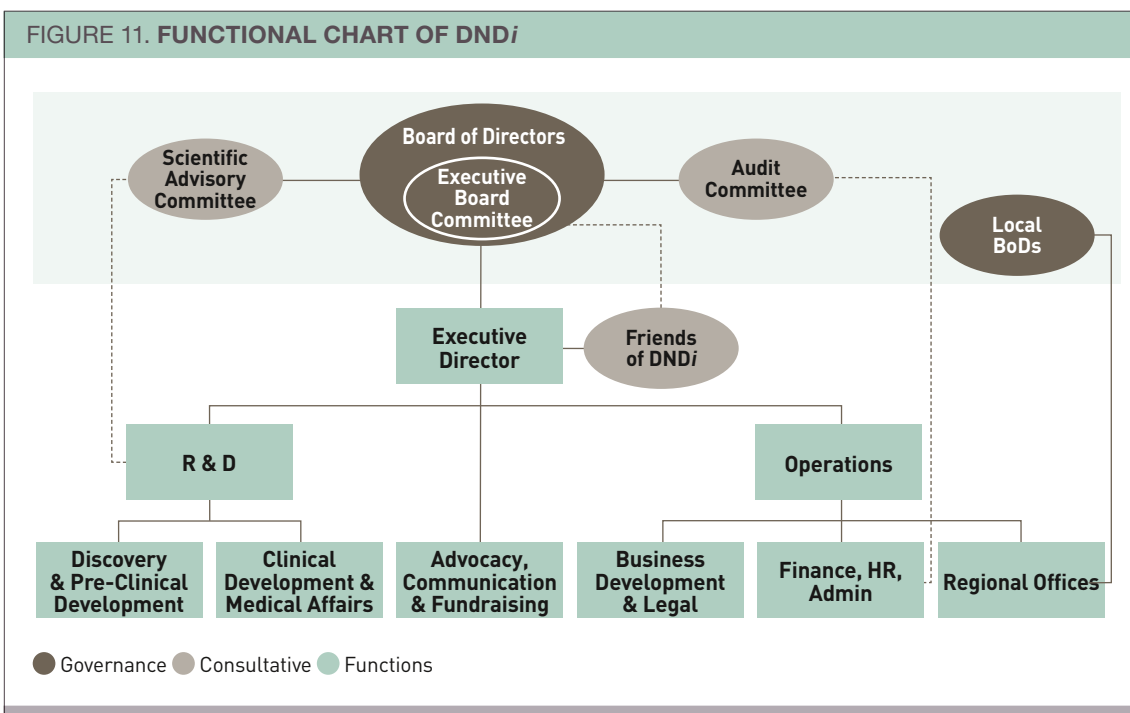
Governed by the Board of Directors, with the Scientific Advisory Committee, Audit Committee, and Executive Board Committee providing key scientific and management guidance for decision making, the DNDi Executive Team implements the R&D strategy, manages the global portfolio, allocates resources, raises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

Fully embedded in DNDi's operating model, Regional Offices will be further empowered to support or drive activities locally.

7.1 | ORGANIZATION & MANAGEMENT OVERSIGHT

DNDi oversight operates at two levels: Governance and Executive. 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 function of the Board of Directors is to exercise ultimate authority over DNDi activities according to the statutory documents (charter and organizational by-laws).

The Board of Directors delegates the coordination and implementation of DNDi's objectives and actions as well as day-to-day management to the Executive Team led by the Executive Director.



7.2 | GOVERNANCE

The **Board of Directors** is comprised of ten to thirteen members with each of the Founding Partners nominating one board member, in addition to at least one patient representative. In 2011, the Board of Directors is composed of twelve members and one permanent observer from WHO/TDR. The chair of the Scientific Advisory Committee and the Executive Director are permanent members.

Both Founding Partners' representatives and additional board members are experts in their respective fields and have been chosen for their commitment to the public interest, technical credibility to oversee executive activity, integrity, and skill in ensuring adherence to DNDi's vision and mission. Procedures for Board of Directors' meetings and Board of Directors' list of duties and powers are defined in the statutory documents.

The Board of Directors deemed necessary the creation of three committees for the implementation of the vision and mission of DNDi:

- The **Scientific Advisory Committee (SAC)** is composed of prominent scientists with expertise in various scientific disciplines relating to drug discovery and development, and/or to the targeted neglected diseases and patients. The SAC operates independently of the Board of Directors and the Executive Team. Its mission is to advise the Board of Directors on matters related to R&D and choice of projects as well as on the quality of DNDi's scientific output. Executive and Scientific Directors can consult with the SAC;
- The **Audit Committee** is responsible for selection and oversight of the work of the auditors, recommending financial policies, reviewing financial statements and supervising DNDi investments. Independent and external to DNDi's operations and management, this committee undertakes controls and monitors compliance to DNDi's statutory provisions and legal standards. The Audit Committee reports to the Board of Directors and to the Swiss Supervisory Board for Foundations any irregularities noted during audits;
- The **Executive Board Committee** oversees all DNDi activities and gives recommendations to the Board of Directors when decisions have to be made. It interfaces between the Board of Directors and the Executive Team, and supports the latter in moving forward to implement DNDi's strategy.

DNDi's operational policy framework includes its Charter and By-laws, Code of Practice of the Scientific Advisory Committee, R&D Guidelines, Intellectual Property Policy, Access Guiding Principles, Human Resources Policy, Fundraising Policy, Travel and Reimbursement Guidelines, and Financial and Management Procedures.

On a yearly basis, the Board of Directors conducts a risk assessment.

7.3 | COORDINATION & IMPLEMENTATION

7.3.1 The Executive Director and the Executive Team

Remaining small and leveraging external expertise, the DNDi Executive Team is led by the Executive Director. This team includes the R&D Director, Medical Director, Discovery & Pre-Clinical Director, Fundraising & Advocacy Director, Finance, Human Resources & Administration Director, Business Development Director, and Operations Director.

The Extended Management Team, in addition to the Executive Team members, includes the Directors of Regional Offices and Heads of Programmes.

The Executive Team is responsible for:

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

The **Executive Director** (ED) reports to the Board of Directors. The ED supervises all operations within DND*i* and maintains an effective, motivated, competent, and regulatory-compliant organization to achieve business goals. The ED is responsible for ensuring that a quality control system is implemented and works with the Board of Directors to develop and implement corporate strategy. The ED represents DND*i*'s vision and mission and drives policy issues.

The **Friends of DND*i***, comprised of representatives from all continents, are leaders in their fields, which are highly relevant to DND*i*'s vision and mission. The Friends of DND*i* function as ambassadors and facilitate access to high-level private and public decision makers. Managed by the Executive Director, they have no decision-making power. Their nomination is approved by the Board of Directors.

An **Access Committee** will be set up as an internal decision-making committee at the management level to develop and control guiding principles, ensure oversight and appropriate allocation of responsibility within the organization (see Section 6.3).

DND*i*'s organization is based on the corporate functions described hereafter.

7.3.2 R&D

The R&D Director's first priority is to maintain a well-balanced project portfolio to deliver upon disease objectives. Supported by the Discovery & Pre-Clinical Director and the Medical Director, the R&D Director oversees disease R&D activities, leads transitioning phases, and ensures optimum involvement of regional collaborators in Asia, Africa, and Latin America. Heads of Programmes play a leading role at project level, leveraging internal and external expertise to design, manage, and evaluate projects and partners in R&D phases. The R&D Director consults with the Scientific Advisory Committee (SAC) as appropriate.

Ad hoc Disease Committees will be set up for each disease to provide input to DND*i* operations. These committees, comprised of external advisors, will neither have decision-making power nor impact scientific choices. Rather, they will provide policy advice, including technical considerations, to support and challenge the DND*i* teams working on specific diseases, and expand networks to facilitate adoption of treatments. Connected with the disease experts of the SAC and the leaders of the platforms, the Disease Committees will be very flexible, working with clear, agreed-upon objectives.

7.3.3 Advocacy, Communication & Fundraising

The Fundraising & Advocacy Director (FAD) is responsible for designing, implementing, and evaluating communication, advocacy, and fundraising strategies. The FAD oversees wide, timely, and strategic dissemination of information on DND*i* and research in the field of the most neglected diseases. Target audiences include national and international political leaders; the scientific community; Founding Partners and Friends of DND*i*; the pharmaceutical and biotechnology industries; donor countries and organizations; and the media.

The development of communication and advocacy tools and the overall communication and advocacy agenda is tailored to support all DND*i* initiatives, from scientific communication to local disease campaigns. In addition, advocacy and communication strategy is coordinated in conjunction with DND*i*'s fundraising strategy. Communication, advocacy, and fundraising staff in Regional Offices are part of the global communication, advocacy, and fundraising team.

7.3.4 Operations

With the maturation of its portfolio, the addition of new disease areas, and the process of empowering Regional Offices, an Operations Director (OD) position has been created. As the OD will manage a large range of operations within DND*i*, including Regional Offices, the Executive Director's leadership will be more strongly focused on strategy, policy-making, fundraising, and access.

The OD has been recruited in 2011 to address coordination needs at the executive level, particularly operational excellence (preparation and implementation of Action Plans fully articulated with DND*i* strategy; operational coordination throughout the organization) and international infrastructure and corporate development.

In this role, the OD will act as an enabler for growth and effectiveness coordinating Regional Offices and support services to the organization.

7.3.5 Finance, Human Resources & Administration

The Finance, Human Resources & Administration Director (FHRAD) oversees accounting, finance, and relationships with auditors and controllers. The FHRAD supports the organization on governance and compliance to legal and regulatory frameworks and is responsible for all human resources. The FHRAD is in charge of setting up and maintaining an efficient global DNDi IT infrastructure. Finance, Human Resources, and Administration will be supervised by Operations. The FHRAD also directly reports to the Audit Committee on relevant issues.

7.3.6 Business Development

Since the set-up of this function in 2007, the Business Development (BD) team has implemented the development of contractual procedures and a contract management system, elaboration of a new contractual framework to better secure patient access to drugs, and greater DNDi presence in the private sector, notably with several major private companies. The BD team has also contributed to identifying strategic R&D opportunities and refining the portfolio of collaboration models and DNDi's intellectual property strategy. Business Development activities will now go beyond service provision (including legal issues): new tools and methods to improve procurement, contract management, and partner performance will be developed, in addition to the management of new partnership frameworks. Supervised by Operations, the Business Development Director will:

- Provide guidance for negotiations and drive the in- and out-licensing processes, including technology transfer;
- Grow understanding and knowledge of market trends and drivers (including supply chain issues);
- Coordinate and lead efforts to assess costs and develop economic analyses throughout the model;
- Coordinate Business Development activities with Regional Offices.

7.4 | AIMING FOR PROCESS EXCELLENCE

DNDi has built its success on the entrepreneurship and stamina of its people. This corporate culture of dedicated team members contributing their skills and expertise to DNDi with passion will be preserved as new members join the organization.

From an effectiveness and risk management perspective, DNDi will further develop processes and operating guidelines to ensure sustainability and alignment, as well as to prepare for growth and new alliances. This process, to be led by the Operations Director, is aimed at developing the organizational tools necessary to manage a 'vision to impact' continuum, including knowledge management tools and practices.

More specifically, appropriate mechanisms will be put in place to enable the empowerment of Regional Offices and thus gain an appropriate balance in what is undertaken locally versus at Headquarters.

7.5 | EMPOWERING REGIONAL OFFICES

The new momentum of Regional Offices is a cornerstone of DNDi's strategy for the coming years. Initially designed to validate the DNDi model and facilitate interaction with Founding Partners, regional 'liaison offices' have increasingly contributed to the success of projects. Considered as 'Regional Support Offices' over the last four years, DNDi is now ready to further empower its 'Regional Offices' as an even more critical component of its model.

7.5.1 International Infrastructure

Regional Offices vary in terms of their status as legal entities, missions, geographies, and platforms. Consistent with its flexibility and pragmatic approach in all components of its alternative model, DNDi does not intend to deploy one single framework and is adapting its international presence to local needs.

In 2011, DNDi is embedded in seven countries, with four offices in endemic countries in Latin America (Brazil), Asia (India and Malaysia), and Africa (Kenya); one affiliate in Northern America (USA); one office in Japan; and one Liaison Office in the Democratic Republic of the Congo. While the latter's initial objective is to contribute to HAT projects, it may also contribute to future projects in DNDi's helminth portfolio.

Based on needs, new offices may be set up in the future, whereas existing offices may make necessary adjustments in their operations accordingly. With the launch of the paediatric HIV portfolio and the adjustments of the Lead Optimization Consortia, DNDi may develop Liaison/Regional Offices in South Africa and China.

Most offices have their own local legal entities (either as branches or under local status for not-for-profit organizations), and some have their own local Board of Directors in compliance with local regulations. In order to ensure consistency within DNDi, appropriate contractual agreements are made to support Regional Offices.

Beyond its institutional presence around the world, DNDi enjoys a network of partnerships in some 40 countries. Nevertheless, DNDi does not intend to 'regionalize' its model (i.e. lead all activities in a given region from the DNDi Regional Office). Instead, Regional Offices will contribute to the identification and management of partners locally.

DNDi's model is unique in that it comprises a diversity of needs-based models that function together to serve one purpose – bringing the best science to the most neglected – with one global organization and strategy.

7.5.2 Scope of Operations

The empowerment of Regional Offices can be understood as a mix of additional responsibilities moving from Headquarters to regions, enabling DNDi to operate in a more effective manner (treatment implementation, national policy-making, drug registration, partner management), combined with more autonomy to identify opportunities and launch initiatives within the scope of DNDi's Action Plan.

Potential responsibilities of the Regional Offices include: identifying potential projects and regional partners; conducting market studies and developing cases for new diseases; undertaking regional advocacy and fundraising work for DNDi; and supporting or leading project management and implementation. Regional Offices will potentially contribute to all activities and processes.

Each office has been developing its own annual Action Plan, which is reviewed by the ED and approved by the Board of Directors as part of the overall Action Plan. From 2012 onwards, each Regional Office will also develop a mid- to long-term strategic plan to have a more sustainable approach to their activities in their region and ensure process alignment with all DNDi activities.

7.5.3 Management

The Regional Offices will be integrated into Operations with a view to achieving coherence in DNDi's international infrastructure as well as for the preparation and implementation of their respective strategies and Action Plans. Regional Office Directors or Heads are an integral part of the Extended Management Team. When an independent legal entity is set up, they are also accountable to their local Board of Directors.

As Regional Offices are embedded in overall DNDi processes and operations, each and every staff member is part of the overall organization, but is also a local employee contributing to DNDi success locally.

Beyond these basic operating principles, the design of a detailed framework of sub-processes and accountabilities mentioned above will facilitate day-to-day management.

7.6 | ACCOUNTABILITY, TRANSPARENCY & ETHICAL PRINCIPLES

DNDi constantly strives for the highest standards of accountability, transparency, and ethics. There are numerous stakeholders to which DNDi is accountable, notably 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 health-related organizations and medical NGOs, and scientific groups that contribute to R&D activities.

The charter and the organizational by-laws oblige the Board of Directors, the Scientific Advisory Committee, and all 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. DNDi will also develop a conflict of interest policy.

It is DNDi's aim to share timely, accurate, and relevant information that enables stakeholders to be aware of its current operations, including critical scientific and financial information. Regular communication via corporate tools such as the annual activity report, e-newsletters, printed publications, website, targeted advocacy, and scientific meetings will be maintained.

DNDi is vigilant regarding ethical issues related to its activities, for instance in the choice of research programmes and projects, and the best use of its resources to address patients' needs. When activities involve human subjects or patients in clinical pharmacology or clinical trials, international ethical standards are followed.

DNDi aims to ensure that appropriate pharmacovigilance activities are included in contracts with pharmaceutical partners and implementers (including Risk Management Plans) and that reporting systems are put into place.

Specifically, as per the R&D Guidelines, 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.

08.

EXPENDITURES

The global forecast for the period 2011 to 2018 is estimated at approximately EUR 300 million, with the desired outcome of five to seven new treatments for neglected diseases and the maintenance of a robust and well-balanced portfolio in the development pipeline to sustain longer-term objectives.

Total expenditure will continue to grow until reaching a maturity level of around EUR 40 million per annum once DNDi has fully developed its new mini-portfolios.

8.1 | TOTAL EXPENDITURE AND ALLOCATION

8.1.1 Overall Expenditures to Meet Objectives

From 2004 to 2010, DNDi brought four new treatments to implementation for a total expenditure of EUR 93.7 million. The growth DNDi has experienced over the last seven years is indicative of the time needed to obtain a balanced portfolio through sourcing in projects at various stages.

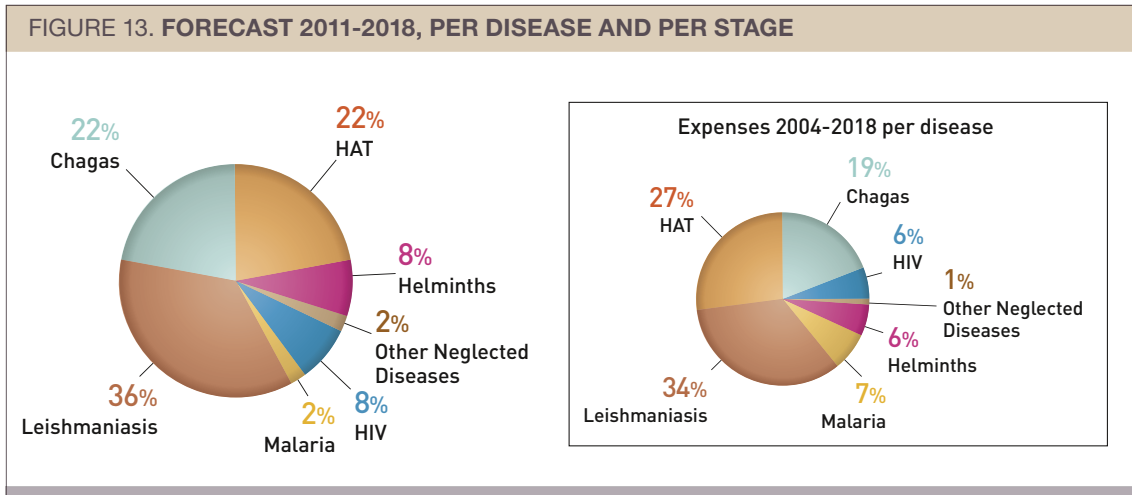
The combination of past spending and forecast for the period 2004-2018 demonstrates that the desired outcome requires an estimated EUR 400 million to reach the objectives.

FIGURE 12. OVERALL INVESTMENT 2004-2018

	2003 -2018	2003 -2010	2011 -2018	2011	2012	2013	2014	2015	2016	2017	2018
Annual budget	395.1	93.7	301.4	29.9	34.3	35.5	40.2	40.8	39.8	40.8	40.1
R&D/project related expenditures	338.4	76.3	262.1	25.6	29.9	30.9	35.0	35.5	34.6	35.5	34.9
Other Social Mission (Policy & Advocacy)	14.4	5.3	9.1	1.0	1.0	1.1	1.2	1.2	1.2	1.2	1.2
Overhead (G&A + Fundraising)	42.4	12.1	30.3	3.3	3.4	3.4	4.0	4.1	4.0	4.1	4.0

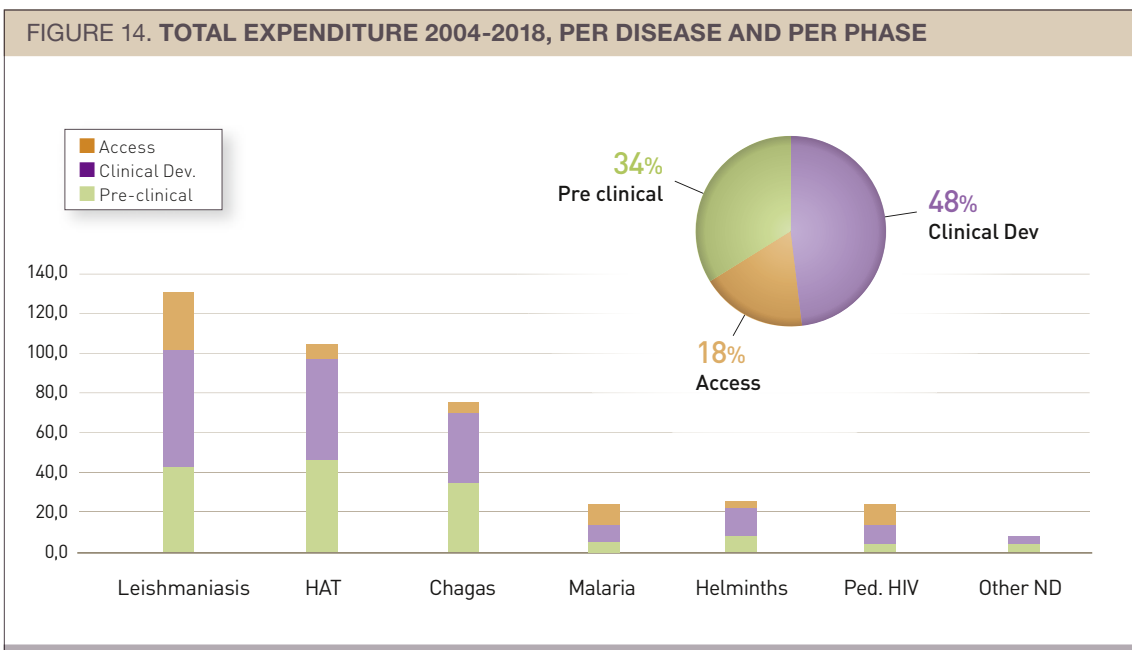
8.1.2 Expenditures by Diseases and by Phase

DNDi's prospective expenditures demonstrate the importance of kinetoplastid diseases in the portfolio, particularly leishmaniasis. DNDi's mini-portfolios (paediatric HIV, helminth infections, malaria, and potentially other NTDs) will represent 20% of overall expenditures, including EUR 6 million to complete the malaria strategy. Overall spending for each of the mini-portfolios will eventually be in the range of EUR 20 million. Budget hypotheses will be confirmed after full development of each business case.



Further analyses by project phase also highlight the distribution of expenditures by disease.

The split of expenditure per disease and per phase highlights the relative importance of investments that will be needed for the implementation phase, as success will grow with new treatments to be registered (or recommended) and made available to patients. Clinical costs remain high as projects move forward in the pipeline, also reflecting the structure of each disease pipeline and the project categories described in the previous sections. Discovery and pre-clinical expenditure demonstrates the ongoing investment of DNDi in providing the best science for the most neglected.



8.2 | METHODOLOGY OF COSTING

Costs were established according to the operational model described in this Business Plan, historical business practices and expenditures of DNDi, detailed 2011-2013 budget projections, and prior benchmarks with similar initiatives.

Elaborating on historical and mid-term budget projections, overall costs over the period were calculated on a probabilistic model associated with attrition, which represented a 'baseline budget' as reported in this Business Plan. This targeted budget must remain flexible as the course of events and the attrition of the projects may induce delays or acceleration of progress. A 10% variation around the baseline should be considered, which also corresponds to DNDi's previous mid-term budgeting exercises.

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 on the ASAQ project, part of the CMC costs were not charged to DNDi, but were considered as in-kind contribution from the partner. In 2010, in-kind contributions were valued at 9% of total expenditure (91% expenditure paid in cash and 9% as in-kind).

DNDi's model does not include any **acquisition cost** for compounds.

Social mission costs and supporting costs are also based on the number of staff employed by DNDi. Current and prospective headcounts are provided in Figure 15, and DNDi's HR policy defines remunerations. Using a balance sheet approach to remuneration, salaries and compensation are adjusted to guarantee an equitable standard of living (whether at Headquarters or in Regional Offices).

Cost estimates include gross salary, social charges and benefits, travels, consumables, IT, and other office costs. Given that DNDi hires highly skilled and motivated individuals who share the organization's mission and vision, salary assumptions have been made accordingly but remain at a reasonable level. On a regular basis, DNDi participates in benchmark studies to assess if its remuneration policy is compliant with the broader not-for-profit sector.

8.3 | COSTS ASSOCIATED WITH R&D, CAPACITY STRENGTHENING, AND IMPLEMENTATION

R&D costs have been estimated on the basis of the projected portfolio:

- For each disease, the number of expected projects to meet 2018 objectives and feed the pipeline for longer term objectives;
- For each project, the development roadmap considering the number of years each project is expected to stay in a given phase.

Costs for each project have been calculated based on an attrition model referred to in Section 5. After seven years of activities, DNDi can look back at historical information and is able to define its estimated R&D costs per phase and per disease. As an example, in 2011, DNDi has four series of compounds in lead optimization for a total budget of approximately EUR 6 million including other R&D costs, with two research consortia, and for three diseases.

Comments on Clinical Development Costs

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

- Clinical development plans will aim to meet regulatory standards by streamlining them as much as possible. They will, for example, focus on the use of new approaches such as adaptive designs whenever possible, that offer the benefit of introducing pre-defined adjustments in the clinical studies, allowing ongoing adaptations (to stop or add a dose, for example), ultimately aiming at reducing time to results;
- The epidemiology of the three primary (kinetoplastid) diseases in terms of geography and morbidity: When a disease affects several regions, efforts will be made to conduct Phase III multicentre international studies, provided that no specific geographical difference was identified in earlier Phase II studies;
- The use and strengthening of existing clinical trial capacities in target disease-endemic countries (i.e. via the LEAP, HAT Platform, Chagas Clinical Research Platform, or other existing clinical trial networks).

DNDi's development costs are relatively close to those of the prior drug development phases, and contrast starkly with development costs for non-neglected disease treatments.

Comments on 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 or the industrial partner for the co-development. 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.

Comments on Implementation Costs within DNDi

Drug candidates such as new chemical entities (NCEs) are developed primarily through partnerships. Registration and recommendation costs are therefore limited.

However, lessons learned from the past experience show that some level of investment in post-registration and uptake phase is still required, especially in deploying pharmacovigilance-related activities. Given DNDi's role of facilitator in the implementation phase, the average time-frame for involvement is four years once treatments are available. Estimated costs have been significantly raised from previous assessments, especially for the first two years of availability, notably because implementation trial studies might be necessary to register a new treatment in a given country.

Comments on Other Costs Integrated in R&D Expenditures

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. In total this represents approximately 15% of the project expenditures. Such costs are related to management and oversight by the R&D team, SAC, Business Development, project selection, Regional Offices in terms of R&D operations, contribution to platforms, and other capacity strengthening activities.

Section 7 provides more details on the contribution of Regional Offices to drug development and treatment implementation.

8.4 | OTHER SOCIAL MISSIONS AND MANAGEMENT COSTS

Advocacy and Communication costs include staff and activities such as external communication, document production, and event organization. These activities are mainly coordinated from Headquarters, but increasingly rely upon the participation of Regional Offices. Historical data show that DNDi on average allocates 4% of its budget to such activities.

Support costs, estimated on an annual basis, utilize a full-cost activity-based method. All associated costs (salaries, social charges, logistics, meetings, travel, office rental, depreciation, IT, etc.) are included in the following expenditure categories:

- **Fundraising** includes activities to target public and private donors as described in Section 9;
- **General management** includes corporate affairs (Board and Audit Committee), executive coordination, human resources, IT, administration, and management of DNDi finances.

Based on several years of DNDi development, these costs are defined as 11% of total budget.

8.5 | COST EFFECTIVENESS

In order to deliver upon its mission, DNDi will not always consider the lowest costs. Serving its capacity strengthening and advocacy objectives may sometime require strategic rather than solely cost-effective choices. With clearly set guidelines, DNDi will need to ensure its resources are delivering the most value to its social mission.

DNDi will continue implementing various initiatives to minimize its costs, including the following:

- Grow its procurement function and project management capabilities to further design project roadmaps and, when appropriate, better identify downstream cost-savings opportunities and in-kind potential;
- Continue challenging some processes, such as Lead Optimization Consortia and more generally consider developing activities in low-cost settings;
- Grow project management capabilities;
- Ask for additional in-kind contributions, especially from pharmaceutical companies, at all stages of development and implementation (annotated series versus mind libraries, time from their employees involved in R&D, knowledge transfer, contribution in endemic countries, and media support for advocacy campaigns);
- Develop *pro bono* partnerships (e.g. with academia: studies on the DNDi model, research outcomes);
- Further consider low cost/high profile individual contributions;
- Develop alliances, especially with other PDPs to synergize costs;
- Contingency planning to handle risks of unmet fundraising objectives.

09.

RESOURCES

DNDi will build on its values and model to grow its core team from 80 to 109 people over the 2011-2018 period. Two-third of this growth will be in Regional Offices.

To reach its objective of EUR 415 million in resources available from 2003 to 2018, DNDi still needs to raise EUR 245 million, including the objective of six months of reserves. DNDi seeks to diversify its funding sources and maintain a balance of public and private donors.

9.1 | HUMAN RESOURCES EVOLUTION

Those working at or with DNDi are proud of their accomplishments, and together, with their unique commitment and skills, have built DNDi's success. **Values** of patient-centredness and concern for the poorest regions and populations of the world, cultural diversity, entrepreneurship, freedom to speak, and pragmatism are critical components of DNDi's first resource: its people. DNDi will continue to look for staff and consultants with diverse origins (geographies, industry, not-for-profit organizations, public or private sector) to sustain this mindset. Surveys are organized every other year to assess job satisfaction.

From the early days when DNDi was launched in an MSF garage, DNDi has grown to a staff of 80 people in Geneva and in Regional Offices. The future state described below reflects positions that are needed to implement the strategy described in this Business Plan, and should be reached by 2014, followed by a period of stabilization.

Two-thirds of the growth of staff will be in Regional Offices, representing a 50% increase of regional staff, whereas staff in Geneva will only increase by 16%.

The figures below include regular staff and expert consultants, and represent full-time equivalents. In 2011, there are 13 FTEs representing **53 individual consultants** throughout the world and who perform various functions.

FIGURE 15. EVOLUTION OF HR – REGIONS AND GENEVA (2011-2018)

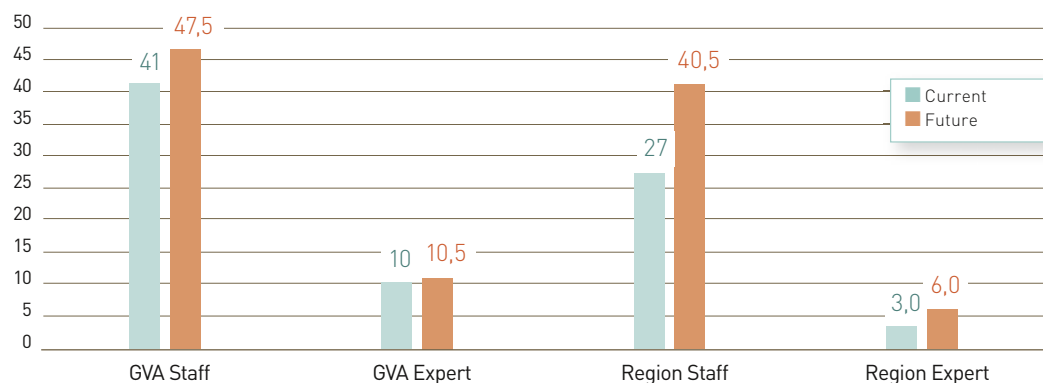
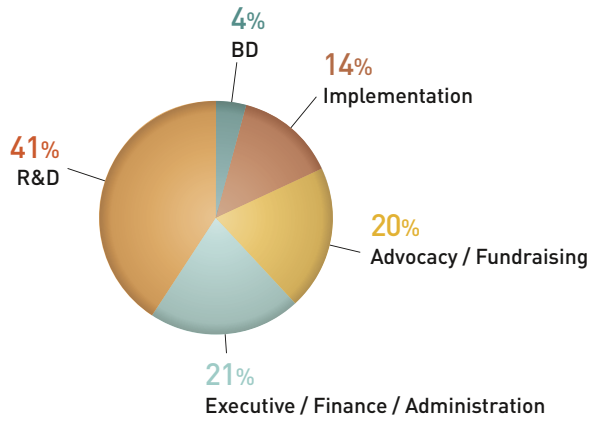


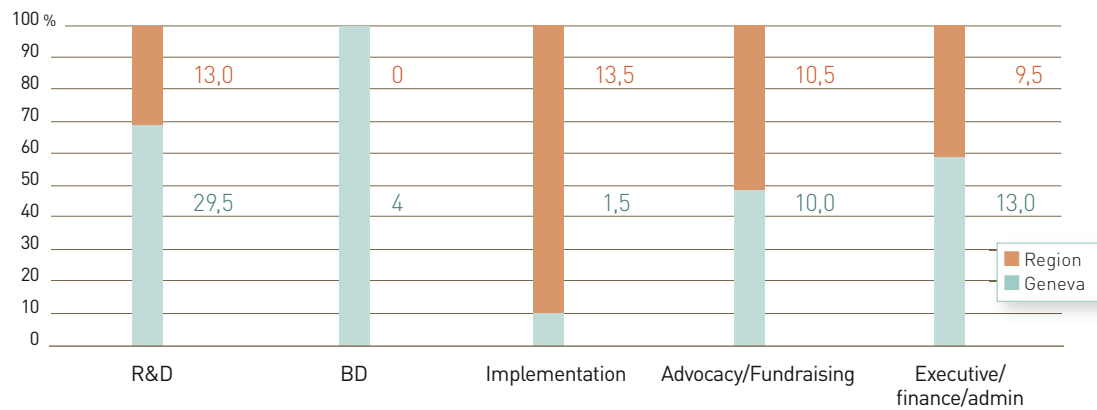
FIGURE 16. BREAKDOWN OF HUMAN RESOURCES BY ACTIVITY



DNDi's mission and achievements have built a reputation, and form a critical asset to be leveraged from a human resources perspective. Increasingly a recognized 'brand', DNDi offers excellent career perspectives in the area of global health and beyond (infectious diseases, communication and advocacy, CSR, to name a few), as well as personal satisfaction. As mentioned in the previous section and beyond its reasonable remuneration policy, DNDi is also willing to further develop its policy to obtain increased involvement of low cost/high potential people (volunteers, trainees, sabbaticals, recently retired) and fine-tune its HR model accordingly.

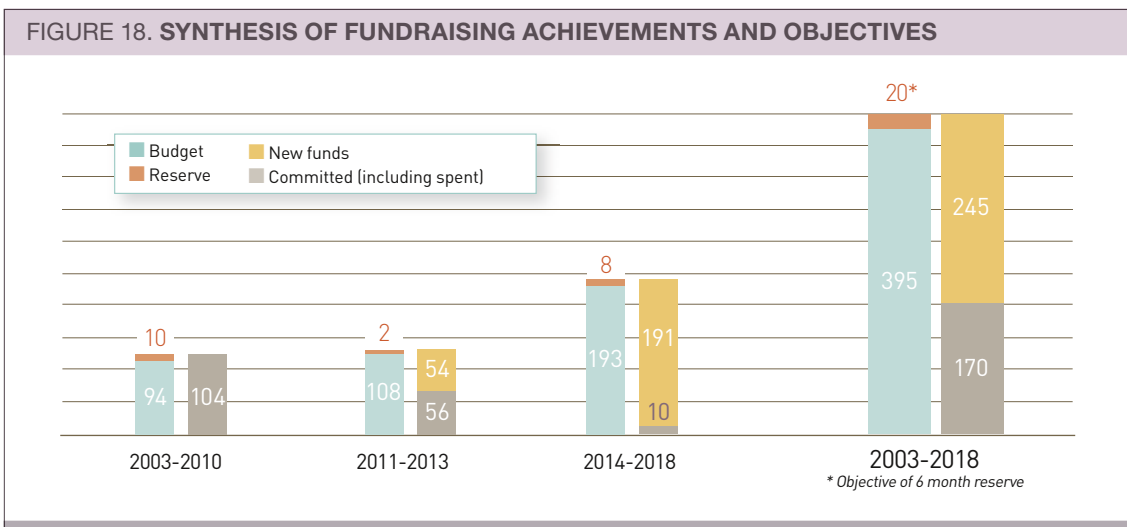
DNDi organizes remuneration benchmarks on a regular basis, with not-for-profit organizations, pharmaceutical industry, PDPs, public health organizations, and academia to adjust its balanced remuneration policy.

FIGURE 17. GEOGRAPHICAL BREAKDOWN OF HUMAN RESOURCES BY FUNCTION (2018)



9.2 | FUNDING STRATEGY & INCOME PLAN

9.2.1 Overall Perspective

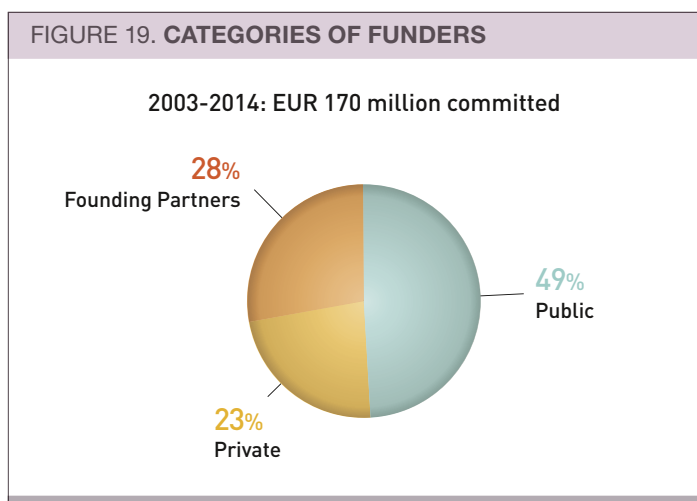


According to expenditures described in the previous chapter, **DNDi needs to raise EUR 246 million in addition to the EUR 170 million already committed or spent.** This amount includes an objective of increasing the reserves by EUR 11 million (in addition to the current EUR 9 million in reserve) to secure six months of activities. This respects good risk management practice for a non-profit organization like DNDi.

9.2.2 Achievements

Including the initial contribution of EUR 25 million from Médecins Sans Frontières, DNDi has successfully raised EUR 170 million since its inception.

This result was achieved with a primary focus on public institutional donors in line with the DNDi objectives of encouraging public responsibility and obtaining substantial public institutional funds. This has been challenging as **few institutions initially had mechanisms to support R&D for neglected diseases and even fewer via product development partnerships such as DNDi.**



During this period, European government agencies such as DFID (UK), DGIS (The Netherlands), AECID (Spain), MAEE & AFD (France), and SDC and Republic and Canton of Geneva (Switzerland) decided to include support to drug portfolio management by PDPs and especially innovation for the most neglected diseases in their respective policies. Other governments may decide in the coming years to increase their commitment to R&D for neglected diseases, as was recently the case with Germany.

To facilitate this process, DNDi targeted advocacy to inform and influence policymakers on the need for R&D for neglected diseases, patient needs, and DNDi's model. However, despite these successes, funding gaps remain.

In addition, major research funding sources such as the FP7 (EU) and NIH (USA) have not yet committed to supporting PDPs, due to the fact that they lack adequate institutional mechanisms to support portfolio management.

With the exception of the Bill & Melinda Gates Foundation, the Wellcome Trust, and Médecins Sans Frontières, few private donors and foundations have supported PDPs. DNDi has managed to secure several grants from private foundations, mainly in Europe. The international financial crisis starting in 2008 was a major obstacle to DNDi's first steps into private fundraising. Nevertheless, DNDi will continue to invest human and financial resources for developing the support from such organizations – primarily in the USA, Europe, and in emerging economies (Latin America, Asia, Middle East).

9.2.3 Fundraising Policy

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

- DNDi's independence is a cornerstone of its development: diversified funding sources are necessary to avoid dependence on any specific donor. Every effort will therefore be made to ensure that no one donor contributes over 25% of all donations, and that earmarked donations are minimized as much as possible. The Board of Directors defines funding parameters that serve to guarantee independence;
- 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, DNDi's priority is to raise unrestricted core funding versus project-specific or earmarked funding. In cases where this is not possible, DNDi will pursue this type of funding without requirements that interfere with the objectives of the project;
- 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 is conducted on DNDi accounts and is made available to the public;
- DNDi reserves the right to pursue its mission and R&D projects based upon patient needs and scientific merit;
- DNDi does not accept contributions from:
 - Corporations (which includes companies and corporate foundations) that derive their income from the production and/or sales of tobacco, alcohol, or firearms
 - Groups and individuals who encourage racism or intolerance
- DNDi provides appropriate recognition of donor support, except when the donor prefers to remain anonymous;
- Before accepting anonymous contributions, the Board of Directors seeks advice from lawyers or national authorities;
- The Board of Directors may refuse contributions that could negatively affect the image or the social mission of DNDi;
- The terms of use of DNDi's logo and brand by the donor and the use of the donor's logo and brand by DNDi are agreed by mutual consent at the time of the contract.

9.2.4 Sources of Funding

DNDi seeks additional in-kind contributions from its development and implementation partners (especially pharmaceutical companies), in order to potentially reduce expenditure or provide more value to projects and ultimately to patients.

DNDi's funding mix will change slightly from year to year. The funding projection will depend on a significant increase in private funding, primarily from foundations and other major donors, the setup of new funding mechanisms, and some general public funding.

Increased in-kind support from partners, especially pharmaceutical companies, will continue to be strongly encouraged during the period and is expected to complement financial income.

FIGURE 20. PROSPECTIVE SOURCES OF FUNDING – MID-TERM ANNUAL ESTIMATES (IN EUR)

Public		Private	
Established public donors for R&D	15-18m	Large foundations	12m
Emerging countries	3m	Founding partners	3-6m
New Funding Mechanisms	3m	Other private funders	3-5m
Total public	21-24m	Total private	18-23m

Governments and International Organizations

DNDi aims to continue to stimulate increased involvement and responsibility of national governments and international organizations in R&D for neglected diseases. In as much as possible, DNDi will strive to obtain, on a cumulative basis over time, **at least half of its funding from public sources**. DNDi can achieve this objective with a mix of a minimum of six already-established public donors with multiyear commitments of EUR 2 to 3 million per year.

Donor prospects for governments and international organizations include:

- Governments that have a clear track record in supporting overseas aid development. In addition to the United Kingdom, France, Switzerland, The Netherlands, and Spain, DNDi will seek to maintain funding from these countries while pursuing support from other countries such as the USA, Germany, Japan, and Nordic countries.
- DNDi also seeks to involve emerging economies and governments in regions where neglected diseases are endemic – in particular Brazil, India, and Malaysia (where DNDi Regional Offices are located).
- Institutional funders and science agencies, such as the EU and the NIH will be encouraged to provide more support to DNDi and PDPs in general. Other international institutions will be approached by DNDi Regional Offices. Mechanisms such as EDCTP could play a critical role in supporting and strengthening clinical research capacities in endemic countries, particularly in Africa and Latin America.
- UN agencies (especially WHO, UNICEF, UNDP), the Global Fund to Fight AIDS, Malaria and Tuberculosis, and the World Bank, will be regularly briefed on DNDi activities due to their influence in recommending, purchasing, and funding developing country purchases of drugs for neglected diseases.
- Innovative and sustainable funding mechanisms, such as UNITAID, should be continually explored and encouraged, in particular for late stage development and implementation phase to ensure successful access to new products being developed.

Private Foundations and Major Private Donors

DNDi will also secure a significant part of its funding from foundations or individual philanthropists based in North America, Europe, Asia, Latin America, and the Middle East. Specific attention will be given to developing private donor prospects in the USA and Europe through regional liaison networks. Prospects will be identified through existing networks and especially via the Friends of DNDi.

Large private foundations, such as the Bill & Melinda Gates Foundation, the Rockefeller Foundation, the Wellcome Trust – all renowned leaders in the field of neglected disease innovation and funding – will be pursued as key partners during this period.

Offering the possibility to any individual to support DNDi's activities is another way of creating engagement in global health and neglected patients' needs. While DNDi is not well suited for mass general-public fundraising campaigns, it will seek limited general-public support through targeted campaigns.

Founding Partners

During the launch period of the initiative (2003-2008), Médecins Sans Frontières provided an initial EUR 25 million to support DNDi, with an additional commitment of EUR 18 million through to 2014. DNDi will seek continued core funding from MSF. To date, other Founding Partners have provided in-kind support such as office space, administrative staff, and meeting organization. For the 2011-2018 period, DNDi will continue to encourage this support and seek an increased commitment of financial and/or in-kind support for project implementation. The targeted Founding Partner support is at least 15% of the total income per year.

DNDi Regional Offices have begun to explore fundraising potential in their respective regions. They will be further engaged in achieving regional fundraising objectives. DNDi will also explore untapped or recent bilateral funding opportunities.

The **Friends of DNDi**, a group of exceptional individuals committed to DNDi's vision and mission, have a crucial supporting role in DNDi's fundraising strategy. Raising awareness of the need for neglected disease R&D in their respective regions and networks, the Friends of DNDi facilitate privileged contacts with private foundations, potential individual donors, and high-level government decision makers.

In conclusion, the funding opportunities and outlook are reasonably favourable. Building on its success to date – strong public and private partnerships and a clear position in the new landscape of R&D for neglected diseases – DNDi is well positioned to obtain the funds necessary to support its vision, mission, and objectives, and maintain its independence. The income and fundraising expense projections in this Business Plan are realistic and based upon the implementation of the strategy and policy described. In short, DNDi today, by learning from eight years of experience and by consolidating its strengths, is aligned as a dynamic organization, ready to continue and increase its drive to respond to the most urgent patient needs.

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DNDi

Drugs for Neglected Diseases *initiative*

Best science
for the most neglected

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