

The logo for DNDi consists of the letters 'D', 'N', 'D', and 'i' in a bold, red, sans-serif font. The 'i' is smaller and positioned below the 'D's. The text 'drugs for neglected diseases initiative' is written in a black, lowercase, sans-serif font, stacked vertically to the left of the logo.

**drugs for neglected
diseases initiative**

DNDi
An Innovative
Solution

Working Draft

Vision

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 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 will collaborate to raise awareness of the need to research and develop drugs for those neglected diseases that fall outside the scope of market-driven research and development (R&D). They will also build public responsibility and leadership in addressing the needs of these patients.

Mission

DNDi will develop new drugs or new formulations of existing drugs for patients suffering from the most neglected communicable diseases. Acting in the public interest, it will bridge the 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 will address unmet needs by taking on projects that others are unable or unwilling to pursue. Although **DNDi's** primary focus will be the development of drugs for the most neglected diseases such as sleeping sickness, kala-azar, and Chagas disease, it will also consider engaging R&D projects on other neglected diseases. As means permit, it will consider the development of diagnostics and/or vaccines.

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

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DNDi : An Innovative Solution

A Brief History

The not-for-profit **Drugs for Neglected Diseases Initiative (DNDi)** is the brainchild of Médecins Sans Frontières (MSF) and the Drugs for Neglected Diseases Working Group, an independent body of international health experts^[1]. **DNDi** seeks to address the need for research and development of new field-adapted, effective, and affordable drugs for patients suffering from ‘neglected diseases’. The idea is simple – to harness accumulated knowledge and cutting-edge science and technology to develop critically needed drugs for neglected diseases, making sure they are suitable for and accessible to the poorer patients of the world. The modus operandi will be to collaborate predominantly with developing country organizations and governments.

MSF’s Campaign for Access to Essential Medicines has extensively documented the chronic crisis of neglected diseases, and made it clear that drug development for the diseases of the poor has virtually ground to a halt. In the absence of new treatments, physicians are forced to continue using old medicines that are increasingly ineffective due to drug resistance. The handful of new medicines produced for neglected diseases tend to be unaffordable and poorly adapted to those who need them. Without a doubt, the absence of access to adequate treatment options for these communicable diseases, most of which are tropical and deadly, has reached crisis proportions.

After two years of study, the DND-Working Group concluded that there was an urgent need to act. They took up the challenge and are creating a new not-for-profit operating model built to foster collaboration both amongst developing countries and between developing and developed countries. Its design is a blend of centralized management to give it a clear project-specific focus, and decentralized operations that mimic modern drug companies. The model relies heavily on support from the public sector with contributions from the private sector, the Founding Partners, and the general public.

This document briefly describes **DNDi**, its aspirations, and how it will succeed.

A Growing Disparity

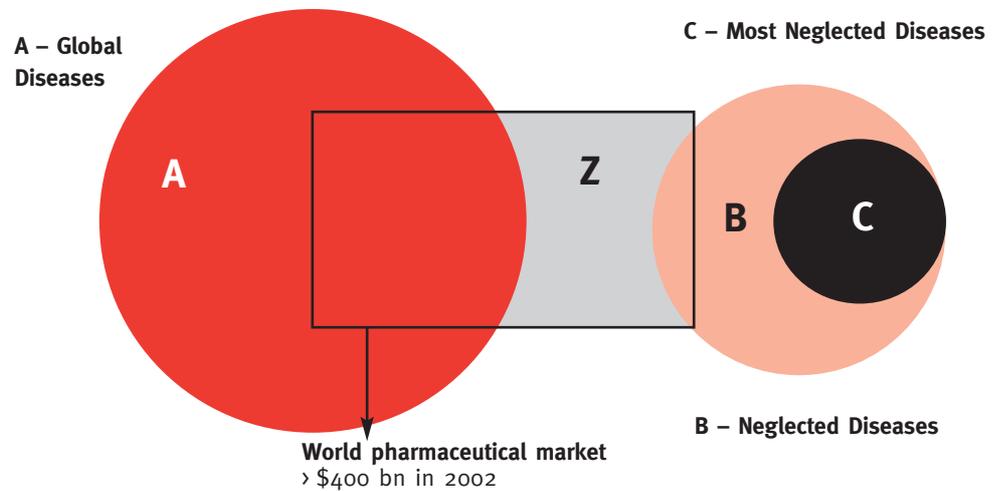
During the last 25 years, the gulf between the development of drugs for tropical and non-tropical diseases has grown.

Tropical diseases such as *chloroquine-resistant malaria*, *human African trypanosomiasis*, *visceral leishmaniasis (kala-azar)*, *lymphatic filariasis*, *Chagas disease*, and *schistosomiasis* continue to cause significant morbidity and mortality. Together with *tuberculosis*, these disabling and/or life-threatening diseases can be collectively called ‘neglected diseases’. These diseases are neglected by the very mechanisms that ensure research and development of new drugs, as the patients suffering from them do not represent a significant market.

Only 1 percent of the 1,393 new drugs registered during 1975-1999 were for tropical diseases and tuberculosis, yet these diseases constitute over 10 percent of the global disease burden. A mere 10 percent of the world’s health research expenditure is spent on diseases that account for 90 percent of the global burden of disease. And neglected diseases get an even smaller share of the pie – of the US \$60-70 billion spent on health research last year, less than 0.001 percent went towards developing new and urgently needed treatments for this category of diseases.

[1] The DND-Working Group was created at a meeting convened in Paris by MSF and UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases (TDR) in 1999. Its mandate was to search for creative new ways to stimulate R&D for neglected diseases and bring drugs to patients suffering from these diseases. MSF gave the entire Nobel prize award to the study of the medical needs of these patients.

Figure 1. Global pharmaceutical market and disease R&D targets



KEY

A – Global Diseases such as cancer, as well as cardiovascular, metabolic, bone and joint diseases affect people all over the world and constitute the major focus of the R&D-based pharmaceutical industry.

B – Neglected Diseases such as malaria and tuberculosis mainly affect people in poor countries, although a small market exists in wealthy countries (e.g. people who contract malaria while travelling), and thus some R&D efforts exist.

C – Most Neglected Diseases almost exclusively affect people in developing countries who are too poor to pay for any kind of treatment. They do not represent a viable market, and therefore fall outside the scope of the drug industry's R&D efforts. Examples of most neglected diseases include human African trypanosomiasis (also known as sleeping sickness), South American trypanosomiasis (also known as Chagas disease), Buruli ulcer, dengue fever, leishmaniasis, leprosy, lymphatic filariasis, and schistosomiasis.

Z (the grey shaded area) – represents the part of the pharmaceutical market for products addressing medicalized or life-style conditions that are not purely disease based (such as obesity, male pattern baldness, obsessive shopping, stress and jet-lag), which nonetheless represent a highly profitable market segment in wealthy countries.

Despite intense scientific scrutiny, the most neglected of these diseases – *Human African trypanosomiasis*, *leishmaniasis*, and *Chagas disease* – have been all but ignored by the pharmaceutical industry, which is almost the only generator of new medicines today. Most of the drugs to combat these diseases are either too expensive, difficult to administer, toxic at recommended doses, or increasingly ineffective due to drug resistance. People affected by these diseases cannot afford to buy the drugs and are thus off the radar screen of drug companies.

The DND-WG set out to uncover the reasons for this chronic crisis and examine current solutions and prospects before designing an innovative approach to tackle it.

The crisis in research and development (R&D) of drugs for neglected diseases is not due to a lack of scientific knowledge, as a great deal is known and information continuously generated, about the biology, immunology, and genetics of the parasites that cause, for example, *human African trypanosomiasis*, *leishmaniasis*, and *Chagas disease*. In fact the crisis is more the result of the failure of both the market and public policy to promote drugs for neglected diseases.

■ Reasons for the crisis

■ Current responses to the R&D crisis

Market failure: The vast majority of R&D of new drugs is conducted in the western world, mainly by the pharmaceutical industry whose research agendas are largely defined by the potential return on investment and reflect market prospects rather than health needs. The populations of poorer nations have limited purchasing power and thus their diseases are ignored.

Public policy failure: In spite of visibly waning private sector interest, governments have been slow to take action against this global problem. In industrialized countries, public policy has long provided incentives such as patents, tax credits, and health-care insurance systems to encourage private-sector investments in drug R&D, but these rarely target neglected diseases. Moreover, in spite of these incentives, there is a bias towards 'me-too' and lifestyle drugs for conditions such as impotence and baldness.

Governments in less developed countries, on the other hand, are confronted with a combination of lack of financial resources, absence of willingness to invest in long-term health development, and failure to establish public policy incentives that foster a viable domestic drug development capacity.

In recent years, awareness of the absence of effective treatments for neglected diseases has been growing. Individuals and groups of scientists in both the private and public sectors have published papers and lobbied governments and industry for a change in the status quo. Different organisations have been created to stimulate R&D and produce health tools adapted to the needs of developing countries. However, these have not been specifically designed to address the most neglected diseases.

UNDP/World Bank/WHO's Special Programme for Training and Research in Tropical Diseases (TDR) was established in 1975 in response to appeals from countries where neglected diseases were endemic. TDR addresses ten tropical diseases and has a two-fold mission, namely to develop new tools and methodologies to combat its target diseases and develop research capacities in developing countries to enable them to better address their needs and contribute to sustainable long-term solutions. Over the past 25 years, it has successfully partnered the development of several new treatments for tropical diseases, but significant unmet curative and preventive medical needs remain, particularly for the most neglected diseases.

Public-private partnerships (PPPs) seek to foster R&D for neglected diseases by matching existing capacity, expertise, and resources from both the public and the private sector. Recent examples of this strategy include the International AIDS Vaccine Initiative (IAVI) and the Medicines for Malaria Venture (MMV). These ventures promote product-specific collaborations between public and private sectors, while offering subsidies, grants, and patent extensions to make R&D of neglected diseases more attractive for industry. However, the incentives are focused on developing drugs for diseases that have markets in the North, such as malaria and TB. No PPPs have been set up to develop drugs for the most neglected diseases, as these do not represent a significant market.

The DNDi Approach

■ Objectives and scope of DNDi activities

DNDi aims to take the development of drugs for neglected diseases out of the marketplace and encourage the public sector to assume greater responsibility. It aspires to harness public and private sector resources with new science and technology, to meet a needs-based research and development agenda for drugs for neglected diseases. This is reflected in the constitution of its Founding Partners that currently include Médecins Sans Frontières, WHO/TDR, Oswaldo Cruz Foundation (Brazil), the Indian Council of Medical Research (India), Institut Pasteur (France), and the Ministry of Health (Malaysia). An additional Founding Partner will be identified within the African **DNDi** network, while efforts are also underway to ensure patient representation.

DNDi's main objective is to develop and make available drugs for neglected diseases on a not-for-profit basis. It will achieve this by building a needs-driven portfolio of short-, medium-, and long-term R&D projects, raising awareness about the issue, and building R&D capacity in countries where these diseases are endemic.

Develop a needs-driven portfolio: The initiative aims to build a balanced project portfolio based on the medical needs of neglected and most neglected patients. Once the needs are identified, it will develop drugs from existing drugs or compounds in short- and medium-term projects, or use known and newly identified targets to organise research on lead compounds for long-term projects. This mixed portfolio reflects the R&D gap in this field and will allow the initiative to have a quicker, more tangible impact.

- **Short- and medium-term projects (3-6 years):** Three IDDPs (Immediate Drug Development Projects) based on existing drugs or compounds, are ongoing in conjunction with MSF, TDR and several other partners: paromomycin for *visceral leishmaniasis* and two artesunate-based fixed dose combinations for *chloroquine-resistant malaria*. Registrations for some of these drugs/combinations will be filed within the next few years. Discussion is underway to enable **DNDi** to launch new projects based on existing drugs such as Nifurtimox for *human African trypanosomiasis*. Other short-term projects could include completing regulatory dossiers of existing drugs, reformulating existing drugs for specific patient populations or indications, and developing drug combinations.
- **Long-term projects (10-12 years):** These will initially focus on each of the parasites responsible for *human African trypanosomiasis*, *Chagas disease*, and *visceral leishmaniasis*. **DNDi** will seek and identify possible targets, known and new, and partner with organizations that will carry out necessary discovery work.

The initiative will catalyse and coordinate research and manage drug development projects. It will outsource most R&D activities – from discovery through predevelopment to development, including clinical trials – while maintaining leadership over the process.

■ The operating model

Project portfolio goals

DNDi will produce a regular supply of innovative compounds, new drug indications or fixed dose combinations. In practice, this means that it must initiate at least two new drug development projects every year. **DNDi** will identify project opportunities in both the public and private sector and a Scientific Advisory Committee will recommend which ones to include in the portfolio.

The goal is to have a maximum of ten projects running simultaneously, and to attain registration of six to seven drugs and a balanced portfolio of eight simultaneous projects by the twelfth year of operation. The odds that a particular project will lead to approval of a successful innovative drug will vary according to the disease, drug, and stage of development.

Raise awareness: A main component of **DNDi's** vision is to raise awareness of the need to research and develop drugs for neglected diseases. This is already taking place via publications, conferences, and meetings bringing together decision-makers, the scientific community, public leaders, and industry. Moreover, as **DNDi** networks become operational, regional collaborators will help identify project opportunities, play a role in building drug development programmes, and raise funds.

Build capacity: Using existing R&D capacity, helping build new capacity, stimulating R&D activity, and transferring technology to disease-endemic countries are essential tools in achieving **DNDi's** vision. Its primary differentiating feature is the aim to foster collaboration between drug developers in developing countries. While other organizations are certainly active in this field, much more needs to be done given the overwhelming and increasing need for these drugs. **DNDi** will collaborate closely with these organizations to ensure synergy and avoid unfruitful competition.

The initiative will not conduct research and scientific work to develop compounds by itself; rather, it will capitalize on existing, fragmented R&D capacity, especially in the developing world, and complement it with additional expertise as needed. As a virtual drug development organization it will thus significantly lower overhead costs.

DNDi will collaborate with partners from both the developing and developed worlds (public and academic institutions, pharmaceutical and biotech companies etc.), and stringently manage legal issues (including intellectual property). The overall goal will always be to ensure the greatest accessibility to and affordability of the results of **DNDi's** work.

Regional partners: Regional collaborators will be vital to the success of **DNDi**. In fact the initiative is already using a collaborative approach to manage the three existing IDDPs (see page 6). Potential partners include key regional (or national) research organizations, leading research institutes, patient care associations, and drug manufacturers.

Initially, the initiative will have four regional offices, operating in small teams, located in South America, Asia, Africa, and Europe. These will actively advocate for **DNDi** and stimulate the growth of regional networks; provide information on available expertise and capacity, as well as patients' needs; and support operations in their area. A Coordination Centre based in Geneva will oversee their support activities.

The People

■ Management Oversight

Legal and regulatory issues: DNDi will give serious consideration to Intellectual Property Rights (IPR) issues when deciding on projects, and adhere to drug regulations.

- **IPR issues:** DNDi will develop an IPR policy with the following imperatives in mind: to develop drugs as public goods whenever possible and ensure that these are affordable to patients who need them. The policy will also consider the fact that its outputs are unlikely to have any commercial value and that R&D agreements will often be made with public sector entities. DNDi will negotiate with IPR owners to obtain the best possible conditions under which drugs can be made accessible to patients.
- **Drug registration:** DNDi will consider drug registration requirements from the earliest phases of the drug development process, and abide by good laboratory, clinical, and manufacturing practices and national requirements of countries where drugs will be registered. In addition to protecting individual study subjects or patients, full adherence to regulatory requirements is the first step in responding to liability concerns.

DNDi has brought together renowned members of the international scientific community as well as individuals dedicated to reducing disparities between the North and the South. The organization will grow in stages as research and implementation needs grow. At present it has three main functions: management oversight, project identification and coordination, and project implementation.

This function is the responsibility of the Founding Partners, Board of Directors, Scientific Advisory Committee (SAC), the DND Working Group, and Associate Members.

Founding Partners: Six Founding Partners from select institutions have joined forces to oversee the start-up phase of DNDi. A representative from the Africa DNDi network and a patient representative from the South will also be designated as Founding Partners. Each member will contribute by providing either financial support or in-kind research contributions, and by representing and gathering support for DNDi interests in wider settings. They will select the initial board members.

Board of Directors: A Board of 10-13 members will be responsible for ensuring that DNDi's vision and mission is clearly understood by the management team and partners. It will select the Executive Director who will recruit an R&D Director and Director of Advocacy and Fundraising, as well as other direct reports.

Scientific Advisory Committee (SAC): This is envisioned as a group of ten prominent scientists from developed and developing countries, renowned for their contributions to various scientific disciplines in drug discovery and development. It will support, advise, and provide recommendations on project selection to the Board and Executive Director.

DND Working Group (DND-WG): This international advisory body to MSF's Campaign for Access to Essential Medicines, and originator of the DNDi concept, will continue to

■ Project Coordination

stimulate debate on critical issues and support **DNDi** activities.

Associate Members: Associate Members will include academic and public research institutions, NGOs, foundations, funders, and pharmaceutical/ biotech companies. Their contributions may include commitment to advocacy, in-kind contributions, access to relevant scientific knowledge, and active assistance to **DNDi** when needed.

■ Project Implementation

Once **DNDi** has been incorporated as a legal entity, the Executive Director will build a Coordination team to select drug development priorities, build a portfolio, and manage scientific and technical activities. A provisional directorate has already been set up, currently housed in Geneva.

Once a project has been selected, the R&D Director will select a Project Manager who will build a team to implement the chosen project. The operations of the multinational project teams will mirror industry equivalents.

Financial Support

■ Funding Strategy

DNDi will tap four major sources of funding to support its work: public donors such as national or regional governments, the EU, international organizations, the World Bank, and UN agencies (WHO, UNDP); private funders such as specialized private foundations and large individual donors; **DNDi** founders; and the general public.

DNDi's funding strategy is based on the principle that it will at all times remain independent and flexible. Seeking funds from diversified sources will ensure that individual donors do not excessively influence the initiative. As one of the primary aims is to bring R&D for neglected diseases back into the arena of public responsibility, at least half of all operations will be funded with public money. During the launch phase, the Founding Partners will provide funding, particularly to cover fixed costs such as human resources, legal costs etc. MSF, for instance, has allocated sufficient resources to launch **DNDi** and support it for five years. During this period, the initiative will gradually start raising funds from public money and private sources on a project-by-project basis.

■ Costs

Costs have been evaluated according to the disease targeted, type of project (short-, medium-, or long-term), and development stage of the drug (existing drug, existing compound, or new chemical entity). At maturity (2007), annual costs for **DNDi** are estimated at US\$25 million, including R&D and fixed costs.

For the launch period (2003-2004), the budget is about US\$20 million, including fixed and exceptional costs to implement the initiative, organization overheads, and development costs for the IDDPs and selected new projects.

Over a 12-year period, the global budget can be estimated at a minimum of US\$255 million for a possible outcome of six to seven drugs registered and a balanced portfolio of eight projects in the development pipeline.

The Path to Success

The **Drugs for Neglected Diseases Initiative** seeks to reduce the disparities that exist between drugs and diseases, prioritizing need over profitability. The goal is simple, but the path to success strewn with challenges. Well aware of these obstacles, **DNDi** will strive to make drugs available and affordable to people suffering from diseases long neglected by the pharmaceutical industry. It will raise awareness about these diseases – *leishmaniasis*, *human African trypanosomiasis*, *Chagas disease*, as well as other neglected diseases, build R&D capacity in developing countries, and catalyse the transfer of technology to them. It is only through global collaboration between developed and developing nations that **DNDi** can fulfil its aspirations.

Successfully meeting the R&D needs for the most neglected diseases of the most neglected patients will depend on the dedication of a group of individuals for whom monetary gain is inconsequential compared to the cost of human lives.

Planning Team

Core Group Members team:

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Glossary of Diseases

- **Leishmaniasis (kala-azar)**

Leishmaniasis is a tropical disease prevalent in 88 countries. It currently affects an estimated 12 million people worldwide. 200 million people are at risk, mostly in the five tropical countries of Bangladesh, Brazil, India, Nepal, and Sudan. It is transmitted through the bite of a sandfly. The disease occurs in three forms of which the most deadly is visceral leishmaniasis, which is accompanied by enlarged abdomen, spleen and liver, fever, diarrhoea and anorexia and is fatal if left untreated. Without treatment, all of the estimated 500,000 affected annually by this form, will die.

The disease also occurs in Southern Europe, where 1,600 people have been diagnosed as infected with kala-azar and HIV up to early 1999.

- **Human African trypanosomiasis (sleeping sickness)**

Human African trypanosomiasis is a tropical disease transmitted through the bites of infected tsetse flies. 500,000 people are currently affected in 36 African countries, leaving 60 million people at risk. The disease was almost eradicated in the 1960s but has made a comeback in the isolated and marshy regions of sub-Saharan Africa due to years of conflict and lack of human and financial resources. In some villages in Congo in the 1990s, MSF found that as many as 70% of the inhabitants were infected.

The drugs available to treat this disease are scarce, toxic, and encounter parasite resistance. The first stage of the disease often goes undiagnosed. The second stage, however, is characterized by neurological symptoms, and without treatment, results in body wasting, somnolence, coma, and death.

- **Chagas disease**

Endemic to Central and South America, the parasite that causes Chagas disease (*Trypanosoma cruzi*) is passed by blood transfusion or with the bite and defecation of the reduviid or “kissing bug”, so named for its tendency to attack around the lips. An estimated 16 – 18 million people are infected with Chagas and about 100 million people are at risk in 21 countries. This is about 25% of the population of Latin America.

Acute symptoms of Chagas disease only occur in about 1% of cases, one to two weeks after infection and include fever, facial swelling around the bite site, and enlarged and painful lymph glands. In general, symptoms last for 4 – 8 weeks and then disappear. In about one-third of the acute cases, chronic forms develop 10 – 20 years after infection. These are cardiac problems, including an enlarged heart, altered heart rate or rhythm, heart failure, or cardiac arrest. Severe chronic disease leads to death. The treatments that exist are not sufficiently effective for chronic patients, be they children or adults.

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For mailing purposes
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