Delivering Innovation and Building a Robust Pipeline

Three new treatments and a strengthened pipeline highlight DNDi’s efforts into 2009.
The Drugs for Neglected Diseases initiative (DNDi) is an independent, not-for-profit product development partnership working to research and develop new and improved treatments for neglected diseases such as leishmaniasis, human African trypanosomiasis, Chagas disease, and malaria. DNDi was founded in 2003 by the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia, France’s Pasteur Institute, Médecins sans Frontières (MSF) and WHO/TDR which acts as a permanent observer to the initiative.

In March 2009, the World Bank estimated that if the current global economic crisis persists, there could be between 200,000 and 400,000 additional child deaths every year – between 1.4 and 2.8 million before 2015 and 100 million of the world’s poorest forced back into poverty. The conclusion of the world leaders was eloquent: “Any reduction in investment in healthcare will have devastating consequences for the sick and untreated, and has the potential to plunge new groups and nations into poverty.”

Now, as we are preparing our annual report, we have no option but to consider this economic breakdown which constitutes a dramatic challenge not only for DNDi and our stakeholders, but also for all those committed to bringing innovation and new tools to those most in need.

Most neglected tropical diseases primarily affect the poor and marginalised who have few resources or possibilities to make a living. The high burden of disease and loss of productivity aggravate poverty which is further compounded by the high cost of long-term care.

For tropical diseases such as sleeping sickness, leishmaniasis, and Chagas disease, for which no adequate treatments or diagnostics exist, research is needed now more than ever, for new, practical, and effective tools, and efficient ways to implement them. With the strongest and most comprehensive drug portfolio for these neglected tropical diseases in history, DNDi continues to engage partners who share our vision and commitment, and to ensure that a well-balanced pipeline is maintained.

For all these R&D disease strategies, DNDi has made major progress in delivering quality, affordable and adapted treatments.

Specifically, advances in combating one of the most neglected diseases - sleeping sickness - are significant, as this is the role, mission, and the “raison d’être” of DNDi. To deliver an improved therapeutic option for this disease, strong partnerships have been set up with national programmes of most endemic countries, NGOs, public and private research institutions, and the World Health Organization (WHO). Oral nifurtimox and intravenous eflornithine combination therapy (NECT) has been included on the WHO Essential Medicines List. NECT, the first improved treatment for sleeping sickness in 25 years, is now available for
use in treating the advanced stage of the disease and could save four to five lives of every 100 patients treated, as it is far less toxic than the arsenic drug that is still being used in some areas. It is a major improvement and source of satisfaction for all the partners who have been engaged in our organisation since its creation in 2003. However, delivering a truly simplified treatment which can be orally administered, implemented at the primary healthcare level, and effective against both stages of the disease, is still our ultimate goal.

One promising drug entering into clinical development this year is fexinidazole – the only new clinical candidate currently in the drug pipeline for sleeping sickness. This project holds great promise for patients and practitioners in the field. Both short- and long-term strategies are considered as the core of our scientific approach, which requires the best scientific resources at all stages of R&D to access compounds, technologies, expertise, and knowledge.

Sleeping sickness is one illustration of DNDi’s continuous progress to boost innovation for the most neglected patients. Another example is our successful track record of collaboration with sanofi-aventis in delivering ASAQ for the treatment of malaria. In 2008, more than 5 million treatment courses were procured and 20 to 30 million more will be delivered in 2009.

Six years on from its founding, DNDi is managing more than 300 partnerships with a wide range of public and private partners and NGOs, and ten clinical trials are ongoing in 2009, with more than 400 people engaged in our programmes.

With focused collaboration, innovative thinking, and political leadership, we will meet the noble goals set by our organisation. We remain firmly engaged in making a major and significant contribution to the Millennium Development Goals and bringing those forgotten patients out of the shadows.

The changes seen in the past decade offer a new landscape for collaboration to improve essential healthcare. At a time when the financial crisis could have significant consequences for the poorest, greater investment from governments and the private sector, complemented with new and adapted funding mechanisms, are needed to ensure that these efforts will be sustained and strengthened.

We would like to thank again all our donors for their support, and particularly those who have reinforced their commitment to most neglected diseases with significant multi-year contributions.

We would also like to pay special tribute to our dedicated team working at DNDi for their outstanding commitment and contribution to our successes. In particular, we would like to thank Els Torreele, one of the main sources of inspiration for our organisation, even prior to its creation, and who has played a major role in the successful implementation of our sleeping sickness projects. Els is moving on to new horizons but, no doubt, will remain committed to neglected diseases in her future job.

Investing in R&D for the most neglected patients goes hand in hand with better health and economic growth for affected marginalised communities. Help us meet our goal.

Simply because their wellbeing matters.

Dr. Bernard Pécoul, Executive Director
Dr. Marcel Tanner, Chairman of the Board of Directors

Bringing innovation and new health tools to those most in need.
Prospects set to improve dramatically for children threatened by sleeping sickness in Mwana-Mputu (Democratic Republic of the Congo), thanks to new treatments developed by DNDi and its partners.
A landmark year for sleeping sickness with two major project milestones achieved: NECT a new and improved treatment approved by WHO and fexinidazole, a new possible drug brought into clinical development.

With the strongest and most comprehensive R&D portfolio in history for the most neglected diseases, DNDi continues to identify and engage partners who share our vision and commitment, to ensure that a well-balanced pipeline is established for the three diseases of primary focus: sleeping sickness (human African trypanosomiasis, HAT), kala-azar (visceral leishmaniasis, VL), and Chagas disease.

Since the launching of two new anti-malarials in 2007 and 2008 - ASAQ and ASMQ – DNDi has taken key steps towards ensuring their effective implementation in endemic countries, while advancing other projects from its portfolio, and expanding its worldwide partnerships. For example as a result of working with our partner sanofi-aventis, ASAQ is now registered in 24 countries, over 20 million treatments have already been delivered in 2009.

Major progress has particularly been achieved in R&D with regard to sleeping sickness. NECT, a combination of nifurtimox and efornithine for the treatment of the disease received approval by the WHO Expert Committee on the Selection and Use of Essential Medicines in April 2009. The approval came after positive efficacy and safety results from the clinical study that was run jointly by DNDi, Médecins Sans Frontières, Epicentre, and national programmes. NECT does not only reduce the risk of resistance emerging but also reduces the duration of drug treatment (with infusions twice a day for ten days), and makes it easier to administer through oral doses.

The major breakthrough, however, is the prospect of a simple oral treatment or a pill to treat the disease. Fexinidazole, a compound ‘rediscovered’ by DNDi, is entering into phase I clinical trial this year, in close collaboration with sanofi-aventis. It is the only new clinical candidate currently in the drug pipeline for sleeping sickness.

In the field of Chagas disease, DNDi is also moving forward with its R&D strategies: we are currently developing a paediatric formulation with LAFEPE (a Brazilian public laboratory) and researching the therapeutic utility of azoles, which already have available drugs. However, more must be done, as the burden of Chagas is significantly underestimated in official statistics: few patients receive any treatment at all, and new diagnostics and treatments are still urgently needed. All these factors have prompted DNDi to launch a Chagas campaign in 2009. (see Chapter 4)

**OBJECTIVES**

**The primary objectives are to:**
- Deliver 6-8 new treatments by 2014 for leishmaniasis, sleeping sickness, Chagas disease, and malaria
- Establish a robust portfolio for new generation of treatments

**Secondary:**
- Use and strengthen existing capacity in disease-endemic countries
- Raise awareness and advocate for increased public responsibility

**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 partners 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.

**MISSION**

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 to find 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 is the development of drugs for the most neglected diseases, such as sleeping sickness (Human African Trypanosomiasis, HAT), kala-azar (visceral leishmaniasis, VL), and Chagas disease, and it will also consider engaging in R&D projects for other neglected diseases. In pursuing these goals, DNDi manages R&D networks built on South-South and North-South collaborations. While using and supporting existing capacity in countries where the diseases are endemic, DNDi helps to strengthen additional capacity in a sustainable manner through technology transfer in the field of drug research and development for neglected diseases.
Over the past five years, the R&D landscape has changed significantly, with greater resources being given to global health and the development of new drugs for poverty-related neglected diseases. However, while much attention has been focused on combating the ‘big three’ neglected diseases (HIV/AIDS, malaria, and tuberculosis), many others have failed to attract sufficient resources, and adequate drugs are not available for many diseases affecting poor, neglected populations in the developing world. In 2007, less than 5 per cent of US$2.5 billion – the total funding allocated to R&D for neglected diseases – went to kinetoplastid diseases1 although those tropical diseases (NTDs) kill more than 100,000 of people each year and aggravate poverty in the developing world. Almost everyone in the bottom billion has at least one of these diseases, which reinforces the poverty trap. These diseases prevent the achievement of the first six Millenium Development Goals even though for some of them their control with low cost and cost-effective interventions could start long-term economic growth and development. For some kinetoplastid diseases, the few treatments available date back to colonial times and are simply inadequate by today’s standards.

THREE CHALLENGES AHEAD...

Despite substantial progress proving that PDPs such as DNDi can successfully manage R&D and translate knowledge into tangible results, we are still facing major challenges on three levels:

EXPANDING INNOVATIVE PARTNERSHIPS

DNDi operates through a virtual model, whereby all of its R&D activities are outsourced, contributing to keeping development costs under control, while providing a high level of flexibility. A consequence of this strategic option is that fostering an efficient drug-development programme requires the establishment of strong agreements within the entire biomedical landscape, so as to leverage and mobilise private and public sector resources. The first DNDi successes show how crucial it is to build new collaborative business models through efficient partnerships, alliances and consortia amongst a broad range of public and private players who share an objective driven by needs, not profit. To put it in perspective: of the 350 agreements signed since the establishment of DNDi, more than 100 have come about since 2008. These include research, technical, and funding agreements with public and private partners such as sanofi-aventis for the development of ASAQ and Fexinidazole, GlaxoSmithKline, Merck, Farmanguinhos, Advaxis, Cipla, BDSI, Griffith University (Aus), University of Antwerp, University of Dundee, Anacor, Scynexis, among many others.

FACILITATING ACCESS TO TREATMENTS

To immediately address the access barriers during the implementation phase, DNDi’s role is upstream, early, and jointly with the implementers such as the national control programmes, NGOs and WHO. DNDi aims to gather relevant information during the development of treatments so as to facilitate their transition to implementers, for rollout into the field, after registration. The DNDi access strategy and activities adopted by the board of directors in December 2008 are guided by the following principles:

- the need to facilitate equitable access to the new treatments developed by DNDi;
- the desire to transition these treatments, in the long run, to their natural implementers, i.e. national ministries of health (MOH) and control programmes (NCP), WHO, and NGOs such as MSF, in order for DNDi to focus on its core activity of research and development, and
- a commitment to contribute to the development of approaches for improved access and dissemination of knowledge.

ENSURING A MORE FAVOURABLE ENVIRONMENT FOR R&D

Moreover, public leadership is needed to implement policy changes and to create a more favourable environment that will support the development of new, essential health tools. This leadership must strive to ensure that affected populations have equitable access to treatments and they must also contribute to the development of innovative needs-based measures. Such measures include intellectual property (IP) management policies to encourage a needs-driven R&D agenda, technology transfer, an enabling regulatory environment and the strengthening of research capacities in developing countries.

Main Progress to 2009

Malaria
ASAQ – fixed-dose combination (FDC) of artemunate and amodiaquine for use in sub-Saharan Africa; launched in March 2007; registered in 24 disease-endemic countries; in landmark partnership with sanofi-aventis; obtained WHO prequalification in October 2008; 5 million treatment courses delivered in 2008 and more than 20 million forecast for 2009.

ASMO – FDC of artemunate and mefloquine for treatment in Latin America and Asia; registered in Brazil in March 2008 in partnership with Farman-guinhos/Fiocruz; South-South technology transfer underway to Cipla for availability in Asia and Africa; in use by Brazilian national authorities.

Human African Trypanosomiasis
NECT - Clinical Trial of Nifurtimox-Eflornithine Co-administration Therapy – promising study presented at ASTMH in December 2008; full dossier submitted to WHO Essential Medicines List (EML) in 2008; in April 2009, NECT is included in the EML list.

Fexinidazole – first compound mining success from DNDi’s nitroimidazoles project; pre-clinical studies finalised; entering into clinical development in 2009 and the only new clinical candidate currently in the drug pipeline for HAT; in May 2009, sanofi-aventis and DNDi sign agreement to develop and make it available.

Lead Optimisation Partnership – two compound series have been advanced as attractive leads progressing from early-stage screening research through innovative partnership with U.S. partners: Scynexis & Pace University.

Visceral Leishmaniasis
VL Combination Trials in Africa, Asia and Latin America – implemented for evaluating safe and short-course combination therapy, using existing drugs in three regions to stave off parasitic resistance and provide a shorter, more effective treatment course.

Visceral Leishmaniasis

Fexinidazole entering into Phase I in 2009.

- Phase III trial (AmBisome, Miltefosine, Paromomycin) designed for India, Bangladesh and Nepal; patient recruitment began in June 2008 in two sites in Bihar (India).
- Paromomycin trial in Africa – more than 1,000 patients included in multi-centre trial in East Africa, aimed to register paromomycin and evaluate the shorter course combination of PM+SSG.
- AmBisome in Africa. Recruitment started in 2009, aimed to achieve geographical extension and potential therapies combination.

Lead Optimisation Partnership – partnership implemented in 2007; with two key partners in India: Advinus and Central Drug Research Institute (CDRI); 2 promising series of compounds identified in 2008.

Chagas disease
Paediatric Benznidazole – agreement with LAFEPE to develop first benznidazole formulation for children, to be affordable and publicly available in 2010.

Strengthening Research Capacities
- Three regional networks for research capacity strengthening:
  - Africa: the HAT Platform and the Leishmaniasis East Africa Platform (LEAP): GCP, ethics, and trial-monitoring training; establishment and training of data safety monitoring board (DSMB); workshops on clinical trial methodology and information sharing on recent clinical research developments.
  - Asia: Pan Asian Network for Neglected Diseases (PAN4ND): screening capacity strengthening in the Asian region for purification and identification of chemicals from plant, soil, and marine organisms.

Consolidation with strategic focus on compound collection, target identification, target validation, assay development, high-throughput screening (HTS), hit identification, and hit to lead selection. For HAT: HTS is available [Eschlin, Scynexis];
Since DNDi’s founding in 2003, seven key stakeholders have helped to propel the initiative. Each Founding Partner is a centre of excellence in neglected disease research and/or patient care.

**DNDi Founding Partners and Worldwide Presence**

**THE KEY ROLE OF THE FOUNDING PARTNERS**

Since DNDi’s founding in 2003, seven key stakeholders have helped to propel the initiative. Each Founding Partner is a centre of excellence in neglected disease research and/or patient care.

**7 Founding Partners**

**4 Regional Support Offices**

**1 Affiliate**

**2 Project Support Offices**

**OSWALDO CRUZ FOUNDATION (FIOCRUZ)**

Founded in 1900, Fiocruz is the largest biomedical research institution in Latin America. Part of the Brazilian Ministry of Health, Fiocruz has facilitated health tool R&D for neglected diseases via the establishment of dedicated centres for vaccine and drug development: Biomanguinhos and Farmanguinhos.

[www.fiocruz.br](http://www.fiocruz.br)

**DNDi NORTH AMERICA**

Established in 2007, the affiliate of DNDi in North America supports the advocacy, fundraising, and R&D efforts of DNDi in the region. Based in New York City, USA, this affiliate operates under the direction of the DNDi North America Board of Directors and collaborates with key partners engaged in a variety of R&D activities.

[www.dndina.org](http://www.dndina.org)

**INSTITUT PASTEUR**

Established in France in 1887, the Pasteur Institut is a non-profit private foundation dedicated to the prevention and treatment of diseases. It focuses on diseases like yellow fever, tuberculosis, poliomyelitis, hepatitis, and HIV/AIDS. With 8 Nobel Prizes awarded to its researchers, the Pasteur Institut is on the forefront of medical research with discoveries of antitoxins, BCG, sulfamides, and anti-histamines, as well as key research in molecular biology and genetic engineering.

[www.pasteur.fr](http://www.pasteur.fr)

**DNDi LATIN AMERICA**

Opened in 2004, the DNDi Latin America regional support office is based in Rio de Janeiro. With the primary aim to support regional R&D activities for Chagas disease, malaria, and VL, the Latin American office also undertakes advocacy and communications activities to increase awareness of neglected diseases in the region.

[www.dndi.org.br](http://www.dndi.org.br)

**DNDi AFRICA**

Established in 2003, the DNDi Africa regional support office is based at the Kenya Medical Research Institute (KEMRI) in Nairobi, Kenya. DNDi Africa provides support to R&D projects in the region, including the paromomycin study, the LEAP and HAT Platforms, and the FACT Project.

[www.dndiafrica.org](http://www.dndiafrica.org)

**DNDi IN THE DRC**

Since 2005, the DNDi office in the Democratic Republic of the Congo (DRC) has provided essential logistical and financial support for the nifurtimox-eflornithine clinical trial (NECT) and the HAT Platform. Based in Kinshasa, the office shares space with key project partner, the Swiss Tropical Institute.

[www.dndinafrica.org](http://www.dndinafrica.org)
**MÉDECINS SANS FRONTIÈRES**

MSF is an independent, private, medical aid organisation that has been operational in emergency medical aid missions around the world since 1971. With offices in 19 countries and ongoing activities in over 80, MSF has also run the Campaign for Access to Essential Medicines since 1999. MSF has received numerous international awards for its activities, including the Nobel Peace Prize in 1999. MSF dedicated this prize to finding long-term, sustainable solutions to the lack of essential medicines crisis (which ultimately led to the founding of DNDi in 2003).

[www.msf.org](http://www.msf.org)

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**THE SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES**

As an independent global programme of scientific collaboration, established in 1975 and co-sponsored by the United Nations Children’s Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO), TDR aims to help coordinate, support, and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged. TDR is a permanent observer of DNDi’s Board of Directors.

[www.who.int/tdr](http://www.who.int/tdr)

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**INDIAN COUNCIL OF MEDICAL RESEARCH (ICMR)**

Established in 1911, it was re-designated in 1949 as the Indian Council of Medical Research (ICMR). Funded by the Government of India, ICMR’s activities are focused on the formulation, coordination, and promotion of biomedical research. The Council has a network of 21 Permanent Research Institutes located in different parts of India that conduct research on tuberculosis, leprosy, and visceral leishmaniasis.

[www.icmr.nic.in](http://www.icmr.nic.in)

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**KEMRI**

Established in 1979, KEMRI conducts health sciences research and shares its research findings with the international community. One of the leading health research institutions in Africa, KEMRI has been making a significant contribution to regional research capacity for many years. With a focus on infectious and parasitic diseases, and on public health and biotechnology research.

[www.kemri.org](http://www.kemri.org)

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**DND/IN JAPAN**

Since 2004, the DNDi office in Japan has provided support in developing discovery projects and on better positioning DNDi in the country by expanding its relationships with academia, pharmaceutical companies, government, and media.

[www.dndijapan.org](http://www.dndijapan.org)

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**DND/INDIA**

Opened in 2004, the regional support office in India is based at the Indian Council for Medical Research (ICMR) in New Delhi. The office functions as a relay for DNDi’s operational activities in India, which are primarily focused on two diseases, malaria and visceral leishmaniasis.

[www.dndiindia.org](http://www.dndiindia.org)

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**MINISTRY OF HEALTH, MALAYSIA (IMR)**

The Institute for Medical Research (IMR), within the Ministry, was established in 1900 to carry out scientific and sustained research into the causes, treatment and prevention of infectious tropical diseases. Initially, it principally focuses on malaria, beriberi, cholera, and dysentery. The IMR is now comprised of eight centres which perform research, diagnostic services, training, and consultative services across diverse health fields.


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**DND/MALAYSIA**

Since 2004, the DNDi office in Malaysia has supported a variety of R&D activities across the Asian region, including key preclinical and early clinical studies for the FACT Project, as well as the fostering of the PANNDi, a regional research platform that is focused on the discovery and development of natural substances as therapeutics to neglected diseases. Based at the Universiti Sains Malaysia, the office also works to facilitate the implementation of ASMQ in the region.

[www.dndiasia.org](http://www.dndiasia.org)

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**DND/ANNUAL REPORT 2008/2009**

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**01. Vision, Mission, Governance**
Governance & People

THE BOARD OF DIRECTORS

The Board of Directors is composed of between ten and thirteen members, including one patient representative. Each of the six funding members nominates one Board member. Board members serve for a term of four years.

01 Marcel Tanner, Chair; Swiss Tropical Institute (STI)
02 Reto Brun, Secretary; Swiss Tropical Institute (STI)
03 Bruce Mahin, Treasurer
04 Alice Dautry, Institut Pasteur, France
05 Christophe Fournier, Médecins Sans Frontières (MSF)
06 Lalit Kant, Indian Council of Medical Research (ICMR)
07 Datuk Mohd Ismail Merican, Ministry of Health, Malaysia
08 Carlos Morel, Oswaldo Cruz Foundation (FIOCRUZ), Brazil
09 Robert G Ridley, TDR (Permanent Observer of Board)
10 Gill Samuels, Global Forum for Health and Research, Geneva
11 Bennett Shapiro, Pure Tech Ventures, formerly with Merck & Co, USA
12 Paulina Tindana, Patient Representative, Navrongo Health Research Centre, Ghana
13 Representative of KEMRI: vacant post

THE SCIENTIFIC ADVISORY COMMITTEE (SAC)

The SAC is composed of sixteen prominent scientists with expertise in various scientific disciplines related to drug discovery and development, and/or the specific reality of neglected diseases and neglected patients. They operate independently of the Board of Directors and the Executive team. The SAC has the mandate to advise the Board of Directors on matters related to research and development and choice of projects, as well as the quality of the scientific output.

01 Julio Urbina, Chair; Venezuelan Institute for Scientific Research (IVIC), Venezuela
02 Kirana Bhatt, University of Nairobi, Kenya
03 Marleen Boelaert, Institute of Tropical Medicine, Antwerp, Belgium
04 Pierre-Etienne Bost, Institut Pasteur, France
05 J Carl Craft, Formerly with Medecines for Malaria Ventures, Switzerland
06 Alan Hutchinson Fairlamb, University of Dundee, UK
07 Chitar Mal Gupta, Central Drug Research Institute, India
08 Maria das Graças Henriquez, Oswaldo Cruz Foundation, Fiocruz, Brazil
09 Paul Herrling, Novartis International AG, Switzerland
10 Marcel Hommel, Institut Pasteur, France
11 Nor Shahidah Kairullah, Infectious Diseases Research Center, Malaysia
12 Shiv Dayal Seth, Indian Council of Medical Research (ICMR), India
13 Mervyn Turner, Merck Research Laboratories, USA
14 Muriel Vray, Institut Pasteur, France
15 Krisantha Weerasuriya, World Health Organization, (WHO), Geneva
16 Haruki Yamada, Kitasato Institute for Life Sciences, Japan
### THE EXECUTIVE TEAM (as of June 2009)

**DND/ HEADQUARTERS, GENEVA (AS OF DECEMBER 2009)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>Bernard Pécoul</td>
<td>Executive Director</td>
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<tr>
<td>Shing Chang</td>
<td>R&amp;D Director</td>
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<tr>
<td>Hyo Jueng Ahn-Degras</td>
<td>Site and Travel Assistant</td>
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<tr>
<td>Jean-François Alessandri</td>
<td>Fundraising and Advocacy Director</td>
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<tr>
<td>Manica Balasegaram</td>
<td>Clinical Project Manager</td>
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<tr>
<td>Severine Blesson</td>
<td>Project Coordinator (as of July 2009)</td>
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<tr>
<td>Bethania Blume de Oliveira</td>
<td>Project Support Officer, [based in Brazil]</td>
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<tr>
<td>Gwenaëlle Carn</td>
<td>Clinical Project Coordinator</td>
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<tr>
<td>Eric Chatelain</td>
<td>Senior Project Manager</td>
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<tr>
<td>Brigitte Crotty</td>
<td>Executive Assistant</td>
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<tr>
<td>Violaine Dällenbach</td>
<td>Communications Officer</td>
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<tr>
<td>Ralf De Coulon</td>
<td>Finance, HR, and Administration Director</td>
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<tr>
<td>Robert Don</td>
<td>Senior Project Manager</td>
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<tr>
<td>Sally Ellis</td>
<td>Clinical Project Coordinator</td>
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<tr>
<td>Karin Génévaux</td>
<td>Fundraising Coordinator</td>
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<tr>
<td>Caroline Gaere Gardaz</td>
<td>Fundraising Officer for Major Donors</td>
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<tr>
<td>Jean-Robert Isset</td>
<td>Screening Coordinator</td>
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<tr>
<td>Sadia Shafaqoj-Kaenzig</td>
<td>Media and Corporate Communications Manager</td>
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<tr>
<td>Jennifer Katz</td>
<td>Head of Fundraising</td>
</tr>
<tr>
<td>Jean-René Kiechel</td>
<td>Senior Product Manager, FACT Project, and Expert, [based in Paris, France]</td>
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<tr>
<td>Delphine Launay</td>
<td>Lead Optimisation Coordinator (as of March 2009)</td>
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<tr>
<td>Denis Martin</td>
<td>Senior Project Manager</td>
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<tr>
<td>Janine Millier</td>
<td>Accountant</td>
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<tr>
<td>Béatrice Mouton</td>
<td>Human Resources &amp; Legal Affairs Manager</td>
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<tr>
<td>Jean-Pierre Paccaud</td>
<td>Business Development Director</td>
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<tr>
<td>Sylvie Renaudin</td>
<td>Research &amp; Development Assistant</td>
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<tr>
<td>Isabela Ribeiro</td>
<td>Senior Project Manager, [based in Rio de Janeiro, Brazil]</td>
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<tr>
<td>Jerôme Saint-Denis</td>
<td>Fundraising Coordinator (as of March 2009)</td>
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<tr>
<td>Ivan Scandale</td>
<td>Lead Optimisation Coordinator</td>
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<tr>
<td>Nathalie Strub-Wourgalt</td>
<td>Clinical Development Director (as of March 2009)</td>
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<tr>
<td>Laurence Vielfaure</td>
<td>Financial Controller</td>
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</tbody>
</table>

**REGIONAL SUPPORT OFFICES & AFFILIATE**

**AFRICA**
- Monique Wasunna, Head of Regional Support Office, Kenya
- Simon Bolo, Finance and Administration Officer, Kenya
- Joy Malongo, Administrative Assistant, Kenya

**ASIA**
- Malaysia
  - Visweswaran Navaratnam, Head of Regional Support Office
  - Lingges Linggi, Administrative Assistant
- India
  - Bhawna Sharma, Head of Regional Support Office
- Sharmita Das, Finance & Administration Officer
- Vikash Kumar, Accountant

**LATIN AMERICA**
- Michel Lotrowska, Head of Regional Support Office, Brazil
- Mariestela de Oliveira Soares, Accountant & Administrative Assistant, Brazil

**DND/ NORTH AMERICA, INC.**
- Jana Armstrong, Director, USA
- Sarah de Tournemire, Development & Administration Manager, USA
- Michelle French, Regional Communications Manager, USA

**PROJECT SUPPORT OFFICES**

- Democratic Republic of the Congo
  - Augustin Kadima Ebeja, Regional HAT Platform Coordinator
  - Richard Mbumba Mvumbi, Logistician, NECT Project

- Japan
  - Fumiko Hirabayashi, DND/Representative

**CONSULTANTS, ASSOCIATED STAFF, AND VOLUNTEERS**

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Consolidating efforts to research and deliver better treatments

One century after Chagas disease was first described, research has provided better understanding of the disease-causing parasite (shown under magnification). However, more activities and partnerships are needed in order to develop and deliver better-adapted diagnostics and treatments for this and other neglected diseases.
Major progress towards addressing the most neglected diseases with better medicines, including DNDi’s 1st treatment for sleeping sickness.

DNDi has made significant progress in establishing a well-balanced pipeline for the 3 diseases of our current primary focus: sleeping sickness (human African trypanosomiasis; HAT), visceral leishmaniasis (VL), and Chagas disease; and in addressing issues on access to these essential medicines.

Promising developments can be seen in each of the disease-specific and discovery portfolios:

- **Discovery phase**: new commitments from pharmaceutical partners like Anacor and GlaxoSmithKline, as well as key academic groups, such as the Drug Discovery Unit at the University of Dundee, and Institute Pasteur Korea
- **HAT**: positive Phase III results and inclusion of NECT onto the WHO Essential Medicines List, advancement of lexitinidazole towards clinical development, and promising lead series from Scynexis and Anacor
- **VL**: combination studies in Asia and Africa are progressing, with new sites and studies added; development of combination strategy for Latin America; excellent progress seen from lead optimisation consortium
- **Chagas disease**: agreement with LAFEPE to develop the only available treatment, DNDi’s 1st treatment for Chagas disease

Each of the disease portfolios consists of a balance of projects designed to serve:

- **Long-term objectives of developing innovative medicines from new chemical entities**
- **Medium-term objectives of identifying existing preclinical or clinical stage compounds suitable for therapeutic switching, or for further improvements via alternative or new formulations**
- **Short-term objectives of making existing drugs available in broader geographic areas and developing better treatments from existing drugs; examples include conducting necessary studies to register drugs not yet available in selected regions, developing fixed-dose combinations, and identifying combinations of existing drugs to reduce treatment duration, improve tolerability and lower the risk of resistance development.**

With the aim to deliver improved treatments for patients with neglected diseases, DNDi manages a spectrum of skilled partners with unique and varied expertise in the research and development of improved treatments for patients with neglected diseases. Discovery efforts are consolidated to allow the maximum efficiency for uncovering compounds with potential antiparasitic activities. Preclinical
and clinical development activities are organised by disease area, and each is focused on the ultimate goal of developing new treatments which reach patients and contribute to improved disease control.

**STRENGTHENING AND STREAMLINING THE PORTFOLIO**

Into 2009, DNDi’s portfolio continues to be strengthened and streamlined. Within the drug research and development process, milestones are defined for each project. Each year, a number of projects reach completion, and resources are reallocated to new projects.

We’d like to acknowledge our partners’ contributions to the following projects that have reached completion in the past year: DNDi continues to work with many of these partners on other projects:

- **COMPOUND SCREENING WITH CDRI (HAT)**: Stage: Discovery; Partner: Central Drug Research Institute (CDRI), India.
- **MICROTUBULE INHIBITORS (HAT)**: Stage: Discovery; Partners: Murdoch University, Australia; Epichem, Australia; Centre for Drug Candidate Optimisation, Monash University, Australia.
- **AMPHOTERICIN B POLYMER (VL)**: Partners: Imperial College, UK; London School of Pharmacy, UK; LSHTM, UK

The R&D portfolio represents a collection of projects that are in-sourced at all stages along the drug R&D process, from early discovery through clinical development, with the objective to bring new, field-relevant tools to patients in the shortest time and most efficient way possible. DNDi utilises a target product profile (TPP) which is a hypothetical “package insert” that guides the development process. The TPP plays a key role in guiding lead optimisation of drug candidates, decision-making within the team, design of clinical research strategies, and constructive communication with regulatory authorities. TPPs can be found for each of DNDi’s target diseases in the following pages.

Sound knowledge of patient needs is essential to a credible TPP. Our clinical project managers have in-depth knowledge about the patients in the field. They solicit input from healthcare workers, patients, health regulators, and policymakers in disease-endemic countries where the drug will ultimately be made available. Input from key opinion leaders and the R&D landscape for each disease area are also important and influential in shaping the TPPs.

With dozens of partners spanning the globe and crossing various sectors related to neglected diseases and drug development, DNDi is firmly on its way to meeting its objectives. However, additional support, from new research partners to governments and other donors, is needed in order to fully deliver the best science for the most neglected.
Consolidated efforts in discovery are feeding a pipeline that will deliver

Discovery research – a three-stage process consisting of screening, lead selection, and lead optimisation – is the one of the earliest stage of drug research and development, and contributes to bringing forward novel drugs that are significantly better than current therapies. DNDi continues its screening efforts into 2009 by consolidating and strengthening activities to ensure a robust pipeline that will deliver.

Many molecular targets or chemicals with therapeutic potential never make it into the drug development process. Although a lot of research has been conducted on the kinetoplastid parasites over the past century, culminating in the publishing of sequencing of its genomes and proteomes in 2005, basic research has yet to translate into new therapeutic tools. DNDi is working to overcome this gap in the discovery stage by: (1) accessing broad chemical diversity through a number of different sources and partnerships such as a natural products screening network and collaborations with pharmaceutical companies, (2) evaluating antiparasitic activity of compounds in vitro and in vivo according to standard operating procedures to ensure that screening at different sites and with different groups are comparable, and (3) increasing screening capacity for the kinetoplastid diseases. A resourceful and pragmatic approach, with a variety of strategies and partnerships, is used to feed the pipeline and deliver suitable leads to the lead optimisation (LO) programme.

Into 2009, important developments within DNDi’s discovery efforts include:
- a high-throughput screening (HTS) assay for the intramacrophagic Leishmania parasite, with the goal to have HTS for all 3 kinetoplastid diseases by end of 2009 – this is already available for T. brucei (the parasite causing human African trypanosomiasis), but remains a rate-limiting step for both Leishmania and T. cruzi
- agreements with pharmaceutical and biotechnology companies – GSK, Anacor, Merck, and many others in discussion
- streamlining/sharing with other PDPs (MMV, TB Alliance), new research agreements with the Drug Discovery Unit at the University of Dundee, and information sharing with the Consortium for Parasitic Drug Development at the University of North Carolina.

DNDi has taken efforts in the past year to consolidate its activities with strategic focus on proactive compound mining, chemical class screening, improved throughput of screening intracellular parasites, and general phenotypic screening. The following projects are part of DNDi’s discovery activities but are by no means comprehensive as DNDi continues to take on new exploratory activities.

**Oxaboroles: A Promising Lead Series**

Oxaboroles, now a promising lead series being optimised as part of the HAT lead optimisation consortium, have a unique boron-based chemistry that allows researchers at Anacor to use rational drug design in creating compounds with unique properties beyond traditional small-molecule drugs. As shown above, boron’s reactive P-orbital allows it to form a tetrahedral structure under certain conditions.

**REFERENCE SCREENING CENTRES**

Dedicated research groups at the London School of Hygiene and Tropical Medicine (LSHTM), Swiss Tropical Institute (STI), and the University of Antwerp serve as reference screening centers for DNDi in our efforts to harness existing expertise as well as to help ensure that screening results are comparable and standard for in vitro and in vivo assays at different sites and with different groups.
**SCREENING OF PROMISING CHEMICAL CLASSES**

**GSK - CYSTEINE PROTEASE INHIBITORS AND PYRIDONES**
- **Target diseases:** HAT, Chagas, and VL
- **Partners:** GlaxoSmithKline, Spain; Swiss Tropical Institute, Switzerland
- **DNDi/project manager and coordinator:** Denis Martin, Jean-Robert Ioset
- **Project start:** March 2008

In early 2008, GSK and DNDi formalized an ambitious collaboration which makes available a large GSK library of new cysteine protease inhibitors and a library of pyridone compounds to DNDi in order to examine their specific activities against kinetoplastid parasites as both compound libraries have shown good parasitic activity. Cysteine proteases (CP) are nearly ubiquitous in protozoan parasites, play a number of key roles in parasite survival (from nutrition to immune evasion), and have well-known structure-activity relationships. Pyridones have demonstrated potent in vitro and in vivo antimalarial activity. In 2009, over 500 compounds have been screened in vitro, and a number of compounds have been selected for further pharmacokinetic and in vivo efficacy testing.

**NITROIMIDAZOLES – PROACTIVE COMPOUND MINING**
- **Target diseases:** HAT, Chagas, and VL
- **Partners:** Swiss Tropical Institute, Switzerland; Fiocruz, Brazil; Ouro Preto University, Brazil; Covance, UK; Absorption Systems, USA; BioDynamics, UK; and a range of worldwide collaborators who have made compounds of interest available for testing, including ENH Research Institute, USA; Tehran Univ of Medical Sciences, Iran; Silesian Univ of Technology, Poland; LaSapienza Univ, Italy; Univ of Alberta, Canada; Univ of Tennessee, USA; Tokushima Univ, Japan; Univ of Auckland, Australia; sanofi-aventis, France; Roche, Switzerland; Novartis/NITD, USA-CH-Singapore; Alkem, India; TB Alliance, USA; Sigma-Aldrich, USA
- **DNDi/project manager:** Els Torreele
- **Project start:** January 2005

Nitroimidazoles are a well-known class of anti-infective compounds; however, the risk for genotoxicity linked to the nitro-group has been a concern for drug development. An extensive, proactive compound mining effort was undertaken by DNDi to ‘revive’ nitroimidazoles as drug leads against the kinetoplastid parasites. Over 700 existing compounds from 15 different sources were identified, accessed, and tested for in vitro and in vivo activity. Active compounds underwent extensive druggability profiling, including possible mutagenic activity, ADME, and pharmacokinetics. This approach has led to the discovery and characterization of fexinidazole as a promising drug candidate for HAT (see page 18) and with promising activity against *T. cruzi* (the parasite causing Chagas disease). Additionally, N-aryl-4-nitroimidazoles have been identified as a new lead series for HAT as a possible back-up for fexinidazole, should it fail in the clinic. Other nitroimidazoles have shown promising activity against *Leishmania* and *T. cruzi*, and are being assessed for their potential for further development. This research shows that it’s possible to select non-mutagenic nitroimidazoles with good antiparasitic activity.

**PHENOTYPIC SCREENING**

**DRUG DISCOVERY UNIT AT THE UNIVERSITY OF DUNDEE**
- **Target disease:** VL
- **Partners:** Drug Discovery Unit at the University of Dundee
- **DNDi/project manager and coordinator:** Eric Chatelain, Jean-Robert Ioset
- **Project start:** December 2008

The collaboration between the Drug Discovery Unit at the University of Dundee is focused on identifying molecules capable of killing the *Leishmania* parasite, which are suitable for further development into safe and effective medicines for clinical trials by DNDi’s partners. The DDU will use, as a starting point, the current knowledge and potential medicines developed within its African sleeping sickness programme. Researchers will utilise both a phenotypic and target-based screening approach in order to identify any promising ‘hits’ to be further developed.

**ESKITIS SCREENING OF NATURAL PRODUCTS**
- **Target disease:** HAT
- **Partners:** Eskitis, Australia; Griffith University, Australia
- **DNDi/project manager and coordinator:** Eric Chatelain, Jean-Robert Ioset
- **Project start:** November 2007

As part of early exploratory activities, DNDi accessed the natural products’ wealth and drug discovery expertise of Eskitis Institute for Cell and Molecular Therapies to examine the in vitro trypanocidal activity of 64,000 natural products from a diverse screening li-
brary of over 200,000 extracts. This unique lead-like peak library of natural products, which possess well-characterized physicochemical properties optimised for drug development, includes representatives of 60% of global plants and 9,500 marine invertebrates. The proprietary lead-like enhancement technology used by Eskitis is a two-step process which enriches extracts in lead-like and drug-like components prior to pre-fractionation; this process maximizes the chance of a positive outcome, i.e., detecting a ‘hit’. In 2008, the first ‘hit’, a marine invertebrate, was identified. As the project continues through 2009, the remaining 136,000 compounds have been screened, and hit expansion with 2 series is due to begin later in the year.

**KITASATO SCREENING OF NATURAL SUBSTANCES**

- **Target disease:** HAT  
- **Partners:** Kitasato Institute (KI), Japan  
- **DNDi/project manager and coordinator:** Eric Chatelain, Jean-Robert Ioset  
- **Project start:** April 2005

Natural products from microbial and plant resources, such as avermectin and artemisinin, have played an important role in the history of parasitic chemotherapy. Likewise, KI has a long history in the research and discovery of anti-infectious drugs from natural products, such as microbial metabolites and plant products. The objective of this specific project is to discover new types of antitrypanosomal molecules from KI natural products via in vitro and in vivo screening. Through March 2009, over 25,000 natural products and their synthetic derivatives have been screened, with 9 compounds having been identified as having high activity. These compounds are now being evaluated for possible lead optimisation at Scynexis, where researchers are currently undertaking hit expansion on one of the compounds, malonomycine; at the same time, KI will continue searching for further ‘hits’ to feed the pipeline.

**INSTITUT PASTEUR KOREA (IPK)**

Developing a technological breakthrough: IPK visual high-throughput screening (HTS)

- **Target disease:** Visceral leishmaniasis (VL)  
- **Partners:** Institut Pasteur Korea (IPK)  
- **DNDi/project manager and coordinator:** Eric Chatelain, Jean-Robert Ioset  
- **Project start:** December 2007

A cell-based, high-throughput visual screening system for *Leishmania* parasites offers the possibility to quickly generate new hits against novel targets. Utilising both the intellectual and technological capacity of the Institute Pasteur Korea, this project seeks to develop a major methodological advance in antileishmanial drug development as this will be the first HTS visual screening assay for the clinically relevant intracellular form of the parasite: intracellular Leishmania amastigotes in macrophages.

Having operationally begun in May 2008, the project first sought to develop and validate the visual assay in the first year so as to then use it in the second year of the project to test confirmed ‘hits’ against *Leishmania*. The project is now at a stage where a 200,000 compound library is being screened, with results expected later in 2009.

When the methodology is validated with the current screening run, this assay will be the first of its kind in the world, and it will then be expanded to include testing against other intracellular parasites such as *T. cruzi*. Such a visual screening would represent a huge advance for antitrypanosomal screening as well. Highlights of the ongoing research efforts were presented during the World Leishmaniasis Congress in February 2009, and the presentation is available on the DNDi website.

Visualization of intracellular Leishmania amastigotes in macrophages.
SLEEPING SICKNESS
Human African Trypanosomiasis (HAT)

At the forefront of DNDi’s efforts to develop new treatments is the need to understand the realities and treatment needs of patients and health care staff in the field. The ultimate goal for human African trypanosomiasis (HAT) is a truly simplified treatment which can be orally administered, implemented at the primary health care level, and effective against both stages of the disease. Currently, both diagnosis and treatment require a complicated series of tests and trained medical supervision. A key issue with HAT is that it affects hard-to-access communities in regions with poor health infrastructure; as a result, there is probably considerable underreporting of the condition. Poor access to medical facilities, a lack of resources and skills, and misdiagnosis all contribute to underreporting. Due to the resource-poor areas where the disease occurs, control efforts are often mobilised into vertical programmes. Consisting of a series of specifically equipped and trained diagnosis and treatment centres and mobile teams in endemic areas, but these programmes are not integrated into regional health centres. There is an immediate need to improve current treatment options, particularly for patients with advanced stage of the disease where the few drugs that are available are toxic, increasingly ineffective in killing the parasite, and difficult to use. Ideally, a treatment will be safe enough to be used in the first stage of the disease and effective enough in the second stage of the disease. In addition to lead optimisation programmes, DNDi has conducted proactive compound mining activities to identify existing compounds with potential against kinetoplastid diseases. The compound mining activities of DNDi have led to the revival of the nitromidazole class as potential drug candidates: the most notable example is fexinidazole, upon which DNDi has begun clinical development for HAT.

Several groups worldwide have specific established expertise and knowledge in drug discovery that are readily applicable to the discovery of new antitrypanosomal drugs. In this context, DNDi has established:

- Partnerships with pharmaceutical / biotechnology / academic groups for interaction and access to natural product as well as synthetic chemical libraries, chemistry, HTS, biological models, and drug design
- A network of key international laboratories to support discovery efforts with pharmacokinetic, pharmacodynamic, and toxicological expertise, and defined synergy between these laboratories.

At the clinical stage of development, DNDi is working to both investigate new medicines and to also strengthen capacity for clinical research on HAT. With the recent inclusion of NECT onto the WHO Essential Medicines List, DNDi is well on its way to meeting its short-term objective to bring a new, short-course, co-administration treatment for stage 2 HAT to the patients. Through this project, DNDi has also built important relationships with other groups involved in HAT clinical research as well as with the WHO, national HAT control programmes and NGOs working to control HAT.
SLEEPING SICKNESS – Human African Trypanosomiasis (HAT)

60 million people at risk in sub-Saharan Africa

WHAT IS THE ANNUAL IMPACT OF HAT?
- 50,000–70,000 cases [1]
- 48,000 deaths [2]
- 1,525,000 DALYs [2][3]

Large proportions of communities can be affected by HAT, with serious social and economic consequences. Epidemics at the end of the 20th century infected up to 50% of population in several villages across rural Africa.

HOW IS HAT TRANSMITTED?
Transmitted to humans by tsetse flies, HAT is caused by two sub-species of the kinetoplastid protozoan parasite, Trypanosoma brucei: T. b. gambiense (west African), T. b. rhodensiense (east African).

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
Available treatments are few, old, and stage-specific.
Stage 1 treatments, pentamadine and suramin, are fairly well-tolerated but still require injections and are mostly ineffective in stage 2.
For stage 2 (where most patients are diagnosed and thus treated), 2 available treatments exist:
- melarsoprol, an arsenic derivative: painful, toxic (killing 5% of those who receive it), increasingly (ineffective up to 50% resistance and treatment failure).
- eflornithine: difficult to administer and requires trained health staff and constant hospitalisation (requiring 56 infusions of 2 hours over 14 days), and resistance an increasing concern.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?
Improved treatment options for this fatal disease are urgently needed, particularly for stage 2.
- A safe, effective, and practical stage 2 treatment would improve and simplify current case management. This drug should ideally work in both stages of disease.
- A simple stage 1 treatment to be used at the local health centre level, would increase access to treatment and coverage.

WHERE DOES HAT OCCUR?
Of the 36 countries considered endemic for HAT, the 7 most affected countries represent 97% of all reported cases (see map). The Democratic Republic of the Congo (DRC) alone accounts for 2/3 of reported cases [4]. HAT primarily occurs in the poorest, most rural areas in Africa, where difficulty of diagnosis, political instability, and lack of health surveillance make estimates of disease prevalence difficult to ascertain.

WHAT ARE THE SYMPTOMS/PRESENTATIONS?
HAT occurs in two stages:
- stage 1 - the haemolymphatic phase – includes non-specific symptoms like headaches and bouts of fever (generally goes undiagnosed without active HAT surveillance).
- stage 2 - the later, neurologic phase – occurs when the parasite crosses the blood-brain barrier (BBB) and can lead to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and, ultimately, results in death without effective treatment.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?
Short term: better use of existing treatments
- Nifurtimox-eflornithine combination therapy (NECT), a simplified treatment for stage 2 HAT, now ready for use

Medium term: rediscovered compounds
- Fexinidazole: first drug candidate entering clinical development from nitroimidazoles project
- Back-up nitroimidazoles

Long term: new compounds and improved research capacity
- New drugs developed from compounds identified (i.e. oxaboroles) in discovery research and progressed through HAT lead optimisation consortium
- Multi-country, multi-partner HAT Platform to strengthen regional research capacity (see Section 3).

By 2014, DNDi aims to deliver from its HAT-specific portfolio:
- 1 new combination therapy recommended by WHO
- 1 new drug registered
- A robust pipeline

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[3] DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.
**HAT R&D Projects - 2009 Outlook**

### DISCOVERY

**LEAD OPTIMISATION CONSORTIUM**
- **Partners:** Scynexis, USA; Pace University, USA
- **DNDi project manager and coordinator:** Robert Don, Ivan Scandale
- **Project start:** April 2007

With an objective to develop optimised leads by progressing ‘hit’ molecules with a good safety profile and activity against *T. brucei* parasites, these consortia bring together expertise in chemistry, biology, screening, and pre-formulation. Optimisation focuses on the molecule’s capacity to be absorbed into the bloodstream, be distributed effectively to the infection, survive in the body, kill the parasite and not harm the patient. With two full lead optimisation teams in place (a total of 18 scientists), a number of hits identified from DNDi screening partners are undergoing hit expansion. Scientists within the consortia use advanced techniques to study how the selected molecules interact with the therapeutic target (i.e. a protein or an enzyme) and optimise the drug-like characteristics of these molecules to ensure that they comply with the target product profile. This phase requires a close, highly interactive collaboration between the biologists and chemists, who form a feedback loop: the biologists test the biological properties of compounds on biological systems while the chemists perfect the chemical structure of these compounds based on information obtained by the biologists. Two compound series have been chosen as lead series:
- oxaboroles, provided by Anacor and possessing a unique boron-based chemistry, were identified as hits against *T. brucei* at the Sandler Centre of the University of California San Francisco, and have shown in vivo activity.
- kinase inhibitors, of which approximately 300 analogs have been synthesized to date. Significant in vitro potency has been developed but only moderate in vivo activity, so further study is ongoing. These two series will continue to be optimised, with the goal to enter preclinical development in 2010 and 2011.

This strategy and the promising early results were presented during the 2008 meeting of American Society of Medicine & Tropical Hygiene, and are available at www.dndi.org.

### CLINICAL

**FEXINIDAZOLE**
- **Stage:** preclinical moving clinical development
- **Partners:** Accelera, Italy; Aptuit, UK; Ayantis, France; Covance, UK; Drugabisl, France; Labor für “Pharma and Umweltanalytik”, Germany; Germany sanofi-aventis, France; Swiss Tropical Institute, Switzerland
- **DNDi Project Manager:** Els Torreele
- **Project start:** February 2007

Fexinidazole as a drug candidate for stage 2 HAT is the first success of the proactive compound mining efforts DNDi has pursued in particular in the nitroimidazoles project (see page 13).
A 5-nitroimidazole that was in preclinical development as a broad-spectrum anti-protozoal by Hoechst in the early 1980s, fexinidazole was rediscovered by DNDi after being an abandoned compound. Extensive profiling by DNDi has shown that fexinidazole is orally active, and readily distributes to the brain and cures mouse models for both acute and chronic infection with African trypanosomes. Importantly, fexinidazole is not mutagenic in a panel of in vitro and in vivo mammalian genetic toxicology tests, confirming its favorable activity/toxicity profile as a drug candidate.

In 2007, a full preclinical programme was established to enable first-in-human studies. This included process chemistry and GMP-manufacturing of the active pharmaceutical ingredient, its preclinical formulation, extensive ADME-PK profiling and confirmatory studies in animal models of HAT, and the regulatory toxicology package (4-weeks repeated dose toxicokinetics in rat and dog, safety pharmacology, and an extensive genetic toxicology package). In June 2008, a full review of the data by DNDi concluded that fexinidazole is suitable for progression into clinical development.

Preparation for first-in human phase I studies are underway, including clinical tablet formulation considered a promising development candidate for HAT. Fexinidazole will enter into Phase I clinical studies in 2009, which would make it the only new drug candidate in clinical development for sleeping sickness. DNDi and sanofi-aventis have announced in May 2009 an agreement for the development, manufacturing and distribution of fexinidazole. Under the terms of the agreement, DNDi will be responsible for non-clinical, clinical, and pharmacological development and sanofi-aventis will be responsible for the industrial development, registration, and production of the drug at its manufacturing sites.

This project and the preclinical results were presented during the 2008 meeting of American Society of Medicine & Tropical Hygiene, and are available at www.dndi.org.

**COMBINATION THERAPY (NECT)**

Now available for use after being added to the WHO Essential Medicines List as treatment against stage 2 sleeping sickness

- **Stage:** clinical
- **Partners:** Epicentre, France; MSF, the national HAT control programmes of the Democratic Republic of the Congo (DRC) and the Republic of the Congo; SCH/STI, Switzerland
- **DNDi/project manager:** Els Torrelee
- **Project start:** April 2004

With the ultimate goal to enable a WHO recommendation on the use of the nifurtimox-eflornithine combination therapy (NECT), the NECT project has shown that the combination is as effective and safe as standard eflornithine monotherapy, but easier to use, and safer than melarsoprol (toxic though still widely used in ~70% of patients with stage 2 HAT).

Begun originally as a single centre study by MSF-Holland and Epicentre in the Republic of Congo (Brazzaville) in 2003, this study was extended, as of 2004, to additional sites in the DRC by DNDi in collaboration with Epicentre, MSF, STI and the national HAT control programmes of the DRC.

This multi-centre clinical study, which enrolled 287 patients and was completed in 2008, compared the safety and efficacy of NECT, a coadministration of the oral drug nifurtimox and the intravenous drug eflornithine, with eflornithine monotherapy, the current first-line treatment for stage 2 T. b. gambiense HAT. As is requisite to establish efficacy in this disease, patients were actively followed up for 18 months after treatment.

The study conclusively demonstrated that NECT is as well-tolerated and efficacious as eflornithine. At the end of 2008, the final efficacy and safety results of the Phase III study were available and led to DNDi’s submission of NECT for inclusion on the WHO Essential Medicines List (EML). The final results are in the process of being published, and were presented by Epicentre during the 2008 meetings of American Society of Medicine & Tropical Hygiene and the HAT Platform, and are available at www.dndi.org. The EML application and support statements of the HAT community are available on the website of the WHO Essential Medicines List.

In May 2009, MSF, Epicentre, and DNDi announced that NECT had been included on the EML. According to the WHO, NECT can now be used in patients and will provide an opportunity to improve the management of HAT cases. The WHO has already made preparations for the arrival of this improved therapeutic opportunity and is working to ensure that patients have access to NECT by providing appropriate training and supplying the drugs and necessary equipment to disease-endemic countries.

DNDi and partners are conducting a field study, which began enrolling patients in April 2009, to further document the safety and ease of use of the combination in real-life field conditions and in special populations like children.

**Recognised as**

“Project of the Year in 2008”
Based on the current R&D landscape, the realities in VL-endemic regions, the limited treatment options, DNDi and partners have determined that the ideal product should be oral, safe, effective, low cost, and short course (≤10-day). Ideally, this treatment will be effective against all forms of the disease and is adequate for use in rural health settings.

As it can take five to ten years to bring a compound through the preclinical and clinical phases of development, DNDi is currently building on previous research by extending the registration and availability of current drugs, while maximizing their potential and minimizing their drawbacks.

Combination therapies of these new treatments represent a critical path forward because they could offer the following important advantages: shorter course of treatment, better tolerability, reduction in the work load on the health systems in resource-limited areas, better affordability, and potential to prevent or retard resistance development and prolong the life span of these drugs.

DNDi has three clinical (active) projects: one examining combination treatments (AmBisome®, paromomycin, miltefosine) in India and two ongoing studies in East Africa. In addition to completing these projects, DNDi will conduct further work to improve combination treatments. Several products including new oral formulations of amphotericin B, 8-aminoquinolines, and potential compounds at late preclinical phase are considered and could be made available to patients as early as possible. In addition, DNDi has a lead optimisation programme which will bring new candidates into clinical development over the next few years. All of these new drugs will also be considered for combination therapy.

Using a multi-disciplinary approach, DNDi will bring practical, safe and effective treatments to VL patients that will be a significant step in helping to control the disease in South Asia, East Africa, and Latin America.
KALA-AZAR – Visceral Leishmaniasis (VL)

200 million people at risk worldwide

WHAT IS THE ANNUAL IMPACT OF LEISHMANIASIS?
- 500,000 cases of VL; 1.5 million cases of CL
- 51,000 deaths
- 2,357,000 DALYs

A lack of surveillance systems and frequency of misdiagnosis means that it is difficult to estimate the true incidence and case-fatality rate of VL.

HOW IS LEISHMANIASIS TRANSMITTED?

Diversity and complexity mark the disease leishmaniasis: more than 20 species of the kinetoplastid protozoan parasite Leishmania are transmitted to humans by ~30 species of phlebotomines sandflies.

WHAT IS LEISHMANIASIS?
Leishmaniasis is a disease with several forms. The two most common are:
- VL: fatal without treatment
- cutaneous leishmaniasis (CL): has a spectrum of presentations: typically with self-healing or chronic lesions on the skin. VL is the primary disease target for DNDi, whereas CL is secondary, mainly because it is typically not life-threatening.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

The number of treatment options has increased in the past decade, but each treatment has numerous drawbacks, such as difficulty to administer, length to treat, toxicity, cost, and increasing parasitic resistance to treatment:
- Pentavalent antimonials: toxic & increasingly ineffective due to resistance; 30-day, hospital-based parenteral treatment
- Amphotericin B: dose-limiting toxicity; 15-20 day, hospital-based IV treatment
- Liposomal amphotericin B (AmBisome®): effective, but expensive
- Paromomycin: registered in India, but efficacy in Africa not yet determined
- Miltefosine: first orally available drug registered in India, but expensive and teratogenic.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?
Patients need a treatment which is oral, safe, effective, low cost, and short course (<10-day course).

WHERE DOES LEISHMANIASIS OCCUR?
Leishmaniasis infects approximately 12 million people in 88 countries.
VL affects poor, remote populations in 70 countries across Asia, East Africa, South America, and the Mediterranean region (see map).
The 7 most affected countries – Bangladesh, Brazil, India, Ethiopia, Kenya, Nepal and Sudan – represent over 90% of new cases.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

Short term:
- Better use of existing treatments through geographical extension and new combinations.
  - Combination in Africa: Registration of paromomycin in 2010, recommendation of combination including paromomycin + sodium, stibogluconate (SSG), registration of AmBisome® in 2011, registration of miltefosine, development of combination with short-course AmBisome®
  - Combination in India: Recommendation in India, Bangladesh and Nepal by 2011
  - Combination in Latin America: Recommendation in 2013

Medium term:
- Registration of one new drug through new formulations of existing treatments and therapeutic switching
  - Alternative formulations of amphotericin B – DNDi is evaluating an oral formulation developed by BioDelivery Sciences International (BDSI)
  - 8-aminoquinolines – DNDi is in discussion with GlaxoSmithKline (GSK) about tafenoquine and sitamaquine for clinical development
  - Potential compounds in-sourced at late preclinical phase – DNDi is actively pursuing potential candidates ready for clinical development in the short term

Long term:
- New compounds and improved research capacity
  - New drugs developed from compounds identified (i.e. 2-quinolines) in discovery research and progressed through VL lead optimisation consortium
  - Multi-country, multi-partner LEAP to strengthen regional research capacity (see Section 3).

By 2014, DNDi aims to deliver from its VL-specific portfolio:
- 1 new drug registered
- 1-3 geographical extensions in endemic regions outside India by 2014
- 1-3 coadministrations recommended by WHO
- A robust pipeline

(4) Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of developing countries as of 2007.
DISCOVERY

LEAD OPTIMISATION CONSORTIUM
- Partners: Advinus, India; CDRI, India
- DNDi project manager and coordinator: Denis Martin, Delphine Launay
- Project start: November 2007

With a full team in place, including 12 team members at the two primary partner sites, assessment of three series of synthetic compounds has been conducted and chemistry-biology activities have begun to bear fruit, with the promising lead series of 2-quinolines. Partners at the "Institut de Recherche et Development" (IRD) originally isolated the 2-quinolines from Bolivian plants, which are used in traditional medicine to treat cutaneous leishmaniasis and malaria. After some promising early results, the DNDi-managed LO consortium has synthesised more than 250 diverse analogues of 2-quinolines. These modified quinolines were significantly more effective than the parent compounds and a few compounds have shown >90% parasite killing at <1.0 μM. Metabolic stability, which is a known liability of this series, has been improved through the introduction of halogen substituents in more than ten compounds. Further studies of the most promising compounds are underway to confirm the druggability and in vivo efficacy and safety. More hits from the other chemical series, including oxaboroles and licochalcones, provided by DNDi screening partners will be continue to be examined by Advinus.

This strategy and the promising early results were presented during the World-Leish4 meeting in February 2009 and are available at www.dndi.org.

PRECLINICAL

BUPARVAQUONE
- Partners: Advinus Therapeutics, India; Drugabilis, France; University Sains, Malaysia; LSHTM, UK
- DNDi project manager: Denis Martin
- Project start: January 2008

Buparvaquone has been shown to exhibit antileishmanial activity in vitro and in vivo. However treatment of dogs infected with visceral leishmaniasis failed to halt disease progression. It was postulated that the disappointing in vivo data, when compared to in vitro potency may be a result of low plasma levels in the experimental animals. Preliminary animal studies at the Universiti Sains, Malaysia, and DNDi-commissioned studies at Advinus Therapeutics have shown that oral absorption of buparvaquone is dissolution-rate limited and that a self-emulsifying drug delivery system (SEDDS) can increase absolute oral bioavailability to greater than 60%. Such an increased bioavailability should be reflected by an improved efficacy.

Buparvaquone efficacy was further tested in a Phase 1a clinical trial with the disappointing in vivo data, when compared to in vitro potency. This strategy and the promising early results were presented during the World-Leish4 meeting in February 2009 and are available at www.dndi.org.
tions (oily suspension) have limitations

at LSHTM in a mouse model. In parallel,
the toxicology profile was also assessed.
Buparvaquone was tested under conditions
allowing maximum exposure. As solubility
is a limiting factor even in lipid-based for-
mulations, the intravenous (iv) route was
preferred. Buparvaquone, when using an iv
formulation leading to maximum exposure,
did not show activity within the non toxic
dose range. It was therefore decided not to
move further with this compound.

Meanwhile, a focused medicinal chem-
istry program was initiated at Advinus,
so as to increase solubility while ensur-
ing the structure-activity relationship. The
rationale is based on the assumption that
buparvaquone’s efficacy is limited by its
poor solubility. A limited number of scaf-
dolds have been synthesized, and decisions
will be made by the end of the 2009 as to
whether to move forward with any of the
scaffolds.

**ALTERNATIVE FORMULATION OF AMPHOTERICIN B POLYMER**

- **Partners:** Polyspherics, UK; London School of Pharmacy, UK; Imperial College, UK; LSHTM, UK; BioDelivery Sciences International (BDSI), United States
- **DNDI Project Manager:** Denis Martin
- **Project start:** September 2006

The goal of this project is to identify an
ampicillin B-based formulation which
shows the most promise in terms of in vivo
efficacy, safety, low cost, and heat stability.
Amphotericin B, under various formula-
tions, has become one of the most efficient
treatments for VL. The standard formula-
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tions, has become one of the most efficient
al formulation has overcome these
limitations, but its cost and stability are
serious limits to its wide-spread use. There
has been very limited use in VL–endemic
regions of Africa and Asia, where disease
burden is greatest, because of its high cost.

Recently, new formulations have emerged
and are approved or under clinical develop-
ment in India. However, their intravenous
route of administration is still a barrier for
appropriate use in the field. Studies aimed
at replacing the lipid-based component
with a narrow molecular weight polymer
are ongoing, with the goal of developing a
soluble complex, cheaper, and exhibiting
increased thermal stability. Polymers can
also prevent the systemic toxicity of am-
photericin B to which they are conjugated,
still allowing the drug intracellular delivery.
The team in the UK has been investigating
a less expensive, modified metacrylic poly-
mer; efforts to establish adequate in vivo
efficacy in a disease model while optimis-
ing key characteristics of the polymer did
not yield promising results, so this part of
project was concluded in early 2009. Re-
cently, two new formulations of amphoter-
icin B – phospholipid-based cochleates and
a lipid-based form with enhanced gastroin-
testinal tract absorption – have been re-
ported to show activity as antifungals when
administered orally in animal models. Early
reports suggest that they also exhibit activ-
ity in murine models of visceral leishma-
niasis. BDSI has developed an oral formul-
ation that is currently in Phase I, targeting
fungal infections. DNDI is conducting an
exploratory preclinical evaluation of this
oral formulation for VL and, if successful,
will proceed to clinical development.

**CLINICAL**

**COMBINATION THERAPY FOR VL IN ASIA (INDIAN SUBCONTINENT)**

- **Partners:** ICMR, India; Kala Azar Medical Research Centre, India; Rajendra Memorial Research Institute of Medical Sciences, India; GVK BIO, India
- **DNDI project manager and coordinator:** Farrokh Modabber, Sally Ellis
- **Project start:** December 2006; revised protocol approved October 2007

With the objective to identify a safe and ef-
fective short-course combination therapy
using existing drugs which could be easily
deployed in control programmes, this four-
arm, definitive phase III combination therapy
study is using drugs already reg-
istered in the region: AmBisome®, miltefo-
sine, and paromomycin. Three arms with a
combination of 2 drugs/arm for a maximum
of 15-day treatment will be compared with the
standard 30-day therapy using amphi-
tericin B. In June 2008, the first patient was
enrolled into the study. Enrolment should
be completed in June 2009, and results are
expected by early 2010. The study has been
designed to provide data for authorities
in India, Bangladesh and Nepal to make
informed recommendations for combina-
tion treatment which can be used in the
elimination programme. Discussions are
ongoing to initiate bridging trials in Bang-
ladesh and Nepal to evaluate the safety of
the same combinations, followed by larger
trials for further evaluation of safety and ef-
cacy. It is anticipated that these combina-
tion treatments will be shorter, safer and
cheaper than the standard treatment.
VL COMBINATION IN AFRICA

A step together in the right direction

LEAP and DNDi study combination therapy for Africa: making the best of what we have, making it better and protecting it for the future

In the next year, DNDi and LEAP will embark on additional clinical research to examine new potential combination therapies, including a geographical extension study on miltefosine, one of the few oral drugs effective against leishmaniasis.

PAROMOMYCIN FOR AFRICA

- **Partners**: LEAP (Leishmaniasis in East Africa Platform) group including Kenya Medical Research Institute, Kenya; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; University of Makarere, Uganda; Ministries of Health in LEAP countries; Médecins Sans Frontières (MSF); 1+ Solutions, the Netherlands; LSHTM, UK; University of Nairobi, Kenya; Institute for One World Health, USA

- **DNDi project manager & coordinator**: Manica Balasegaram; Sally Ellis

- **Project start**: November 2004

In Africa, visceral leishmaniasis is difficult to treat with existing drugs due to various issues, such as toxicity, emerging resistance, difficulty of use, and cost. Paromomycin (PM), an aminoglycoside antibiotic that was identified as an antileishmanial in the 1960s, has the potential to be an improved treatment at a lower cost when combined with the standard treatment of sodium stibogluconate (SSG).

Currently being made available throughout the Indian subcontinent by fellow PDP, Institute for One World Health (IOWH), paromomycin is being studied in parallel by DNDi and the Leishmaniasis East Africa Platform (LEAP) in Ethiopia, Kenya, Sudan, and Uganda. The aim is to register paromomycin as a new treatment in each region, to have it adopted in national treatment guidelines, and to evaluate the shorter course combination of PM+SSG as an alternative treatment for VL.

After early results showed the initial dosage of paromomycin did not work as well in Africa as it did in India, LEAP decided to increase the dose and is now examining a higher-dosage regimen to determine if it is more effective. Over 1000 patients have been recruited so far into the various arms of the study.

In 2008, the study is continuing to recruit patients at sites where infrastructure has been improved or built (see section 3). Initial data was presented during the 2007 RSTMH symposium, and final results of the early part of the study were presented during the WorldLeish4 meeting in February 2009; are in the process of being written up for publication, and are available at www.dndi.org. The study is due to complete in 2009, with final results being ready by the spring of 2010.

AMBISOME® FOR VL IN AFRICA

- **Partners**: LEAP (Leishmaniasis in East Africa Platform) group including Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Ministry of Health, Ethiopia; Kenya Medical Research Institute, Kenya; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; University of Makarere, Uganda; Ministries of Health in LEAP countries; 1+ Solutions, the Netherlands; LSHTM, UK; Gilead, USA

- **DNDi project manager & coordinator**: Manica Balasegaram; Sally Ellis

- **Project start**: Approved in May 2006; study start in May 2009

Ambisome®, a liposomal formulation of amphotericin B manufactured by Gilead, has been used with increasing frequency to treat VL, especially in Europe, over the past decade. Unfortunately, in Africa and Asia, where disease burden is high, drug access is poor because of the high cost of the drug. With recent preferential pricing offered by the manufacturer to patients in the public sector in East Africa, it is possible that Ambisome® could become economically feasible for treatment, even in resource-poor countries.

The goal of this project, therefore, is to determine the minimum dose of Ambisome® that is efficacious, safe, and cost effective in the treatment of VL in Africa, to reduce the length of hospital stay, and to facilitate registration and adoption of Ambisome® in the region. Identifying the minimum dose for monotherapy will be an important step in developing combinations for Africa and in preventing the development of drug resistance. Early in 2009, DNDi has received approval from both the national ethics committees and from the Ethiopian regulatory authority. The study began enrolling patients in May 2009.

LEAP, who coordinates and runs both of these studies, has been recognised as “Partnership of the Year in 2008”
Until recently, the primary focus for disease control has been interruption of transmission by vector control programmes and screening of blood donors. Major initiatives began in the Southern Cone countries in 1991 and 1992. Most central and southern American countries joined the initiative over the following decade. Despite these advances in reducing the incidence of T. cruzi infection, the burden of Chagas heart disease is expected to continue in the future since virtually all of the burden of Chagas heart disease comes from individuals already infected who progress from the indeterminate phase to the chronic phase.

Current therapy for Chagas disease is limited to two nitroheterocyclic drugs, nifurtimox and benznidazole. Unfortunately, these drugs are limited to treatment of acute infection in children with conflicting evidence for treatment of indeterminate disease and no evidence to support their use as therapy for symptomatic chronic disease. Even in children, who are more able to tolerate the considerable toxicity associated with treatment, the cure rate is only around 60%. No new anti-T. cruzi drugs are in the clinical development pipeline and only one class of drugs, the antifungal triazoles, have demonstrated potential for therapeutic switching to the treatment of Chagas disease.

The Chagas disease-specific portfolio is a balance of objectives. In the short- and midterm, the aim is for better use of existing treatments through new formulations, therapeutic switching and combination therapy. In the long term, new chemical entities must be developed. Another important element in DNDi’s strategy in Chagas disease is to address the methodological constraints that impact the design of clinical studies.

**Chagas Disease**

<table>
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<tr>
<th>PRIORITY TARGET</th>
<th>PRODUCT PROFILE FOR CHAGAS</th>
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<tr>
<td><strong>A new treatment</strong> for adults and children for acute and early chronic disease</td>
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<td>Priority is a pediatric formulation</td>
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WHAT IS THE IMPACT OF CHAGAS DISEASE?
Approximately 8 million cases (1)
14,000 deaths (2)
667,000 DALYs (2)(3)
Chronic Chagas disease results in significant disability with great social and economic impact including unemployment and decreased earning ability. In Brazil alone, losses of over US$ 1.3 billion in wages and industrial productivity were due to Chagas disease (4).

HOW IS CHAGAS DISEASE TRANSMITTED?
Caused by the kinetoplastid protozoan parasite Trypanosoma cruzi, Chagas disease is primarily transmitted by large, blood-sucking reduviid insects widely known as “the kissing bugs” in endemic countries. Other ways of transmission are blood transfusion, organ transplantation, as well as congenital and oral transmissions.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
Current treatments can cure infected patients, but highest efficacy is seen early in infection.
– Benznidazole, nifurtimox to treat acute & early indeterminate disease:
  • Long treatment period (30-60 days)
  • Dose-dependent toxicity
  • High rate of patient non-compliance
  • No paediatric strengths
No treatment for chronic disease.

WHAT ARE THE PRIORITY PATIENT TREATMENT NEEDS?
– A paediatric strength which is affordable, age-adapted, safe, and efficacious would cure patients early on in the disease.
– A new drug for chronic disease that is safe, efficacious, and adapted to the field, and ideally would work in both stages of the disease.

WHERE DOES CHAGAS DISEASE OCCUR?
Endemic in 21 countries across Latin America, Chagas disease kills more people in the region each year than any other parasite-born disease, including malaria. Patient numbers are growing in non-endemic, developed countries, due to increased movement of unknowingly infected people unknowingly carrying the parasite in their blood (see map).

WHAT ARE THE SYMPTOMS/PRESENTATIONS?
The disease has two clinical stages:
– acute (in which 5% of children die) - characterised by fever, malaise, facial oedema, generalised lymphadenopathy, and hepatosplenomegaly – often spontaneously resolves in four to six weeks
– chronic disease has two phases:
  – chronic asymptomatic “indeterminate” disease, during which patients can transmit the parasite to others while showing no signs of the disease, can last 10 years to life
  – chronic symptomatic disease develops in 10% to 30% of infected patients and most often involves the heart or gastrointestinal tract.
Chagas disease is a leading cause of infectious heart disease (cardiomyopathy) worldwide.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?
Short term: better use of existing treatments through new formulations
– Paediatric strength of benznidazole: first treatment designed specifically for children
Medium term: development of new treatments through therapeutic switching and combination therapy
– Azoles: clinical development of a well-known compounds already developed against fungal infections for use as Chagas disease monotherapy and/or in combination with existing drugs
Long term: new drugs, and improved research & treatment capacity across region
– Nitroimidazoles: a well-known class of anti-infective compounds
– New drugs developed from promising compounds identified in discovery activities (such as GSK library of pyridones and cysteine protease inhibitors) and progressed through Chagas lead optimisation consortium.
– A multi-country, multi-partner Chagas clinical research platform in preparation (see Section 3).

By 2014, DNDi aims to deliver from its Chagas-specific portfolio:
– 1 new paediatric strength available
– 1 new drug registered
– A robust pipeline

(3) DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. (4) Moncayo A, Ortiz Yanine M. Ann Trop Med Parasitol. 2006;100:1-15.
In 2008, a lead optimisation consortium was set up by DNDi so to engage in a critical, iterative process that helps to optimise the efficacy of a lead compound while minimizing its toxicity. This consortium includes institutions in Australia (Monash and Murdoch Universities and Epichem) and Brazil (Universidade Federal de Ouro Preto) and consists of a group of analytical and medicinal chemists, pharmacologists and parasitologists with rapid turnaround facilities or compound assessment. A full lead optimisation team has been now been put in place to assure the speed of the highly iterative process. Into 2009, five classes of compounds identified in DNDi screening programmes were further assessed in hit-to-lead studies. Work is ongoing to select a single series for lead optimisation by the end of the year.

A new generation of antifungal triazoles including posaconazole, voriconazole and ravuconazole show considerable promise as antiparasomal agents. The marketed antifungal drug posaconazole (Noxafil®, Schering-Plough), has previously been shown to induce parasitological cure in mice with acute and chronic infections, including benznidazole-resistant strains. It is considered the leading azole candidate for proof-of-concept evaluation. DNDi has been in discussion and negotiation with Schering-Plough since 2006. Two other triazole derivatives, ravuconazole (Eisai) and TAK-187 (Takeda) have shown encouraging in vitro and in vivo results. Both products have completed Phase I testing and are good candidates for further assessment as potential treatments. In 2009, DNDi continues to progress on the goal of advancing either posaconazole or another azole into clinical research on Chagas disease patients, if data and conditions are favorable, and to examine other molecules from the same family as potential drug candidates.

Patients with Chagas disease often live in rural and remote settings. Chagas disease both afflicts the poor and, like other neglected tropical diseases, "promotes poverty" through its impact on worker productivity, premature disability, and death.
Chagas disease leaves a memorable impression in the areas where the disease is endemic.

Preclinical combination studies with azoles. A main treatment limitation in Chagas disease is the poor tolerability reported with currently available treatments. Side effects of benznidazole and nifurtimox are both time- and dose-dependent. Combination therapy could improve treatment efficacy, reduce dose, treatment duration and toxicity, and could also prevent the potential development of resistance to anti-infective drugs. Azole derivatives have shown synergistic anti-T. cruzi effects, in vitro and in vivo, with benznidazole and other compounds involved in the sterol biosynthesis pathway. Taking these results into consideration, DNDI has begun preclinical studies with the objective of reducing the dose and duration of current Chagas treatments by systematically evaluating, in animal models, several azole compounds as monotherapy and in combination with the two existing drugs available for Chagas disease. Preliminary in vivo results demonstrated a clear synergistic effect for both combinations with posaconazole, with reduction of mortality and parasitaemia suppression observed in animals. These data will be confirmed in further studies, and will help to inform future clinical evaluation of the azole class.

Meeting an acute patient need...

By developing and making available the only paediatric formulation for Chagas disease

- **Stage:** clinical
- **Partners:** Pharmaceutical Laboratory of Pernambuco State (LAFEPE), Brazil; Tulane University – Centro Nacional de Diagnostic o e Investigacion de Enfermedades (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK
- **DNDI project manager and coordinator:** Isabela Ribeiro, Bethania Blum
- **Project start:** June 2008

Since the 1990s, there is consensus for early diagnosis and treatment of children and adolescents in the early indeterminate (chronic) phase of Chagas disease. Young children remain an important target population for treatment despite decreasing vectoral transmission, because congenital infection may remain an important mode of transmission for at least another generation.

This is not reflected in the current treatment options as current drugs are formulated as tablets for adults, not adapted to children weights. Tablet fractionation and extemporaneous formulations are needed to treat most children: these procedures increase the likelihood of improper dosages and raises safety concerns, particularly in the very young and malnourished, reduced efficacy (due to the addition of diluents) and stability concerns.

Benznidazole, one of only two products registered for Chagas disease, can be highly efficacious in children yet no paediatric formulation exists. For the majority of children, the 100-mg tablet must be fractionated (broken into pieces). A number of approaches have been examined to best meet the need of developing a new paediatric formulation which is affordable, age-adapted, and easy to comply with.

With the goal to develop an adapted, dispersible tablet of benznidazole, DNDI and LAFEPE signed a development deal in July 2008. Since then, the project team has been engaged in pre-formulation and analytical development activities. Using current benznidoazole dose recommendations, dosing practices, and patient age and weight profiles from 10 centers which treat children with T. cruzi infections as a guide, the team has determined the most appropriate paediatric tablet formulation, strength and associated dosing regimen. Work is progressing, with batch production and stability testing planned for later in 2009.

Currently, benznidazole tablets are fractionated by hand into 1/2 and 1/4 tablets (as seen at a health post in Honduras). Fractionation of tablets is not ideal - a paediatric formulation would improve the proper use of benznidazole.
Further progress made in fighting an old disease as FACT products gain ground in Africa and Latin America

The past year has seen efforts by DNDi and our industrial partners take further hold in the field of malaria treatment, particularly with the WHO prequalification of ASAQ, its growing use in the public market, and the proactive monitoring plan of ASAQ in “real-life” conditions, which includes the most ambitious proactive pharmacovigilance programme ever launched in Africa, for any drug. Important progress has also been seen with ASMQ as the first purchase was made by Brazilian authorities in April 2009, and plans for technology transfer to Asia and study of its possible use in Africa are afoot.

As we in the world malaria community move forward in meeting the needs of those suffering from malaria, one of the main strategies for malaria prevention and control is prompt and effective treatment. It has been well established that drug combinations are a strategic and viable option in improving efficacy, and in delaying development and selection of resistant parasites (after lessons learned with widespread resistance to chloroquine and SP).

Artemisinin-based combination therapy is nowadays the best therapeutic option for treating drug-resistant malaria and retarding the development or spread of parasite resistance. Since 2001, the WHO has recommended combination therapies containing an artemisinin derivative and, in 2006, strengthened its recommendations to say that fixed-dose combinations (FDCs) should be used wherever possible.

The advantages of using FDCs have been well documented in several disease areas, including malaria, tuberculosis and HIV/AIDS. FDCs offer several potential advantages: increasing patient adherence to treatment, delaying the development of parasite resistance, decreasing total treatment cost (including production, storage, and transport), reducing the risk of me-
Malaria

3.2 billion people at risk

WHAT IS THE ANNUAL IMPACT OF MALARIA?
350 to 500 million new cases
Over 1 million deaths
42,280,000 DALYs

Malaria is the leading parasitic cause of morbidity and mortality worldwide, especially in developing countries where it has serious economic and social costs.

Malaria is thought to slow annual economic growth by 1.3% in endemic areas with high prevalence. The economic cost of malaria in Africa alone is estimated at US$12 billion every year.

HOW IS MALARIA TRANSMITTED?
Transmitted from person to person by the bite of anopheline mosquitoes, malaria is caused by the Plasmodium parasite.

Four species are involved: P. falciparum, P. malariae, P. vivax, and P. ovale. P. falciparum is the main cause of severe clinical malaria and death.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
- Widespread drug resistance: chloroquine, one of the easiest to use and most available malaria treatments, is no longer effective, with parasite resistance at more than 90% in some parts of the world.
- Existing combination therapies, now adopted as first-line treatment in most malaria-endemic countries, can be expensive and have complicated treatment regimens.
- Limited access of neglected patients to the few paediatric strength, fixed-dose ACTs which are available.
- The countries suffering the most from malaria lack the necessary capacity and funding to deliver the drugs to the patients who need them.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?
Patients in malaria-endemic countries need inexpensive, efficacious, and field-adapted drugs.

WHERE DOES MALARIA OCCUR?
Malaria is present in over 100 countries and threatens half of the world’s population.

In sub-Saharan Africa, where it is the single largest cause of death for children under five, malaria kills one child every 30 seconds – approximately 3,000 children every day.

WHAT ARE THE SYMPTOMS/PRESENTATIONS?
Malaria begins as a flu-like illness 8 to 30 days after infection. Symptoms include fever (with or without other signs or symptoms such as headache, muscular aches and weakness, vomiting, diarrhea). Typical cycles of fever, shaking chills, and drenching sweats may then develop. Death may be due to brain damage (cerebral malaria), or damage to vital organs.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi’s malaria-specific portfolio aims to facilitate the widespread availability of the two products delivered by its diverse partners in the Fixed-Dose Artesunate Combination Therapy (FACT) Project.

Because of numerous antimalarial R&D activities (eg. Medecines for Malaria Venture), DNDi is phasing out its malaria activities to focus on the kinetoplastid diseases.

The FACT Project has produced 2 fixed-dose ACTs which are:
- Easy to use as given in a single daily dose of 1 or 2 tablets for 3 days
- A 2-in-1 fixed-dose combination (FDC) of drugs that ensures both drugs are taken together and in correct proportions
- Age-based dosing to facilitate proper dosing in rural, remote areas
- ASAQ – FDC of artesunate and amodiaquine for treatment of malaria in sub-Saharan Africa; now registered in 24 countries
- ASMQ – FDC of artesunate and mefloquine registered in Brazil in March 2008 and in use by Brazilian national authorities as part of ongoing intervention study

Through 2014, DNDi will support the proper use to work to facilitate access to these FACTs along with the other effective ACTs so as to maintain the effectiveness of artemisinin as a first-line treatment.

[2] DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.
dication errors by prescribers or patients themselves, and preventing the risk of medication given in combination to be taken only as monotherapy.

Following the recommendations of WHO and independent malaria experts, DNDi developed fixed-dose combination of ACTs (FDC-ACTs or FACTs) as part of its overall R&D efforts begun in 2003. In building partnerships with industrial partners – sanofi-aventis for ASAQ and Farmanguinhos/Fiocruz for ASMQ - from an initial network of public partners, DNDi has ensured that these products be developed as non-exclusive public goods and at cost so that the largest potential global health benefit could be attained.

As a result of these efforts, new effective, easy-to-use and affordable FDC-ACTs are now available or under development. Through DNDi and its partners, artesunate-amodiaquine (ASAQ), and artesunate-mefloquine (ASMQ) are now available. In addition, efforts by Medicines for Malaria Venture (MMV), have led to the availability of a paediatric version of artemether-lumefantrine (AL), and the development of dihydroartemisinin-piperaquine (DHA/PQ), which is expected to become available in the second quarter of 2010.

Although the existing armamentarium of FDCs for the treatment of uncomplicated malaria is relatively limited nowadays, there are an increasing number of FDC-ACT manufacturers. With the April 2009 launch of the AMFm, DNDi joined MSF in its call for the exclusive use of FDC to further incentivise drug makers to enlarge the FDC-ACT pipeline.

Among the most studied ACTs is the three-day treatment with artesunate (AS) and mefloquine (MQ), which has shown to be a highly effective therapy against uncomplicated falciparum malaria. Used in the field for 16 years, the combination of AS and MQ has been one of four ACTs recommended by WHO since 2001 as first-line treatment for uncomplicated falciparum malaria.

ASMQ, the new co-formulation of AS and MQ, offers a simple regimen for children and adults that is as easy as 1-2-3: a single daily dose of one or two tablets over three days. This co-formulation was one of two malaria projects undertaken in 2002 by a number of public and private partners coordinated by TDR and MSF (who turned over the project to DNDi upon its foundation) as part of the FACT (Fixed-Dose, Artesunate-Containing Therapy) Project.

April 2008 marked an important milestone for ASMQ as the first public order was completed by Brazil. DNDi’s public industrial partner Farmanguinhos/Fiocruz successfully registered ASMQ in April 2008, and the co-formulation has been used by Brazilian national authorities as part of an intervention study, where preliminary results after one year show a greater than 70% drop in P. falciparum malaria cases and an approximate 65% reduction in malaria-related hospital admissions. The study has now treated over 23,000 patients with ASMQ. Work is ongoing to clean the data set and finalise the results.

In 2009, registration processes for ASMQ in 2 or 3 other countries in Latin America are being navigated; it will be submitted for PAHO prequalification; and Farmanguinhos/Fiocruz will continue its technology transfer to the Indian generics manufacturer, Cipla, in order to facilitate its future availability in Southeast Asia. Further clinical research with partners is in preparation to examine the potential therapeutic value of ASMQ in pregnancy and in Africa. A clinical study in India has recently been completed, with analysis ongoing, and a dossier for registration in India will be submitted by the end of 2009.

ASMQ is the only fixed-dose ACT available with a 3-year shelf life. Optimised for rural and remote settings. An innovative weight- and age-based dosing regimen, of 180,000 individuals, This work, as well as preliminary results from the Brazilian intervention study, was presented during the 57th American Society of Tropical Medicine & Hygiene in December 2008 and is available at www.dndi.org
**ASAQ, FIXED-DOSE ARTESUNATE/AMODIAQUINE COMBINATION THERAPY**

More than 20 million of ASAQ treatments to be delivered for African malaria patients during 2009

- **Stage:** Phase IV post-registration monitoring and access
- **Target disease:** malaria
- **Partners:** sanofi-aventis, France; Medicines for Malaria Venture, Switzerland; National Centre for Research and Development on Malaria, Burkina Faso; University Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Mahidol University, Thailand; Ellipse Pharmaceuticals, France; MSF; Epicentre, France; TDR; Catalent, USA; KEMRI, Kenya; ICMR, India; GVK BIO, India; Quintiles, USA; Cardinal Systems, France; Epicentre, France; MS; Komfo Anokye Teaching Hospital, Ghana
- **DNDi/project managers and coordinator:** Jean-René Kiechel, Gwenaëlle Carn
- **Project start:** January 2002.

ASAQ, the new fixed-dose combination (FDC) of artem- sunate (AS) and amodiaquine (AQ), was the first drug to be made available by DNDi. Over 5.3 million treatments were distributed in 2008. Now available in 24 countries in sub-Saharan Africa, with over 20 million treatments to be delivered in 2009, the continuing focus of this post-registration project is to support sanofi-aventis the implementation of ASAQ for the treatment of uncomplicated falciparum malaria after its registration in endemic countries, mainly in sub-Saharan Africa, India, and Indonesia.

ASAQ provides a true innovation in patient treatment by being a tropical-stable bilayer co-formulation, which allows AS and AQ to be taken together and in the correct proportions in a simplified three-day dosing regimen where the most vulnerable population, children under the age of five, take one tablet per day.

To continue their pioneering efforts as the 1st public-private partnership to deliver a needs-adapted antimalarial medicine, sanofi-aventis and DNDi continue to work to enlarge the partnership by involving national malaria control programs and pharmacovigilance systems, as well as international organizations and agencies.

DNDi, sanofi-aventis and additional partners, in particular MMV and national malaria control programmes, are implementing a comprehensive “ASAQ Deployment Monitoring Plan” that aims to collect high-quality data on ASAQ effectiveness and safety profile in “the field”. This programme includes a series of proactive clinical studies conducted in several countries of sub-Saharan Africa with different levels of disease transmission. Some of the studies are underway while others are still in the design phase.

Key ongoing studies include two post-registration studies being done in collaboration with MSF, Epicentre, and the national malaria control programme in Liberia: 1300 patients have been enrolled in these studies, which will assess the tolerability and efficacy of ASAQ in comparison with artemether-lumeflantrine (Coartem™). In Ivory Coast, two clinical studies are being set up in a collaboration between sanofi-aventis, MMV, and DNDi: these studies will collect relevant ‘real-life’ efficacy, effectiveness and pharmacovigilance data in over 15,000 patients at a district level.

**Ultimately, more than 20,000 patients will be followed as part of this monitoring plan.** These results will provide a comprehensive overview of the efficacy and safety of ASAQ in the long run and will also allow innovative pharmacovigilance methods to be developed, suited to the needs and resources of countries in sub-Saharan Africa.

The deployment monitoring plan as well as additional clinical data supporting the use of ASAQ has been presented over the past 6 months at international meetings such as ASTMH and the 3rd Annual East African Health Sciences in March 2009. Highlights of these data and the plan can be found on www.actwithasaq.org.

- **Just published:** ASAQ is found to be efficacious and well-tolerated in pivotal Phase III field study carried out in Burkina Faso children: the study showed 28-Day PCR-corrected parasitological and clinical cure rates were ≥95% in both arms comparing the fixed-dose ASAQ combination with the non-fixed AS+AQ association in 750 children with uncomplicated P. falciparum malaria. Sirima SB, et al. *Malar J.* 2009 8(1):48.
- A recent population pharmacokinetic analysis has shown that there is a pharmacological equivalence of ASAQ with the well-established separate products
- Meta-analyses – individual and aggregate – presented at ASTMH and in the process of publication
- Results published in Eur J Clin Pharmacol in May 2009 show that ASAQ is well-tolerated and with a comparable pharmacokinetic profile as the separate products
- A multi-center, non-inferiority trial comparing ASAQ with Coartem® [fixed-dose artemether-lumeflantrine] in Cameroon, Madagascar, Mali, and Senegal, has shown that ASAQ is as efficacious and well-tolerated as Coartem® in a total of 941 patients including in 112 paediatric patients less than 5 years old. Nadiaye et al. *Malaria J*; 8 (125)
Conducting clinical trials on neglected diseases often means that research must be carried out in some of the most remote areas like here in Amudat, Uganda, areas where little infrastructure of any kind, yet alone health, exists and where political instability is also frequent.
As part of its mission and objectives, DNDi synergises efforts to build sustainable research capacities in disease-endemic countries. The process of strengthening existing capacities, at the individual and institutional level, helps in transferring ownership of the solutions and responsibility to the affected country.

INVESTING IN INFRASTRUCTURE, TRAINING, RESEARCH, AND PARTNERSHIPS

Effective clinical research requires adequate infrastructure, solid partnerships, and leadership of ethical and regulatory authorities to ensure that good clinical practices are observed throughout the entire process of clinical development. In disease-endemic countries, where many of DNDi clinical trials are taking place, challenges are huge as most of these trials take place in very remote areas.

- **Building infrastructure, training, and research capacities in the trial sites.** The physical upgrading of facilities related to clinical research (such as patient wards and diagnostics laboratories) is undertaken by DNDi at trial sites so as to ensure they are compliant with Good Clinical Practices (GCP) standards. These facilities are not owned by DNDi. In addition to physical infrastructure, trained staff are needed to carry out GCP-compliant trials. Training is important not just at the start of a trial, but is a continuous process which involves upskilling existing staff and training new members. From external consultants to the experienced trial site staff, the sharing of better practices principles helps to motivate teams working in difficult field conditions. Independent monitors are encouraged to make site visits on a regular basis to ensure that sites are following good clinical and laboratory practices, and standard operating procedures. This monitoring and auditing further educates staff and reinforces the importance of conducting clinical trials to international standards. In 2008-2009, DNDi constructed clinical trials wards in the Dooka clinical trials site, Sudan, and upgraded wards used for the same purpose in two new trials sites – Kimalel centre, Kenya, and Amudat hospital, Uganda. Moreover, DNDi has installed solar panels and repaired the incinerator at the Katanda health centre in the Democratic Republic of the Congo (DRC). More than 164 principle investigators, lab technicians, and monitors have received GCP training and 24 people attended the AmBisome trial initiation.

- **Building sustainable partnerships.** In partnership with scientists and academics in endemic regions, the regional research platforms of the human African trypanosomiasis (HAT) Platform and the Leishmaniasis East Africa Platform (LEAP) aim to strengthen clinical research capacity in a coherent manner to facilitate the availability of new medicines developed. The national control programmes of the most endemic countries are essential members of both platforms, and they play a key role in areas where clinical investigations are taking place. In order to leverage the biodiversity potential of the Asian region in drug discovery efforts for neglected diseases, the Pan-Asian Network for Neglected Diseases (PAN4ND) aims to translate the discovery of new bioactive molecules from natural, local resources into drugs effective against neglected diseases by sharing screening technologies between institutions. Acting as transnational support networks, these platforms enable partners to share different experiences, knowledge, and problem-solving techniques.

- **Building transparent working relations with regulatory authorities and national ethics committees at all levels.** In many of the countries where trials could be conducted, the governing and regulatory authorities at local, regional and national levels play a crucial role in evaluating and approving clinical protocols, ensuring drug availability (by registering drugs and facilitating drug importation, in terms of logistics), and making changes to national treatment guidelines and protocols. National ethics committees also play a critical role.
**REGIONAL PLATFORMS**

**LEAP**
Leishmaniasis East Africa Platform

- **2003**: Founded in Khartoum
- **4** endemic countries
- **44** members
- **More than 1,000 patients** enrolled in clinical trials
- **More than 802 patients treated** outside the clinical trials in 2008/09

Dr Ahmed Mudawi Musa of the Institute for Endemic Diseases, and LEAP Chair, Sudan: “As important as the effort to find a new drug or a combination of drugs to treat VL is, LEAP is addressing other critical issues associated with clinical research for neglected populations: capacity-building with excellent training of African scientists and support staff and concrete community participation in the development and infrastructure strengthening in rural areas. With the help of LEAP and DNDi, we have facilities that allow us to serve unprivileged and marginalised communities with medicines at village level at the Kassab Hospital and Dookah Centre.”

**Objectives**
- Facilitate clinical testing and registration of new treatments for VL in the region (Ethiopia, Kenya, Sudan and Uganda)
- Evaluate, validate and register improved options that address regional needs for VL
- Provide capacity strengthening for drug evaluation and clinical studies in the region

The DNDi Scientific Advisory Committee (SAC) voted LEAP as ‘The Best Partnership of the Year 2009’. The selection was based on the following three criteria: quality and effectiveness of the partnership, strengthening capacities in disease-endemic countries, and knowledge gained that can lead to therapeutic innovation.

**Recognised as “Partnership of the Year in 2008”**

**Partners**
- Center for Clinical Research, Kenya Medical Research Institute, Kenya
- Ministry of Health, Kenya

**HAT PLATFORM**

- **2003**: Founded in Kinshasa
- **5** endemic countries

“There is limited clinical research activity to assess and/or improve treatments and diagnostics for HAT, in part because patients are usually very spread out, living in remote areas. The national control programmes of the five most affected countries, in collaboration with DNDi, the Swiss Tropical Institute (STI), and a number of other partners, have established this platform for capacity-building in clinical trials for HAT. The overall aim is to build and strengthen clinical trial capacities in these endemic countries so that new and promising interventions for this fatal disease can be rapidly and effectively evaluated, registered and made available to the patients,” said Dr Victor Kande, Director of the HAT National Control Programme of the DRC, member of the HAT Platform.

**Objectives**
- To strengthen clinical trial capacity for sleeping sickness
- To overcome health system challenges for clinical research
- To share information on HAT research progress
- To improve HAT clinical trial methodologies

**Partners**
- National HAT control programmes of most affected endemic countries: Democratic Republic of the Congo, Republic of the Congo, Angola, Uganda, and Sudan
- DNDi, Swiss Tropical Institute (STI)
- Research institutes including Institute of Tropical Medicine in Antwerp (ITMA), Institut National de Recherche Biomédicale (INRB), Centers for Disease Control and Prevention (CDC), Kenya Agricultural Research Institute – Trypanosomiasis Research Centre (KARI-TRC)
- NGOs as MSF, Epicentre
- FIND, WHO

**PAN4ND**

Pan Asian Network for neglected diseases

- **2006**: Founded in Tokyo, Japan

“This network forms part of a long-term research collaboration between DNDi and the Kitasato Institute, that will make a significant contribution to bringing new treatments to patients suffering from neglected diseases,” says Professor S. Ōmura, President of the Kitasato Institute.

**Objectives**
- To link natural products researchers and institutes as a collaborative network
- To incorporate neglected diseases into our drug candidate screening programmes
- To standardise network screening methodologies against parasitic targets and other pathogens (> 200 cases) that are recognized by the FDA from 1981 to 2002 were natural products or natural-product derivatives.

DNDi has been acting as a catalyst by supporting the creation and initial steps of the Pan-Asian Screening Network over a three-year period.

**Partners**
- Central Drug Research Institute (CDRI), India; Eskitis Institute, Australia; Forest Research Institute Malaysia (FRIM); Institute Pasteur Korea (IPK); Kitasato Institute (KI), Japan; Malaysian Institute of Pharmaceuticals and Neutracueticals (MIPN), Malaysia; Novartis Institute of Tropical Diseases (NITD), Singapore; Shanghai Institute of Materia Medica (SIMM), China.

**Financial support**
Financial support from the Sasakawa Peace Foundation, DNDi and MOSTI (Ministry of Science, Technology and Innovation, Malaysia).
**Achievements**

**Capacity building – training**
- Training of clinical monitors, Data and Safety Monitoring Board (DSMB) members, and investigators in good clinical practice (GCP)
- Providing career development training on a case-by-case basis for key members of the LEAP group / trial site teams
- Capacity strengthening of parasite classification research through technology transfer and training

**Clinical trials**
- Development and conduct of the LEAP 0104 paromomycin multi-centre clinical trial comparing paromomycin, sodium stibogluconate (SSG), and combination of paromomycin and SSG for treatment of VL (expected to be completed in Q4 2009. see page 25)
- Adoption by LEAP of phase II study AMBI 0106 to determine the minimum effective single dose of AmBisome
- Development of phase II clinical trial to assess safety and efficacy of miltefosine alone, AmBisome + miltefosine and AmBisome + SSG

**Capacity building – infrastructure**
- Building and opening leishmaniasis research and treatment centres in Ethiopia: Arba Minch 2006; Gondar 2008
- Upgrading infrastructure at Amudat Hospital and initiating it as a clinical trial site
- Treatment centre opened in Kimalel, Kenya in January 2009 and treatment centre / laboratory training centre is planned to open in Dooka (late 2009)

**Communications**
- Development of manual on drug screening for kinetoplastid diseases
- Four platform newsletters published in English and French; presentations at various scientific congresses
- Launch in August 2005, and annual platform meetings (Nairobi, 2006; Khartoum, 2007; Brazzaville, 2008); seven steering committee meetings held – in conjunction with annual meetings as well as in Basel (June 2007), and Kampala (June 2008)

**Meetings**
- Support to the NECT Phase III and to the ongoing NECT-Field Studies

**Financial support**
- European Union FP6
- Ministry of Foreign and European Affairs (MAE), France
- In addition, core organisational funding from the following donors has been used by DNDi to support its research efforts with the HAT Platform:
  - Department for International Development (DFID), UK
  - Médecins Sans Frontières (MSF)
  - Spanish Agency of International Cooperation for Development (AECID), Spain
  - Other private foundations and individual donors who wish to remain anonymous

**Achievements**

**Training**
- Drug screening workshop at CDRI, Lucknow (February 2007); drug metabolism, pharmacokinetics, toxicology workshop at NITD, Singapore (February 2008); and a training programme in Kuala Lumpur December 2008 which covered natural product extraction and purification together with a seminar series on structure elucidation.
- Strengthening capacities: three training visits of platform scientists to reference screening centres (Kitasato Institute, Swiss Tropical Institute, University of Antwerp) between June and December 2007

**Communications**
- Development of manual on drug screening for kinetoplastid diseases in collaboration with LSHTM, STI, and CDRI; organisation of five regional scientific events: four annual meetings (Tokyo, May 2006; Shanghai, June 2007; and Tokyo, June 2008; Kuala Lumpur, December 2008) and two natural substances drug discovery and development meetings (Kuala Lumpur, November 2006 and 2007). Development of a website dedicated to PAN4ND: www.pan4nd.org
People are denied access to drugs by a variety of factors, including a lack of tools, a lack of funding, and a lack of healthcare infrastructure.

Increasing awareness and mobilising resources for neglected diseases.
Product Development Partnerships (PDPs) are proving to be an effective means of delivering innovation to the most neglected.

Of the five new treatments delivered for neglected diseases in the past five years, DNDi has delivered three. However, governments and global actors need to scale up efforts to foster innovation on a broader scale. A range of alternative market, policy and financing mechanisms must be developed and implemented to stop the suffering of millions of patients. Sustainable funding and strong public support for research and development (R&D) are urgently needed to develop new health tools, including diagnostics and treatments. Recognising the importance of fostering a supportive environment for neglected tropical disease (NTD) research, DNDi works to raise awareness of critical NTD issues and to mobilise public and private resources to meet the needs of the most neglected patients. For example, in June 2008, before the G8 Summit in Japan, DNDi released a statement endorsed by the World Health Organization (WHO) urging the G8 governments to support both control programmes and R&D initiatives for NTDs. The Summit Leaders Declaration issued at the close of the conference asserts that the G8 will ramp up commitments to neglected diseases, and includes a specific reference to neglected disease research.

In February 2009, in conjunction with the UN Special Event on Philanthropy and the Global Public Health Agenda [see box], DNDi and Médecins Sans Frontières called for a scale-up of R&D in the form of increased governmental and private-sector commitments to combat deadly neglected diseases that afflict millions of the world’s poorest.

In July 2009, on the occasion of the centenary of the discovery of Chagas disease, DNDi and its partners will launch a campaign to draw attention to the huge gaps in treatments for Chagas patients. The Chagas Advocacy Campaign, with the theme ‘Wake Up. Chagas kills – Time to Treat!’ will bring to light the stark realities surrounding the disease. The burden of Chagas disease is significantly underestimated in official statistics, and few infected patients receive any treatment at all. The only available treatments today are two medicines developed more than 30 years ago with limited efficacy in the chronic phase, toxic side effects, and which are not readily accessible to patients due to complicated supply procurement and drug registration limitations. New, improved diagnostics and treatments are urgently needed. These initiatives represent some of DNDi’s continuous worldwide activities aimed at increasing awareness about most neglected diseases in various forums.

MORE SUSTAINABLE RESOURCES NEEDED

Despite the establishment of PDPs like DNDi and new commitments from public and private donors, funding for scientific and medical innovation for diseases that disproportionately affect the developing world remains inadequate. The R&D funding gap is particularly severe for the most neglected tropical diseases, which offer virtually no commercial market to product developers. Greater investment, complemented with innovative funding mechanisms and incentives, are needed from both governments and the private sector to ensure that these efforts are sustained and strengthened.

Global neglected disease R&D funding in 2007 totalled US$ 2.5 billion, (including malaria, tuberculosis and HIV/AIDS). Of this amount, only US$ 125 million – less than 5% – was spent on the kinetoplastid diseases (sleeping sickness, leishmaniasis, and Chagas disease), which are the focus of DNDi’s efforts. DNDi requires a total of EUR 274 million to achieve its objectives of building a robust pipeline and delivering 6-8 new treatments by 2014. As of April 2009, EUR 110 million...
DNDi seeks to ensure balanced financial support from public and private sectors, allowing the organisation more flexibility and sustainability, while also preserving its independence. Accordingly, to promote responsible management, DNDi ensures transparency regarding its decision making and use of donors’ funds. Up to April 2009, a total of EUR 110 million had been committed to DNDi (see Financial Report), which enabled all of its activities to be funded since 2003. However, DNDi still needs a total of EUR 164 million by 2014 to achieve its business plan objectives.

TARGET:
EUR 274 million

TO DATE:
EUR 110 million

NEW GRANTS RECEIVED IN 2008/2009

GBP 18 Million from the UK Department for International Development (DFID)
The UK Department for International Development granted DNDi GBP 18 million over five years in unrestricted initiative funding. This grant builds on the 2005 grant from DFID, which provided the first major government funding to DNDi over the three-year period 2005 – 2008. The grant covers a broad spectrum of drug research, development, and access activities undertaken by DNDi and its partners.

EUR 18 Million from Médecins Sans Frontières (MSF)
MSF has committed EUR 18 million over the next six years to DNDi and continues to provide support through its field programmes to the operational and clinical research needed to advance DNDi’s drug-development portfolio. As a founding partner, MSF committed EUR 25 million in start-up funding to DNDi in 2004.

EUR 1 Million from the German Agency for Technical Cooperation (GTZ)
The GTZ, on behalf of the Government of the Federal Republic of Germany, granted DNDi EUR 1 million to support discovery, lead optimisation and preclinical projects for Chagas disease and HAT.

US$ 200,000 from the Starr International Foundation, Switzerland
The Starr International Foundation granted DNDi US$ 200,000 of unrestricted initiative funding to be used in 2009. The Foundation supports DNDi’s mission to develop new drugs for patients suffering from HAT, VL and Chagas disease.

was committed to DNDi from a diversified group of public and private donors.

ENABLING R&D ENVIRONMENT
Public leadership is needed to implement policy changes that will support development of new, essential health tools, to ensure equitable access for affected populations; and to contribute to the development of innovative, needs-based measures such as intellectual property management policies to encourage needs-driven R&D, technology transfer, an enabling regulatory environment and strengthening of research capacities in developing countries.

VARIOUS ADAPTED “PUSH” AND “PULL” MECHANISMS
Although a comprehensive, sustainable solution to the problem of neglected disease R&D has not yet emerged, governments, experts, and industry have proposed a number of new ideas, including both “push” mechanisms to finance R&D, and “pull” incentives to spur private sector investment.

Some new mechanisms specifically focused on neglected diseases have been launched by donor governments, such as the U.S. FDA’s Tropical Disease Priority Review Voucher, and a number of other public and private initiatives have been proposed or initiated, such as prize funds, UNITAID, the Fund for R&D in Neglected Diseases (FRIND), and the Advance Market Commitment for Pneumococcal Vaccines, or patent pools.

PATENT POOLS
In July 2008, UNITAID approved a proposal to establish a patent pool for medicines. The initiative aims to provide patients in low- and middle-income countries with increased access to more appropriate and affordable medicines. Through a collective management structure for medicine patents, UNITAID seeks to improve access to patents and foster the development and production of more affordable and more suitable medicines. The initial focus will be in the area of paediatric antiretroviral medicines (ARVs) and
new combinations. The principle is to facilitate the availability of new technologies by making patents and other forms of intellectual property (IP) more readily available to entities other than the patent holder.

In February 2009, GlaxoSmithKline (GSK) announced that it is making its IP available to help bridge the gap in research, development, and access to medicines for treatment of 16 NTDs in the least developed countries. GSK offered to put its patents and processes relevant to NTDs into a pool to allow third party access for the development of new drugs and formulations for NTDs to be used in least developed countries.

DNDi welcomes these initiatives. Obtaining access to proprietary IP is one of DNDi’s primary challenges and can take up to two years of negotiations. Accessing proprietary IP through standardised licensing terms incorporated in patent pools could save precious time in delivering new treatments to patients.

At the same time, the WHO has established an expert working group to examine current financing and coordination of R&D, as well as new proposals to stimulate innovation related to Type II (that occur in both rich and poor countries such as HIV/AIDS and tuberculosis) and Type III diseases (those overwhelmingly or exclusively occurring in the developing countries such as sleeping sickness and African river blindness). This group, which will build on the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property adopted by the 2008 World Health Assembly, is accepting and evaluating submissions during 2009 and should deliver a plan to the World Health Assembly (WHA) in 2010. While the potential value of some of the new mechanisms for malaria, HIV/AIDS, and TB has been assessed, there has been little analysis of their potential impact on neglected disease research. To help inform the debate, DNDi has commissioned a research study to analyse the value of different funding mechanisms and incentives for the most neglected diseases.

**DNDi SUPPORTS CALLS FOR INCREASED U.S. GLOBAL HEALTH R&D COMMITMENT**

The U.S. government is one of the largest funders of medical research in the world, yet today a disproportionately small level of funding goes to neglected disease research. Recognising this imbalance, DNDi has actively supported calls by the Institute of Medicine, Families USA and the Global Health Technologies Coalition (GHTC) for the U.S. government to increase its commitment to R&D for neglected diseases.

The Institute of Medicine, in a report entitled ‘The U.S. Commitment to Global Health: Recommendations for Public and Private Sectors’, calls for the U.S. to make global health a key component of foreign policy, to double global health spending by 2015, and to support neglected disease research and PDPs like DNDi. Dr Bennett Shapiro, Board member of DNDi, serves on the Committee on the U.S. Commitment to Global Health, which prepared the report.

Families USA’s report, ‘The World Can’t Wait: More Funding Needed for Research on Neglected Infectious Diseases’, found that U.S. government spending on neglected infectious disease research totalled only US$ 366 million in 2007, an “inadequate” sum for diseases that affect 1 billion people. Of that, just US$ 8 million was dedicated to drug development for three of the most neglected diseases – Chagas, HAT and VL.

The Global Health Technologies Coalition, a coalition of over two dozen nonprofit organizations, including DNDi, works to accelerate the development and delivery of new health products to prevent HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases. GHTC educates U.S. policymakers about the benefits of new vaccines, microbicides, drugs, and diagnostics to improve health in developing countries, and has made specific funding and policy recommendations to both the Administration and Congress.

As it has from its inception, DNDi continues to advocate for increased resources to carry out R&D for neglected diseases, and the need for innovative sustainable mechanisms to finance and stimulate it (see box). Moreover, DNDi is itself an example of a push mechanism that has successfully attracted new public and private funding to this field.

DNDi is encouraged by the breadth of ongoing discussions and proposals aimed at stimulating innovation and creating sustainable funding for NTD research. These discussions are critical to moving forward. However, concrete action must be taken if we are to bring new treatments to patients who desperately need them.

**Kinetoplastids R&D funding by funder type in 2007**

Funding for kinetoplastids R&D was predominantly from philanthropic organisations ($67.9 million or 54.3%) and public funders in the West and IDCs (40.6% of funding or $50.9 million), making up 94.9% of total global funding.
FRIENDS OF DNDi

In 2007, DNDi inaugurated “Friends of DNDi”, a group established to recognise select individuals who support DNDi’s mission and vision by engaging global influencers, policymakers, and donors to help DNDi succeed in reaching its objectives.


Yves Champey: Former Chair of Genethon Laboratory (France); former Chair of DNDi’s Board of Directors (2003-2007); former Senior Vice President, International Drug Development, at Rhone Poulenc (1995-1997).

Nirmal K. Ganguly: Former Director General of the Indian Council of Medical Research (ICMR); Founding Partner of DNDi.

Stephen Lewis: Chair of the Board of the Stephen Lewis Foundation (Canada); former Minister of Foreign Affairs in Canada; former member of the United Nations Special Envoy for HIV/AIDS in Africa.

Morten Rostrup: Physician in the Department of Acute Medicine at Ullevaal University Hospital in Oslo, Norway; former International President of Médecins Sans Frontières (2001-2004); former DNDi Board member (2003-2005).

Dyann Wirth: Chair of the Department of Immunology and Infectious Diseases, Harvard School of Public Health; former Chair of DNDi’s Scientific Advisory Committee (2003-2007).

Yongyuth Yuthavong: Former Minister of Science and Technology of Thailand; former member of DNDi’s Scientific Advisory Committee (2003-2006).

INCREASING AWARENESS

INCREASING AWARENESS

Scientific Publications in 2008 by Team and Partners


- ‘New lycorine-type alkaloid from Lycoris traubii and evaluation of antitrypanosomal and antimarial activities of lycorine derivatives’. Toriiizuka Y, Kinoshita E, Kogure N, Kitajima M.
VARIOUS TOOLS, EVENTS AND PUBLICATIONS HAVE BEEN DEVELOPED TO RAISE AWARENESS ABOUT KINETOPLASTID DISEASES AND DNDi’S ACTIVITIES.
SOME EXAMPLES OF WORLDWIDE MEDIA COVERAGE:

• The Lancet Infectious Diseases, ‘Ongoing neglect of leishmaniasis’, May 15, 2009
• The Guardian, ‘New treatments rise hope of cutting sleeping sickness deaths’, May 15, 2009
• Voice of America, In focus, ‘Malaria Day’. April 23, 2009
• British Medical Journal, ‘Patent pools: an idea whose time has come’, April 20, 2009
• Chemical & Engineering News, ‘Paying attention to neglected diseases. The Drugs for Neglected Diseases initiative is mobilizing public/private partnerships’, April 20, 2009
• Radio France Internationale, Priorité Santé, ‘L’OMS et DNDi parlent des maladies négligées’. April 13, 2009
• Europa Press, ‘Una de cada cuatro enfermedades en el mundo tiene como origen el descuido del medio ambiente, según la OMS’, March 27, 2009
• Global Post, ‘When two drugs are less deadly than one’. February 24, 2009
• PharmaTimes, ‘R&D for neglected diseases needs political leadership’, March 4, 2009
• Agence Congolaise de Presse, ‘NECT: Une amélioration thérapeutique contre la maladie du sommeil’, February 5, 2009
• Le Monde, ‘Bernard Pécoul à la recherche de traitements contre les maladies négligées’. December 25, 2008
• The Parliament, ‘Sending out the message’. November 10, 2008
• SCRIP, ‘DNDi invests EUR 8.5 million in neglected disease R&D’, October 21, 2008
• Canadian Medical Association Journal, ‘G8 attention to neglected diseases research welcomed’, August 12, 2008
• El Tiempo, ‘Brasil producirá para Latinoamérica versión pediátrica de fármaco contra Chagas’. July 7, 2008
• SCRIP, ‘G8 urged to address neglected diseases’, July 1, 2008
• The Parliament, ‘Addressing the R&D Challenges in Making New Drugs Available for Human African Trypanosomiasis: Potential in the Pipeline and Recent Clinical Results’
• DNDi India Public Symposium New Delhi, India, October 13, 2008
• DNDi focused on: ‘India: Catalyst in Drug Development for Neglected Diseases?’
• XVIIth International Congress for Tropical Medicine and Malaria - from Bench to Field Jeju Island, Korea, September 29-October 3, 2008
• DNDi and sanofi-aventis session: ‘Antimalarial medicines: artemesunate-modaquine and beyond’
• 13th International Congress on Infectious Diseases (ICID) Kuala Lumpur, Malaysia, 19-22 June, 2008
• DNDi Symposium on ‘Neglected Diseases Drug R&D’
A year of milestone achievements!

DNDi, along with its partners, remains driven by a steadfast determination to make a difference for people affected by neglected diseases, in the most timely and cost-effective way.
PERFORMANCE REPORT

SUMMARY
In 2008, DNDi delivered a second combination drug for malaria. ASMQ, a new fixed-dosed combination of artesunate and mefloquine was registered and made available for patients in Brazil, through a partnership with a public Brazilian pharmaceutical company. In addition to delivering a new treatment, DNDi continued to develop a robust R&D portfolio of potential new treatments for Chagas disease, leishmaniasis, and sleeping sickness, consisting of 20 projects and several exploratory screening activities with the diverse range of DNDi partners, from the pharma industry, the academic world and organisations involved in the fight against neglected diseases.

DNDi’s expenditure reflected this dynamism and grew to EUR 17.6 million from EUR 11.8 million in 2007. This growth in expenditure was matched with income growth, as total donations and contributions rose to EUR 20 million in 2008 compared with EUR 15.9 million in 2007. For the fifth year of its existence, DNDi’s donors demonstrated the confidence they have in the initiative and their support for DNDi’s strategy to produce new treatments for neglected diseases.

STATEMENT OF ACTIVITIES

INCOME (in thousand Euros)

| Public Institutional Funding | 9,895 | 9,563 |
| Private Resources | 10,175 | 6,290 |
| **Total Income** | **20,071** | **15,852** |

EXPENDITURE

| Research & Development | 13,649 | 8,577 |
| Strengthening Capacities | 1,111 | 974 |
| Advocacy | 864 | 658 |
| Fundraising | 694 | 363 |
| General & Administration | 1,247 | 1,251 |
| **Total Expenditure** | **17,564** | **11,823** |
| Operating Surplus | 2,506 | 4,029 |
| Other Income (net) | 231 | 83 |
| **Net Surplus for the year** | **2,737** | **4,113** |

STATEMENT OF OPERATIONS for the year ended December 31, 2007 (Summary in EUR)

2008 | 2007
--- | ---
Public Institutional Funding | 9,895 | 9,563
Private Resources | 10,175 | 6,290
**Total Income** | **20,071** | **15,852**
Research & Development | 13,649 | 8,577
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DISCLAIMER

- The present financial and performance report is written in accordance with the regulations of the Swiss Generally Accepted Accounting Principles, Swiss GAAP, specifically FER/RPC 21, which is applicable to charitable and social not-for-profit organisations.
- The report provides financial information and some efficiency indicators regarding DNDi’s activities in 2008, notably the social mission ratio and the breakdown by stage of development and disease. It also highlights the evolution of public institutional versus private sources of funds and the independence ratio pertaining to the diversity of resources.
Financial & Performance Report

DNDi Annual Report 2008/2009

In March 2008, DNDi launched its second new treatment launched by DNDi in 2007, compared to EUR 0.7 million in 2007. The main efforts were dedicated to the production of ASMQ and the transfer of technology between Farmanguinhos and Cipla in India. Fixed-dose combination therapy of artemesunate (AS) and amodiaquine (ASAQ), the first new treatment launched by DNDi in 2007, is now registered in 24 disease-endemic countries. Produced in a landmark partnership with sanofi-aventis, the new treatment obtained WHO prequalification in October 2008. More than 5.4 million treatments were distributed in 2008. Expenditure remained stable between 2007 (EUR 1 million) and 2008 (EUR 1.1 million). The main effort was focused on post-registration activities including pharmacovigilance studies, complementary studies in India, and communication with national programmes about ACT (Artesunate Combination Therapy) and ASAQ.

Highlighted below are the projects for human African trypanosomiasis (HAT) which represented the main expenditure increase in 2008: EUR 5.9 million in 2008 as compared to EUR 2.9 million in 2007.

**DNDi KEY ACCOMPLISHMENTS**

For HAT
- The multicentre clinical trials in DRC were completed (287 patients) for the Nifurtimox-Elornithine combination therapy (NECT) - a simpler, less toxic treatment for stage 2 sleeping sickness. The partners that support this project in 2008 are PNLTHA (National Programme in DRC), Epicentre (France) and Swiss Tropical Institute (Switzerland). This combination therapy was added to the WHO Essential Medicines List in April 2009. EUR 0.5 million was spent in 2008.
- In 2008, the lead optimisation consortium for HAT progressed with Scynexis and Pace University, its partners in the USA. Two compounds series have been advanced from early-stage screening to attractive leads. Expenditure in 2008: EUR 3.3 million as compared to EUR 1.3 million in 2007 when the project started (Q4 2007). This is the most significant increase in DNDi expenditure (about + 250%) for 2008.
- The preclinical studies for the fexinidazole project were successfully finalised in 2008. The project will enter phase I clinical trials in 2009. The main partners are based in Europe and include: Aptuit, Covance and Nerviano. Expenditure reached EUR 1.3 million in 2008 as compared to EUR 0.5 million in 2007.

For VL
- The budget increased by EUR 1 million in 2008 and reached EUR 3.1 million.
- Three clinical trials are underway to test combinations of existing medicines for less toxic, more affordable shorter-course treatments and to retard the onset of drug resistance. The actual costs for these clinical trials in 2008 reached EUR 1.9 million against EUR 1.5 million in 2007.

1. More than 1,000 patients have been included in the paromomycin multi-

---

**RESEARCH & DEVELOPMENT EXPENDITURE**

During 2008, DNDi continued to build a dynamic portfolio for the three diseases: visceral leishmaniasis, human African trypanosomiasis, and Chagas disease. As of December 2008, 20 R&D projects and several exploratory activities were being managed by seven DNDi Project Managers and four Project Coordinators with total project expenditures of EUR 13.6 million.

In 2008, DNDi continued its steady growth with an increase of 59% in R&D expenditure compared to the previous year (46% growth increase in 2007). In March 2008, DNDi launched its second new treatment in Brazil – ASMQ – in collaboration with Farmanguinhos, a Brazilian public pharmaceutical company. ASMQ is the first fixed-dose combination therapy of artemesunate (AS) and amodiaquine (ASAQ), the first new treatment launched by DNDi in 2007, is now registered in 24 disease-endemic countries. Produced in a landmark partnership with sanofi-aventis, the new treatment obtained WHO prequalification in October 2008. More than 5.4 million treatments were distributed in 2008. Expenditure remained stable between 2007 (EUR 1 million) and 2008 (EUR 1.1 million). The main effort was focused on post-registration activities including pharmacovigilance studies, complementary studies in India, and communication with national programmes about ACT (Artesunate Combination Therapy) and ASAQ.

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1. More than 1,000 patients have been included in the paromomycin multi-

---

**Breakdown by disease**

The percentage breakdown of R&D expenditure by disease highlights the continuation of DNDi’s investment in HAT R&D in 2008. The percentage of Chagas projects increased because the lead optimisation project started at the beginning of 2008. The proportion of malaria projects in terms of total project expenditure, decreased since the project entered the post-registration phase (see above). Leishmaniasis project expenditure remained stable. Most of the expenses concern three ongoing clinical trials.

**R&D expenditure by disease**

<table>
<thead>
<tr>
<th>Disease</th>
<th>2007 EUR 8.6 million</th>
<th>2008 EUR 13.6 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>24%</td>
<td>31%</td>
</tr>
<tr>
<td>Chagas</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>31%</td>
<td>28%</td>
</tr>
<tr>
<td>Projects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chagas</td>
<td>42%</td>
<td>50%</td>
</tr>
<tr>
<td>Malaria</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

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Financial & Performance Report
centre trials in Ethiopia, Kenya, Su-
dan, and Uganda.

2. More than 200 patients were recrui-
ted between May and December 2008
for the VL combination trials in India.

3. Preparation for the AmBisome clini-
cal trials has been ongoing in 2008:
staff training, protocol approval and
shipments.

In addition, the VL lead optimisa-
tion consortium identified two promis-
ing series of compounds. Key partners
for this project are Advinus and Cen-
tral Drug Research Institute (CDRI) in
India. A new agreement was signed
in 2008 with Institut de Recherche et
Développement (IRD), France. Another
agreement was signed with a new partner in 2008 - Anacor (USA).

The early-stage project was initi-
ated at the end of 2007 with expendi-
ture of EUR 0.1 million, which grew to
EUR 0.9 million in 2008.

For Chagas disease

The budget reached EUR 0.6 million in
2008 against EUR 0.2 million in 2007.
The consortium for Chagas lead optimisa-
tion was established in 2008 with three
partners: Centre for Drug Candidate
Optimisation (CDCO, Australia) Epichem
& Murdoch University (Australia) and
the Federal University of Ouro Preto (Brazil).

The consortium is testing promising drug
candidates identified by DNDi´s global
network of discovery research partners.
2008 expenditure equalled EUR 0.4 million.
DNDi established an agreement with the
Pharmaceutical Laboratory of Per-
nambuco (LAFEPE) in Brazil in 2008
to develop the first benznidazole formulation
for children. 2008 expenditure equalled
EUR 0.2 million.

In 2008, the discovery stage was con-
solidated with nine projects underway
to bring new drug candidates to the
preclinical stage.

DNDi has a global network of part-
ers who specialise in screening
chemical libraries: Institut Pasteur
Korea, Kitasato Institute Japan, Eskitis
and Epichem Australia, CDRI India,
and Fiocruz Brazil. Total EUR 1.3 mil-
lion in 2008.

Following screening, promising
compounds are fed into DNDi’s three
lead optimisation consortia. Total

Potential drug candidates are tested
for safety and efficacy in the laboratory
in preparation for clinical trials.

In 2008, four projects were in the pre-
clinical stage, for a total EUR 1.1 million.
In December 2008, DNDi had seven
projects in clinical development, amount-
ing to EUR 4.7 million.

STRENGTHENING CAPACITIES EXPENDITURE

Strengthening capacities expenses in-
creased to EUR 1,110,724 in 2008 as
compared to EUR 1 million in 2007. These
expenses integrate the cost of disease
platforms for strengthening existing re-
search capacity in Africa for VL and HAT.
The main activities included:

- Construction (Dooka clinical trial
  site in Sudan), and rehabilitation (Ki-
  male centre in Kenya and Amudat
  Hospital in Uganda) of wards that are
  used for clinical trials in East Africa.

- Training of partners’ staff to en-
hance their skills and knowledge: GCP
  (Good Clinical Practice), ethics, trials
  monitoring and methodology, and in-
formation sharing on recent clinical
research development.

- Local representatives and offices
to support DNDi’s field activities (Penang, New Delhi, Nairobi and Rio).

COMMUNICATIONS & ADVOCACY EXPENDITURE

Communications and Advocacy ex-
penditures increased by 31% between 2007
EUR 657,580) and 2008 (EUR 864,009).
In 2008, DNDi Advocacy efforts were
focused on: raising awareness of the
lack of tools to treat neglected patients;
exchange of information; and shared
communication. DNDi facilitated meet-
ings at regional and national level, par-
ticipated in international congresses
and conferences, produced educational
material (newsletters, video and websites)
regarding the three target diseases and
malaria, and published the results of its
ongoing clinical studies in peer-reviewed
medical journals. A key event in 2008
was the launch of ASMQ on 17-18 April
in Rio de Janeiro, Brazil.

The Communications and Advocacy
activities were essential to influence
countries and national programmes for
the deployment of ASMQ and prepare the
ground for the implementation of ASMQ
and NECT, as well as to facilitate DNDi’s
fundraising activities.
FUNDRAISING & GENERAL MANAGEMENT EXPENDITURE

Fundraising expenditure increased by 91% in 2008 (EUR 694,486 in 2008 and EUR 363,084 in 2007). This increase is mainly due to the activity of the New York office, which opened at the end of 2007 and was officially launched in 2008. This office is dedicated to private fundraising in North America and complements the fundraising team based in Geneva. In line with the expenditure, the 2008 fundraising objective was to actively pursue private fundraising in North America. DNDi’s overall fundraising priorities remain the same: securing sustainable and diversified new funds from a mixture of public and private sources and raising unrestricted core funding. Fundraising expenses represent the costs to raise funds: personnel, travel and document production.

General Management & Administration total expenditure remains relatively constant in 2008 (EUR 1,246,694 in 2008 and EUR 1,251,076 in 2007). Expenditures increased slightly due to normal inflation, though total expenses were higher in 2007 due to exceptional costs related to the recruitment of a new R&D Director, the setting up of a new position of Business Development Director and consultant fees related to writing the 2007-2014 Business Plan. General Management and Administration expenses represent costs of managing the organisation: expenses incurred by the Board of Directors, the Executive Director and the Financial and Administration Department.

THE FUTURE

In 2006, DNDi launched a process to review and update its Business Plan, with the support of Ernst & Young Business Advisory Services, to reflect the significant changes in the landscape of neglected disease research and to incorporate new information gathered during the first years of DNDi’s operations. The outcome, approved in July 2007 by the Board of Directors, constitutes a benchmark for the development of new treatments by 2014 for visceral leishmaniasis, human African trypanosomiasis, and Chagas disease. The annual budget is projected to grow from EUR 4 million in 2004 to EUR 40 million in 2014. The overall expenditure during this period is projected to be EUR 274 million, with a possible outcome of six to eight new treatments for neglected diseases and the creation of a healthy portfolio of projects throughout the development pipeline. DNDi will dedicate the majority of funding towards the development of treatments for visceral leishmaniasis (34%), human African trypanosomiasis (35%), and Chagas disease (17%).

Projects will be divided into five categories:
1. New drugs developed from novel compounds identified through screening and lead optimisation
2. New drugs from compounds with known antimicrobial/antiparasitic activities (could start at lead optimi-
sation or preclinical development)
3. New indications for existing medicines in the field of the most neglected diseases (therapeutic switching)
4. Reformulations and combinations better adapted to field conditions (paediatric, long acting, new route of administration; fixed-dose combinations, co-packaging, or coadministration)
5. Existing drugs for target diseases (geographical extension of registration to additional geographic areas; completion of regulatory dossiers of existing drug candidates)

On average, the vast majority of funds will be devoted to R&D (84%), with a secondary programmatic focus on strengthening capacities (4%) and advocacy (3%). This focus shows a clear emphasis on the social mission with 91% of the funds allocated to this area. From a disease perspective, two thirds of overall expenses are devoted to visceral leishmaniasis and human African trypanosomiasis R&D, which shows DNDi’s commitment to these two diseases.

An update of the Business Plan will be made in 2010.

**DIVERSIFICATION OF DONORS**
To develop its activities and achieve its objectives, DNDi seeks diverse funding including: cash donations, in-kind contributions, grants, sponsorships, and legacies – from individuals, governments, public institutions, companies, foundations, NGOs, and other mechanisms. Since its founding, DNDi has been working to diversify its funding to include a mix of public and private donors and project, portfolio and initiative funding. As a key component of its mission is to stimulate increased involvement and to compel national governments and international organisations to assume their responsibilities in R&D for neglected diseases, DNDi strives to obtain half of its funding from public sources. DNDi works to achieve a balance of public and private funding, with total public institutional contributions amounting to EUR 9,895,423 (49%) as compared to EUR 10,175,249 (51%) in private grants in 2008. In addition to its continued funding from the American, British, Dutch, French, and Spanish governments, the Canton of Geneva, Switzerland, and the EU, the German government joined the public funders of DNDi with a grant of EUR 1 million for 2008-2009. The increase in private funding is a result of the grant from the Bill & Melinda Gates Foundation, awarded in 2007, with funding beginning in 2008.

In 2008, DNDi launched a major fundraising effort with the opening of DNDi North America, and also began actively pursuing private funds in the Swiss market where DNDi is headquartered. The results of these efforts started to bear fruit at the end of 2008 and beginning of 2009 with
several new grants awarded for 2009 funding, including grants from Fondation André et Cyprien, Fondation Pro Victimis and the Starr International Foundation, all in Switzerland. From North America, US$ 34,655 was raised from different private donors by the end of 2008.

DNDi accepts donations of unrestricted initiative funding (core funding) to the organisation, restricted or earmarked support to a project, or a contribution to several projects pertaining to one or multiple diseases. However, to allow for maximum 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 initiative funding. In cases where this is not possible, DNDi will pursue project-specific or earmarked funding without requirements which might interfere with the objectives of the project. At the end of 2008, the cumulative funding mix of EUR 110 million was 31% restricted and 69% unrestricted grants. This bias toward unrestricted funding is both by design and a result of two new grants awarded at the end of 2008 of unrestricted initiative funding from the UK Department for International Development of GBP 18 million and from Médecins Sans Frontières of EUR 18 million (2009-2014). These significant and multi-year commitments are critical to the success of DNDi for the next years.

As the financial crisis impacts on private and public budgets and thus, fundraising efforts, we cannot stress enough the importance of commitments such as these to ensure that the advances made towards achieving the Millennium Development Goals and other commitments are not lost. Thanks to all its donors DNDi is able to deliver new treatments for the most neglected patients.

From 2003 to the end of 2008, a total of EUR 110 million was contributed to DNDi

In 2008, DNDi was pleased to welcome the German Agency for Technical Cooperation (GTZ) on behalf of the Government of the Federal Republic of Germany as a new public donor.

As of April 2009, EUR 110 million has been committed to DNDi to fund its activities from 2003 - 2014

Restricted versus unrestricted grants committed to DNDi from 2003 – 2014

Evolution of public/institutional versus private and founding members funding since 2004 and in 2008, as compared to forecast from the DNDi business plan

Sources of Funds: Public Institutional, Private and Founding Members

Total: EUR 274 million forecast from 2004 to 2014

Public Institutional Donors 51%
Foundations & Major Donors 32%
Founding Members 17%

Total: EUR 20 million in 2008

Public Institutional Donors 49%
Foundations & Major Donors 23%
Founding Members 28%
## Statement of activities

### FINANCIAL STATEMENTS AND AUDIT REPORT

#### BALANCE SHEET AT DECEMBER 31, 2008 (with 2007 comparative figures)

<table>
<thead>
<tr>
<th>ASSETS (expressed in EUR)</th>
<th>Notes</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CURRENT ASSETS:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cash and cash equivalent:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cash and banks at head office</td>
<td></td>
<td>2,445,817</td>
<td>901,226</td>
</tr>
<tr>
<td>Cash and banks at RSOs and affiliate</td>
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<td>295,373</td>
<td>87,880</td>
</tr>
<tr>
<td>Time deposits</td>
<td></td>
<td>11,722,000</td>
<td>11,053,320</td>
</tr>
<tr>
<td>Total cash and cash equivalent</td>
<td></td>
<td>14,463,190</td>
<td>12,042,426</td>
</tr>
<tr>
<td>Current accounts and receivables:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advances to officers and liaison offices</td>
<td></td>
<td>27,349</td>
<td>79,968</td>
</tr>
<tr>
<td>Advances to partners related to projects</td>
<td></td>
<td>505,771</td>
<td>524,959</td>
</tr>
<tr>
<td>Receivables from public institutional donors</td>
<td></td>
<td>1,081,410</td>
<td>2,766,989</td>
</tr>
<tr>
<td>Receivables from founders</td>
<td></td>
<td>6,746</td>
<td>37,887</td>
</tr>
<tr>
<td>Other receivables</td>
<td></td>
<td>132,405</td>
<td>54,492</td>
</tr>
<tr>
<td>Prepaid expenses</td>
<td></td>
<td>89,525</td>
<td>115,575</td>
</tr>
<tr>
<td>Total current accounts and receivables</td>
<td></td>
<td>1,843,206</td>
<td>3,579,870</td>
</tr>
<tr>
<td><strong>Total current assets</strong></td>
<td></td>
<td>16,306,396</td>
<td>15,622,296</td>
</tr>
<tr>
<td><strong>NON-CURRENT ASSETS:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tangible fixed assets, net</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bank guarantee</td>
<td>3</td>
<td>150,655</td>
<td>53,379</td>
</tr>
<tr>
<td>Total non-current assets</td>
<td></td>
<td>26,175</td>
<td>15,491</td>
</tr>
<tr>
<td><strong>Total non-current assets</strong></td>
<td></td>
<td>176,830</td>
<td>68,870</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>16,483,226</td>
<td>15,691,166</td>
</tr>
</tbody>
</table>

#### LIABILITIES & CAPITAL (expressed in EUR)

<table>
<thead>
<tr>
<th>Current liabilities</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bank overdraft</td>
<td></td>
<td>544,153</td>
<td>0</td>
</tr>
<tr>
<td>Payables to partners related to projects</td>
<td></td>
<td>77,888</td>
<td>251,942</td>
</tr>
<tr>
<td>Accounts payable to founders</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other payables and accrued expenses</td>
<td></td>
<td>1,462,309</td>
<td>1,018,873</td>
</tr>
<tr>
<td>Deferred income</td>
<td></td>
<td>4,968,692</td>
<td>7,840,731</td>
</tr>
<tr>
<td>Provisions</td>
<td>4</td>
<td>283,104</td>
<td>169,995</td>
</tr>
<tr>
<td><strong>Total current liabilities</strong></td>
<td></td>
<td>7,336,146</td>
<td>9,281,562</td>
</tr>
</tbody>
</table>

**Capital of the organisation**

| Paid-in capital |       | 32,510 | 32,510 |
| Internally generated unrestricted funds | | 9,114,570 | 6,377,094 |
| **Total capital of the organisation** | | 9,147,080 | 6,409,604 |
| **TOTAL**      |       | 16,483,226 | 15,691,166 |
Statement of activities

**STATEMENT OF OPERATIONS for the year ended December 31, 2008** (with 2007 comparative figures)

<table>
<thead>
<tr>
<th>Notes</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public institutional funding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Govern. &amp; public int. organs. unrestricted</td>
<td>6,289,508</td>
<td>5,440,744</td>
</tr>
<tr>
<td>Govern. &amp; public int. organs. restricted</td>
<td>3,605,915</td>
<td>4,121,999</td>
</tr>
<tr>
<td>Total public institutional funding</td>
<td>9,895,423</td>
<td>9,562,743</td>
</tr>
<tr>
<td>Private resources</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private foundations, corporations, and individuals, unrestricted</td>
<td>177,694</td>
<td>152,035</td>
</tr>
<tr>
<td>Private foundations, corporations, and individuals, restricted</td>
<td>4,466,965</td>
<td>892,735</td>
</tr>
<tr>
<td>Total private resources</td>
<td>4,644,659</td>
<td>1,044,770</td>
</tr>
<tr>
<td>Resources from founders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Médecins Sans Frontières, unrestricted</td>
<td>5,530,590</td>
<td>5,244,800</td>
</tr>
<tr>
<td>Total resources from founders</td>
<td>5,530,590</td>
<td>5,244,800</td>
</tr>
<tr>
<td><strong>Total income</strong></td>
<td>5</td>
<td>20,070,672</td>
</tr>
<tr>
<td><strong>Social mission expenditure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research &amp; development expenditure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research &amp; development coordination and supervision</td>
<td>1,265,594</td>
<td>1,329,644</td>
</tr>
<tr>
<td>Human African trypanosomiasis projects</td>
<td>5,934,243</td>
<td>2,907,810</td>
</tr>
<tr>
<td>Leishmaniasis projects</td>
<td>3,118,089</td>
<td>2,118,230</td>
</tr>
<tr>
<td>Chagas disease projects</td>
<td>577,108</td>
<td>230,382</td>
</tr>
<tr>
<td>Other projects</td>
<td>2,057,398</td>
<td>1,744,814</td>
</tr>
<tr>
<td>Portfolio building</td>
<td>696,074</td>
<td>246,373</td>
</tr>
<tr>
<td>Total research &amp; development expenditure</td>
<td>13,648,506</td>
<td>8,577,253</td>
</tr>
<tr>
<td>Strengthening capacities</td>
<td>7</td>
<td>1,110,724</td>
</tr>
<tr>
<td>Advocacy expenses</td>
<td>8</td>
<td>864,009</td>
</tr>
<tr>
<td><strong>Total social mission expenditure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fundraising</td>
<td>8</td>
<td>694,486</td>
</tr>
<tr>
<td>General and administration</td>
<td>8</td>
<td>1,246,694</td>
</tr>
<tr>
<td><strong>Total non-social mission expenditure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total expenditure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operating surplus</td>
<td>2,506,253</td>
<td>4,029,278</td>
</tr>
<tr>
<td><strong>Other income (expenses)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial income (expenses), net</td>
<td>373,862</td>
<td>134,338</td>
</tr>
<tr>
<td>Exchange loss, net</td>
<td>(199,476)</td>
<td>(72,850)</td>
</tr>
<tr>
<td>Other income</td>
<td>56,837</td>
<td>21,895</td>
</tr>
<tr>
<td><strong>Total other income, net</strong></td>
<td>231,223</td>
<td>83,383</td>
</tr>
<tr>
<td>Net surplus for the year prior to allocations</td>
<td>2,737,476</td>
<td>4,112,662</td>
</tr>
<tr>
<td>Allocation to internally generated unrestricted funds</td>
<td>(2,737,476)</td>
<td>(4,112,662)</td>
</tr>
<tr>
<td><strong>Net surplus for the year after allocations</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DRUGS FOR NEGLEGTED DISEASES initiative (DNDi), GENEVA

Funds Flow Statement for the year ended December 31, 2008 (with 2007 comparative figures)

<table>
<thead>
<tr>
<th>Fund Flow from Operations</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net surplus for the year</td>
<td>2,737,475</td>
<td>4,112,661</td>
</tr>
<tr>
<td>Depreciation of fixed assets</td>
<td>90,959</td>
<td>34,768</td>
</tr>
<tr>
<td>Increase (decrease) in provisions</td>
<td>113,109</td>
<td>40,147</td>
</tr>
<tr>
<td>(Increase) decrease in advances</td>
<td>71,807</td>
<td>50,538</td>
</tr>
<tr>
<td>(Increase) decrease in receivables from donors</td>
<td>1,685,578</td>
<td>(1,949,556)</td>
</tr>
<tr>
<td>(Increase) decrease in founders and other receivables</td>
<td>(46,772)</td>
<td>230,101</td>
</tr>
<tr>
<td>(Increase) decrease in prepaid expenses</td>
<td>26,050</td>
<td>(28,565)</td>
</tr>
<tr>
<td>Increase (decrease) in payables to partners related to projects</td>
<td>(174,074)</td>
<td>87,265</td>
</tr>
<tr>
<td>Increase (decrease) in accounts payable to founders</td>
<td>0</td>
<td>(1,596)</td>
</tr>
<tr>
<td>Increase (decrease) in other payables and accrued expenses</td>
<td>987,589</td>
<td>289,858</td>
</tr>
<tr>
<td>Increase (decrease) in deferred income</td>
<td>(2,872,039)</td>
<td>7,081,621</td>
</tr>
<tr>
<td>Funds flow from operations</td>
<td>2,619,682</td>
<td>9,772,712</td>
</tr>
</tbody>
</table>

Funds flow from investing activities

<table>
<thead>
<tr>
<th>Funds flow from investing activities</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Increase) decrease of investments in tangible fixed assets</td>
<td>(188,234)</td>
<td>(37,888)</td>
</tr>
<tr>
<td>(Increase) decrease in bank guarantee</td>
<td>(10,684)</td>
<td>(795)</td>
</tr>
<tr>
<td>Funds flow from investing activities</td>
<td>(198,918)</td>
<td>(38,683)</td>
</tr>
</tbody>
</table>

Funds flow from financing activities

<table>
<thead>
<tr>
<th>Funds flow from financing activities</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash increase (decrease)</td>
<td>2,420,765</td>
<td>9,734,029</td>
</tr>
<tr>
<td>Cash and cash equivalent - beginning of year</td>
<td>12,042,426</td>
<td>2,308,397</td>
</tr>
<tr>
<td>Cash and cash equivalent - end of year</td>
<td>14,463,190</td>
<td>12,042,426</td>
</tr>
</tbody>
</table>

Statement of Changes in Capital for the year ended December 31, 2008 (with 2007 comparative figures)

<table>
<thead>
<tr>
<th>Internally generated funds</th>
<th>Opening balance</th>
<th>Allocation</th>
<th>Internal fund transfers</th>
<th>Closing balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paid-in capital</td>
<td>32,510</td>
<td>–</td>
<td>–</td>
<td>32,510</td>
</tr>
<tr>
<td>Internally generated unrestricted funds</td>
<td>6,377,094</td>
<td>–</td>
<td>2,737,476</td>
<td>9,114,570</td>
</tr>
<tr>
<td>Surplus for the year</td>
<td>–</td>
<td>2,737,476</td>
<td>(2,737,476)</td>
<td>–</td>
</tr>
<tr>
<td>Capital of the organisation</td>
<td>6,409,604</td>
<td>2,737,476</td>
<td>–</td>
<td>9,147,080</td>
</tr>
</tbody>
</table>
NOTES TO THE FINANCIAL STATEMENT FOR THE YEAR ENDED DECEMBER 31, 2008

1. GENERAL INFORMATION

a) Legal aspects
The Drugs for Neglected Diseases initiative (DNDi) is a Swiss foundation, established as a not-for-profit legal entity, registered in Geneva under statutes dated July 17, 2003. DNDi is managed by a Board, an Executive Director, and three senior managers. With its head office in Geneva, DNDi aims to:

a) stimulate and support research and development of drugs, as well as vaccines and diagnostics for neglected diseases;
b) seek equitable access and development of new drugs, to encourage the production of known effective drugs, diagnostic methods and/or vaccines for neglected diseases;
c) adapt new treatments for neglected diseases, to meet patients’ needs, as well as to meet the requirements of delivery and production capacity in developing countries;
d) raise awareness of the need to research and develop drugs for neglected diseases.

As with all Swiss foundations, DNDi is monitored by the Swiss Federal Supervisory Board for Foundations.

b) Income tax
DNDi is exonerated from Swiss federal income tax for an indeterminate period, and from income tax from the Geneva Cantonal tax authorities for a five-year period, commencing 2003, which was renewed in September 2008 for a period of ten years until 2018.

c) Situation of Regional Support Offices (RSO) and Affiliate
DNDi has five Regional Support Offices and one Affiliate to help identify patients’ needs, support Project Managers, identify and support regional partners, seek funding, and undertake regional advocacy work for DNDi. The RSOs, together with regional networks, ensure the participation of disease-endemic countries and foster South-South collaboration. In addition, RSOs can explore fundraising opportunities in their regions. Their tasks and duties are further developed in the DNDi Business Plan.

RSOs are usually hosted by a Founding Partner, often at no cost, and are represented by an experienced senior person as the RSO Director bearing a consultant contract with DNDi. For local or operational reasons, DNDi may deem it necessary to establish the RSO as a legal entity, usually a branch of the DNDi Foundation or as a corporation, in accordance with the needs and local regulations and requirements. Establishment of a DNDi legal entity outside Switzerland requires the authorisation of the Board of Directors.

As of December 2008, DNDi has established legal entities in Kenya (2006) and in Brazil (2008) in the form of branches for its African and Latin American RSOs. The establishment of a branch in India is still pending. The fourth DNDi RSO is in Penang, Malaysia and the process to have it registered as a branch in this country is already underway. Additionally DNDi has two Project Support Offices in Japan, and the Democratic Republic of Congo. RSOs’ accounting is fully incorporated into DNDi accounts.

Affiliate: Drugs for Neglected Diseases initiative North America, Inc., a Delaware not-for-profit corporation exempt from U.S. Federal income taxation pursuant to Section 501(c)(3) of the U.S. Internal Revenue Code (DNDi NA (North America)), was established in February 2007. This affiliate is based in New York City, New York, USA and operates under the Direction of DNDi NA Board of Directors. The affiliate was formed exclusively for charitable and educational purposes including conducting activities to support or benefit the Drugs for Neglected Diseases initiative (DNDi). It awards grants to support programmes, projects and activities to stimulate and support research and development of drugs for neglected diseases, and raising awareness in the region about the need for increased research and development for neglected diseases.

DNDi NA presents an annual report comprising the financial statement of the calendar year. This report is certified by an independent Certified Public Accounting (CPA) firm selected by its Board of Directors. The firm auditing DNDi NA accounts as of 2008, is Tait, Weller & Baker LLP, Philadelphia, Pennsylvania, USA.

Start-up funding is provided via annual grants from DNDi and is accounted for in the DNDi financial statements by combining DNDi NA accounts, following the method of full integration (i.e. all income and expenditures are incorporated into the DNDi financial statement).

DNDi NA’s 2008 financial position as of December 31, 2008 is the following:

- Total liabilities and net assets: US$ 128,011;
- Total revenue and other support: US$ 530,980, of which a total grant from DNDi to DNDi NA, amounting to US$ 496,000 and unrestricted contributions from eight individuals and one student association ranging from US$ 5 to US$ 20,000 for a total of US$ 34,655 plus US$ 1,500 as in-kind services donated;
- Total expenses: US$ 464,092 including US$ 1,500 as professional consultancy in-kind services, and
- An excess of revenue over expenses (change of net assets) of US$ 68,388.

Lastly, in September 2004, a legal entity was set up in France in the form of a not-for-profit association for administrative purposes. This legal body is not a RSO.

2. SIGNIFICANT ACCOUNTING POLICIES

a) Statement of compliance
The financial statements have been prepared in accordance with Swiss GAAP RPC. They include:

a) Balance sheet,
b) Basis of preparation
The financial statements have been prepared on a historical cost basis. The principal accounting policies are set out below.

c) Social mission expenditure
Social mission expenditures represent expenses made according to the purposes defined in Article 5 of the DNDi statutes. They are defined in the present general notes under point 1.a Legal aspects. R&D, strengthening existing capacities, and advocacy are the three chapters that comprise “Social mission expenditure.”

d) Functional currency
The Board of DNDi has determined that the assets, liabilities, and operations should be measured using EUR as the functional currency. The environment in which the entity primarily generates and expends cash determines this decision. All amounts presented in the financial statements are stated in EUR, except when otherwise specifically stated.

e) Foreign currency translation
Transactions in currencies other than the entity’s measurement and reporting currency (EUR) are converted at the average monthly rate of exchange. Year-end balances in other currencies are converted at the prevailing rates of exchange at the balance sheet date. Resulting exchange differences are recognised in the statement of operations. The following are the principal rates of exchange used at the end of the year to revalue the balance sheet items to EUR for reporting purposes:

<table>
<thead>
<tr>
<th>Currency</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>USD</td>
<td>0.7100</td>
<td>0.6796</td>
</tr>
<tr>
<td>CHF</td>
<td>0.6706</td>
<td>0.6034</td>
</tr>
<tr>
<td>GBP</td>
<td>1.0259</td>
<td>1.3563</td>
</tr>
<tr>
<td>100 CDF</td>
<td>0.1274</td>
<td>0.1207</td>
</tr>
<tr>
<td>100 INR</td>
<td>0.9120</td>
<td>1.0740</td>
</tr>
<tr>
<td>100 JPY</td>
<td>0.7868</td>
<td>0.6063</td>
</tr>
<tr>
<td>100 BRL</td>
<td>30.4247</td>
<td>38.1709</td>
</tr>
</tbody>
</table>

f) Income
Restricted public and private institutional donations based on annual or multiyear agreements are recorded over the life of the agreement, as and when the milestones set out in the agreement are achieved. Unrestricted public and private institutional donations based on annual or multiyear agreements are recorded on an accruals basis over the life of the agreement. Other donations are recorded on a cash basis.

g) Funding committed to projects
After Board approval of the annual action plan and budget comprising the approved projects to be funded by DNDi, one or more contracts are drawn up and signed by two Directors, including the Executive Director or the R&D Director for contracts above EUR 50,000, as detailed in the agreement signature process. Thereafter, funds are allocated to the partner(s) in charge of the project. Expenditures are recorded:
- according to a financial report presenting expenditures incurred during the year on an accrual basis; or
- if financial reports are unavailable as per the deadline of 15 March of the following year, an estimated amount is calculated on a prorata temporis basis, based on the time between the contract signing date and 31 December. This estimated amount is considered as an accrued expense following Swiss GAAP RPC to be regularised in the following year. The unpaid portion remaining at year-end is included under current liabilities.

h) Expenditures incurred for projects and activities
The annual action plan and budget are approved by the Board. They include funding for projects subcontracted to partners and current expenditures required to achieve the objectives for the year. A budget revision is approved by the Board at mid-year. All expenditures incurred on behalf of a project or for any activity of DNDi are recorded on an accrual basis.

i) Credit risk, cash-flow management
DNDi’s liquid assets are maintained in cash, low-risk, short-term deposits or capital guaranteed investments. At the balance sheet dates, there are no significant concentrations of credit risk. The maximum exposure is primarily represented by the carrying amounts of the financial assets in the balance sheet, including accounts receivable and cash.

j) Tangible fixed assets
Tangible fixed assets are stated at cost less accumulated depreciation. Depreciation is charged to the statement of operations on a straight-line basis over the estimated useful lives of the tangible fixed asset items. The rates of depreciation used are based on the following estimated useful lives:

<table>
<thead>
<tr>
<th>Asset Category</th>
<th>Useful Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office fittings and equipment</td>
<td>20%</td>
</tr>
<tr>
<td>IT equipment</td>
<td>33%</td>
</tr>
</tbody>
</table>

k) Bank guarantee
Guarantees are presented as non-current assets. To date, DNDi has four guarantees representing three deposits related to office rental in Tokyo, New York and parking space rental in Geneva; and a letter of guarantee pertaining to the Geneva premises. It is recoverable, subject to prevailing contract terms, upon vacating the premises.

l) Provisions
A provision is recognised on the balance sheet when the organisation has a legal
or constructive obligation as a result of a past event, and it is probable that an outflow of economic benefits will be required to settle the obligation. Provisions are measured at the management’s best estimates of the expenditure required to settle that obligation at the balance sheet date.

m) Capital of the organisation
The founding capital (paid-in capital) of EUR 32,510 (CHF 50,000) referenced in the statutes was received from the founding members of DNDi, including the Indian Council of Medical Research, the Institut Pasteur, the Kenya Medical Research Institute, and the International office of Médecins Sans Frontières. The capital is fully subscribed.

n) Restricted and unrestricted reserves
Restricted and unrestricted reserves represent the excess of income over expenditure since the inception of DNDi. Restricted reserves are available to DNDi for future operations and project funding costs as its evolving research and development project pipeline dictates. Unrestricted reserves will be utilised for expenditures of DNDi as incurred.

o) In-kind donations
Gifts-in-kind are not recorded but disclosed in the notes to the financial statements at fair market values according to the following principles:
- Goods transferred to a DNDi project or services rendered to DNDi must be free.
- They must be clearly identifiable and part of DNDi’s projects and activities as defined by DNDi’s action plans and budgets.
- Recognisable as a visible contribution to DNDi’s projects and activities, benefiting DNDi, and in-line with DNDi’s mission and objectives.
- Partners’ voluntary involvement in joint projects and activities, in particular if the partner does not aim to achieve DNDi’s project objectives, are not considered as gifts-in-kind.
- For goods or services paid at below market prices, the difference between real payment and current market price is not considered as gifts-in-kind, but the current market price reached after negotiations is.
- Fair market value is defined as the price DNDi would have paid to utilise the good or service. Fair market value can be suggested by partners. However, DNDi will be careful not to overestimate such valuations in compliance with Swiss GAAP RPC 3 basic principles of materiality and prudence.
- Gifts-in-kind estimated at EUR 5,000 and above are taken into account. Exceptions can be made by DNDi when it serves the purpose of providing consistency and completeness of a project’s accounts.

3. Tangible Fixed Assets, Net

<table>
<thead>
<tr>
<th></th>
<th>Computer Equipment</th>
<th>Office fittings &amp; Installations</th>
<th>Office Equipment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Net carrying amounts 1.1.</strong></td>
<td>21,586</td>
<td>19,513</td>
<td>12,280</td>
<td>53,379</td>
</tr>
<tr>
<td><strong>Gross values of cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beginning of the period 1.1</td>
<td>135,757</td>
<td>44,899</td>
<td>22,366</td>
<td>203,022</td>
</tr>
<tr>
<td>Additions</td>
<td>33,543</td>
<td>71,006</td>
<td>83,684</td>
<td>188,233</td>
</tr>
<tr>
<td>Disposals</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>End of the period 31.12</td>
<td>169,300</td>
<td>115,905</td>
<td>106,050</td>
<td>391,255</td>
</tr>
<tr>
<td><strong>Cumulated amortisation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beginning of the period 1.1</td>
<td>(114,172)</td>
<td>(25,385)</td>
<td>(10,085)</td>
<td>(149,642)</td>
</tr>
<tr>
<td>Systematic amortisation</td>
<td>(25,771)</td>
<td>(34,390)</td>
<td>(30,796)</td>
<td>(90,958)</td>
</tr>
<tr>
<td>End of the period 31.12</td>
<td>(139,943)</td>
<td>(59,775)</td>
<td>(40,881)</td>
<td>(240,600)</td>
</tr>
<tr>
<td><strong>Net carrying amounts 31.12</strong></td>
<td>29,357</td>
<td>56,130</td>
<td>65,169</td>
<td>150,655</td>
</tr>
</tbody>
</table>
### 4. PROVISIONS

<table>
<thead>
<tr>
<th></th>
<th>Provision for taxes</th>
<th>Provision for HR expenses (holidays not taken)</th>
<th>Provision for running expenses (other)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrying amount as per 1.1.2007</td>
<td>123,779</td>
<td>0</td>
<td>6,070</td>
<td>129,849</td>
</tr>
<tr>
<td>Creation</td>
<td>48,682</td>
<td>54,787</td>
<td>0</td>
<td>103,469</td>
</tr>
<tr>
<td>Utilisation</td>
<td>[57,253]</td>
<td>0</td>
<td>[6,070]</td>
<td>[63,323]</td>
</tr>
<tr>
<td>Reversal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carrying period as per 31.12.2007</td>
<td>115,208</td>
<td>54,787</td>
<td>0</td>
<td>169,995</td>
</tr>
<tr>
<td>Carrying period as per 1.1.2008</td>
<td>115,208</td>
<td>54,787</td>
<td>0</td>
<td>169,995</td>
</tr>
<tr>
<td>Creation</td>
<td>24,405</td>
<td>70,801</td>
<td>69,957</td>
<td>165,163</td>
</tr>
<tr>
<td>Utilisation</td>
<td>0</td>
<td>(52,054)</td>
<td>0</td>
<td>(52,054)</td>
</tr>
<tr>
<td>Reversal</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Carrying period as per 31.12.2008</td>
<td>139,613</td>
<td>73,534</td>
<td>69,957</td>
<td>283,104</td>
</tr>
</tbody>
</table>

### 5. INCOME

#### a) Cumulative donations committed to DNDi and/or received by 2008 (in EUR)

<table>
<thead>
<tr>
<th>Donor</th>
<th>Total Commitment in currencies*</th>
<th>Total Commitment in EUR</th>
<th>As per Statement of Operations 2008 in EUR</th>
<th>To be used after 2008 in EUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Médecins Sans Frontières</td>
<td>EUR 42,566,228</td>
<td>42,566,228</td>
<td>5,530,590</td>
<td>17,565,484</td>
</tr>
<tr>
<td>UK Government DFID</td>
<td>GBP 24,500,000</td>
<td>28,203,392</td>
<td>3,789,508</td>
<td>17,875,500</td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>USD 25,729,285</td>
<td>17,906,784</td>
<td>4,203,373</td>
<td>13,703,411</td>
</tr>
<tr>
<td>French Government MAEE/AFD</td>
<td>EUR 7,455,000</td>
<td>7,455,000</td>
<td>1,835,526</td>
<td>2,451,415</td>
</tr>
<tr>
<td>Spanish Government AECID</td>
<td>EUR 5,000,000</td>
<td>5,000,000</td>
<td>2,500,000</td>
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<tr>
<td>Dutch Government DGIS</td>
<td>EUR 2,975,000</td>
<td>2,975,000</td>
<td>1,000,000</td>
<td>550,000</td>
</tr>
<tr>
<td>German Government GTZ</td>
<td>EUR 1,000,000</td>
<td>1,000,000</td>
<td>324,190</td>
<td>675,810</td>
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<tr>
<td>USA Government NIAID</td>
<td>USD 1,375,633</td>
<td>958,954</td>
<td>190,364</td>
<td>621,424</td>
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<tr>
<td>UBS Optimus Foundation</td>
<td>CHF 1,250,000</td>
<td>792,193</td>
<td>166,588</td>
<td>181,062</td>
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<td>Medicor Foundation</td>
<td>EUR 650,000</td>
<td>650,000</td>
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<td>0</td>
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<tr>
<td>Canton of Geneva</td>
<td>CHF 1,000,000</td>
<td>643,860</td>
<td>126,860</td>
<td>134,120</td>
</tr>
<tr>
<td>European Union FP5 &amp; FP6</td>
<td>CHF 581,335</td>
<td>581,335</td>
<td>128,975</td>
<td>49,412</td>
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<tr>
<td>Sandoz Family Foundation</td>
<td>CHF 500,000</td>
<td>308,700</td>
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<tr>
<td>Sasakawa Peace Foundation</td>
<td>EUR 241,350</td>
<td>241,350</td>
<td>97,004</td>
<td>3,896</td>
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<tr>
<td>Tuscany Region</td>
<td>EUR 200,000</td>
<td>200,000</td>
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<tr>
<td>Various other donors</td>
<td>EUR 170,060</td>
<td>170,060</td>
<td>0</td>
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</tr>
<tr>
<td>Anonymous Donation</td>
<td>CHF 201,229</td>
<td>138,108</td>
<td>138,108</td>
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<tr>
<td>Leopold Bachmann Foundation</td>
<td>EUR 91,900</td>
<td>91,900</td>
<td>0</td>
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<tr>
<td>Swiss Government DDC</td>
<td>CHF 120,000</td>
<td>77,045</td>
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</tr>
<tr>
<td>Various individual donors</td>
<td>EUR 41,997</td>
<td>41,997</td>
<td>39,586</td>
<td>0</td>
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</tbody>
</table>

**TOTAL DONATIONS (EUR)**

|                               | 110,001,906 | 20,070,672 | 53,811,534 |

*Exchange rates used for “Total Commitment in Euros” and “As per Statement of Operations 2008” are real exchange rates following DNDi exchange rate policy. Exchange rates used for “To be used after 2008” appear in Euro at the USD/EUR, CHF/EUR and GBP/EUR exchange rates as per 31.12.2008 (see note 2). Total Donations yield therefore an approximate value, as exchange will vary over time.*
### b) Funding per project (restricted and unrestricted) (in EUR)

<table>
<thead>
<tr>
<th>Project Description</th>
<th>UK Government DFID* (Unrestricted)</th>
<th>Spanish Government AECID (Unrestricted)</th>
<th>French Government MAEE (Restricted)</th>
<th>Dutch Government DGIS (Restricted)</th>
<th>German Government GTZ (Restricted)</th>
<th>United States Government NIH**</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT (ASAQ &amp; ASMQ) for Malaria</td>
<td>514,030</td>
<td>485,442</td>
<td>901,648</td>
<td></td>
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<tr>
<td>Nifurtimox + Efline for HAT</td>
<td>58,619</td>
<td>467,353</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Paromomycin for VL</td>
<td>16,572</td>
<td>384,415</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambisome for VL</td>
<td>2,228</td>
<td>137,757</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Combination therapy for VL</td>
<td>13,444</td>
<td>273,903</td>
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<td></td>
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<tr>
<td>Clinical Projects for Chagas</td>
<td>202,692</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Preclinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B polymer for VL</td>
<td>10,965</td>
<td>48,896</td>
<td>159,228</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Buparvaquone for VL</td>
<td>3,386</td>
<td>49,338</td>
<td></td>
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<tr>
<td>Feixinidazole for HAT</td>
<td>665,888</td>
<td>300,509</td>
<td>197,573</td>
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<tr>
<td>Discovery</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>VL Consortium Lead Optimisation</td>
<td>31,071</td>
<td>13,960</td>
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<tr>
<td>Chagas Consortium Lead Optimisation</td>
<td>36,100</td>
<td>313,521</td>
<td>16,813</td>
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<tr>
<td>HAT Consortium Lead Optimisation</td>
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<td></td>
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</tr>
<tr>
<td>Exploratory activities (Dundee, Otsuka,..)</td>
<td>114,238</td>
<td>42,381</td>
<td>403</td>
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<td></td>
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<tr>
<td>Discovery Projects (Screening, 7 projects)</td>
<td>657,508</td>
<td>39,115</td>
<td>4,921</td>
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<td>R&amp;D Coordination, Supervision costs</td>
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<td>23,091</td>
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<tr>
<td>HAT &amp; LEAP Platforms</td>
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<td>0</td>
<td>276,790</td>
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<td>Other Strengthening Capacities activities</td>
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<td>13,242</td>
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<td>Advocacy</td>
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<td>70,833</td>
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<td>Fundraising</td>
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<td>22,479</td>
<td>3,622</td>
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<td>General Management before retreatment</td>
<td>364,453</td>
<td>88,463</td>
<td>27,514</td>
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<tr>
<td>Year-end result</td>
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<tr>
<td><strong>TOTAL GRANTS ONLY</strong></td>
<td>3,789,508</td>
<td>1,835,526</td>
<td>1,000,000</td>
<td>324,190</td>
<td>190,364</td>
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</tr>
</tbody>
</table>

* DFID: the grant considered for 2008 is comprised of 2 grants = 1st grant: 2005-2008 and 2nd grant 2008-2013
** NIH: the grant considered in 2008 covers 2 NIH periods: part of year 1 = January to August 2008 and part of year 2 = September to December 2008
*** MSF donation includes a restricted grant for the “Paromomycin for VL” project of EUR 530,597 and an unrestricted grant of EUR 5,000,000
<table>
<thead>
<tr>
<th>European Union FP6 HAT (Restricted)</th>
<th>Switzerland Canton of Geneva (Restricted)</th>
<th>Médecins S. Frontières*** (Unrestricted &amp; Restricted)</th>
<th>Bill &amp; Melinda Gates Foundation (Restricted)</th>
<th>UBS Optimus Foundation (Restricted)</th>
<th>Anonymous Grant (Unrestricted)</th>
<th>Sasakawa Peace Foundation (Restricted)</th>
<th>Individual Donors from USA (Unrestricted)</th>
<th>Guy’s, King’s &amp; St. Thomas giving week</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>156,278</td>
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<td>126,724</td>
<td>117,337</td>
<td>16,074</td>
<td>1,259,498</td>
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<td>2,057,398</td>
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<td>13,539</td>
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<td>598,377</td>
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<td>539,511</td>
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<td>421,429</td>
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<td>219,089</td>
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<td>430,118</td>
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<td>80,707</td>
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<td>139,760</td>
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<td>3,310,426</td>
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<td>3,442,186</td>
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<td>69,467</td>
<td>752,588</td>
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<td>867,086</td>
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<td>366,434</td>
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<td>366,434</td>
</tr>
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<td>0</td>
<td>3,310,426</td>
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<td>3,310,426</td>
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<td>95,572</td>
<td>496</td>
<td>5,740</td>
<td>23,513</td>
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<td>455,973</td>
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<td>79,310</td>
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<td>143,302</td>
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<td>8,912</td>
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<td>864,009</td>
</tr>
<tr>
<td>13,664</td>
<td>439,706</td>
<td></td>
<td>17,092</td>
<td></td>
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<td>694,486</td>
</tr>
<tr>
<td></td>
<td>641,261</td>
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<td>90,823</td>
<td>1,245, 20,771</td>
<td>986</td>
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<td>1,246,494</td>
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<td></td>
<td>2,506,253</td>
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<td></td>
<td></td>
<td>2,506,253</td>
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<tr>
<td>128,975</td>
<td>126,860</td>
<td>5,530,590</td>
<td>4,203,373</td>
<td>166,588</td>
<td>138,108</td>
<td>97,004</td>
<td>23,513</td>
<td>16,074</td>
<td>20,070,672</td>
</tr>
</tbody>
</table>
### 6. R&D PROJECTS RELATED EXPENDITURE

#### Recognised in 2008 and 2007

<table>
<thead>
<tr>
<th>Clinical/Post-Registration Projects</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifurtimox – Efollorinthe coadministration for stage 2 T.b.gambiense HAT</td>
<td>539,511</td>
<td>391,583</td>
</tr>
<tr>
<td>Paromomycin for V Leish. in East Africa</td>
<td>1,259,498</td>
<td>1,281,593</td>
</tr>
<tr>
<td>Artesunate+Amodiaquine for Malaria</td>
<td>1,122,506</td>
<td>1,041,260</td>
</tr>
<tr>
<td>Artesunate+Mefloquine for Malaria</td>
<td>934,892</td>
<td>703,554</td>
</tr>
<tr>
<td>Imiquimod for Cutaneous Leishmaniasis</td>
<td>832</td>
<td>93,737</td>
</tr>
<tr>
<td>Combination therapy for VL</td>
<td>457,121</td>
<td>165,858</td>
</tr>
<tr>
<td>Ambisome for VL</td>
<td>139,985</td>
<td>18,770</td>
</tr>
<tr>
<td>Clinical projects for Chagas (Ped. Benznidazole, Posaconazole...)</td>
<td>210,675</td>
<td>28,870</td>
</tr>
<tr>
<td><strong>Total Clinical/Post-Registration Projects</strong></td>
<td><strong>4,665,020</strong></td>
<td><strong>3,725,225</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preclinical Projects</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexinidazole HAT</td>
<td>1,327,587</td>
<td>526,344</td>
</tr>
<tr>
<td>Amphotericin B polymer</td>
<td>219,089</td>
<td>293,856</td>
</tr>
<tr>
<td>Buparvaquone VL</td>
<td>52,724</td>
<td>6,880</td>
</tr>
<tr>
<td><strong>Total Preclinical Projects</strong></td>
<td><strong>1,599,400</strong></td>
<td><strong>827,080</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discovery (Selection &amp; Optimisation) Projects</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysteine Protease Inhibitors for HAT</td>
<td>0</td>
<td>2,197</td>
</tr>
<tr>
<td>Kitasato screening Tryps</td>
<td>180,825</td>
<td>155,482</td>
</tr>
<tr>
<td>Nitroimidazoles for HAT</td>
<td>230,081</td>
<td>226,717</td>
</tr>
<tr>
<td>Trypanothione reductase inhibitors for Leishmania &amp; Trypanosomes</td>
<td>0</td>
<td>104,182</td>
</tr>
<tr>
<td>Microtubule Inhibitor</td>
<td>163,147</td>
<td>189,295</td>
</tr>
<tr>
<td>EskiSis Natural Product Screening for HAT</td>
<td>182,666</td>
<td>0</td>
</tr>
<tr>
<td>EHS Image Screening / Institut Pasteur Korea (exploratory in 2007)</td>
<td>122,585</td>
<td>0</td>
</tr>
<tr>
<td>Screening Assays (STI, LSHTM, Antwerp, Murdoch)</td>
<td>356,832</td>
<td>292,587</td>
</tr>
<tr>
<td>Various Discovery (CDRI &amp; Scynexis in 2008)</td>
<td>56,067</td>
<td>122,653</td>
</tr>
<tr>
<td>HAT Consortium Lead Optimisation</td>
<td>3,310,426</td>
<td>1,299,743</td>
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<tr>
<td>VL Consortium Lead Optimisation</td>
<td>867,085</td>
<td>56,025</td>
</tr>
<tr>
<td>Chagas Consortium (...) Lead Optimisation</td>
<td>366,434</td>
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<tr>
<td><strong>Total Discovery Projects</strong></td>
<td><strong>5,836,148</strong></td>
<td><strong>2,448,931</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Exploratory Activities to Build the Portfolio</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other exploratory activities (Dundee, Otsuka, Ouro Preto, FUNDEF...)</td>
<td>282,343</td>
<td>246,373</td>
</tr>
<tr>
<td><strong>Total Exploratory Projects</strong></td>
<td><strong>282,343</strong></td>
<td><strong>246,373</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Project-Related Variable Expenditure</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coordination &amp; Supervision</td>
<td>1,265,594</td>
<td>1,329,644</td>
</tr>
<tr>
<td><strong>TOTAL OF PROJECT RELATED EXPENDITURE</strong></td>
<td><strong>13,648,505</strong></td>
<td><strong>8,577,253</strong></td>
</tr>
</tbody>
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Main partners:
1. Swiss Tropical Institute, Epicentre, France; PNLTHA, Democratic Republic of the Congo; CIVIT, Uganda; Médecins Sans Frontières; WHO-TDR; sanofi-aventis, France; Bayer, Germany; Roche, Switzerland
2. Kenya Medical Research Institute, Kenya; Institute of Endemic Diseases, Sudan; Gondar University & University of Addis Ababa, Ethiopia; Makerere University, Uganda; Médecins Sans Frontières; LSHTM, UK; IDA, Netherlands
3. University of Bordeaux, Tropica, Epicentre, IRD & Ellaiss, France; CNRFP, Burkin Faso; KEMRI, Kenya; ICMR, India; Médecins Sans Frontières; University of Oxford, UK; WHO-TDR University Sains, Malaysia; University of Oxford, UK; CIPLA, India; Mahidol University Shoklo Malaria Research Unit in Mael Sot, Thailand; Catalent, UK; ICMR & GKV, India; Institut FarManguinhos, Brazil; WHO-TDR
4. McGill University, Canada; Universidade Paruana Cayeto Heredia, Peru; IMI Pharmaceutical
5. ICMR & GVA-BID, India
6. University of Addis Ababa & Gondar University, Ethiopia; Armauer Hansen Research Institut & LSHTM, UK
7. Lafa & Universidade Federal do Ouro Preto, Brazil; Tulasne University, USA; University of Liverpool, UK
8. Ayentis, France; Swiss Tropical Institute; Novartis, Italy; Covance & Aptuit, UK; KARI-TRC, Kenya
9. Imperial College London, London School of Pharmacy & LSHTM, UK
10. Aids, India; University Sains Malaysia; LSHTM, UK; Tera Q, Australia; Drugabils, France
11. Kitasato University & Institute, Japan
12. Swiss Tropical Institute, Fiocruz Institute & Ouro Preto University, Brasil; Covance & BioDynamics, UK; Absorption Systems, USA
13. Murdoch University, Monash University & Epicium, Australia
14. EskiSis Institut at Griffith University, Australia
15. Institut Pasteur, Korea - France
16. Swiss Tropical Institute; LSHTM, UK; Antwerp Tropical Institut, Belgium; Murdoch University, Australia
17. CDRI, India
18. Scynexis Inc & Pace University, USA
19. Aids, India; University Sains Malaysia; LSHTM, UK; Tera Q, Australia; Drugabils, France
20. CDIO Monash University, Epicium & Murdoch University, Australia; University of Washington, USA; University of Ouro Preto, Brazil
7. STRENGTHENING CAPACITIES EXPENDITURE

DNDi expenditures on strengthening existing capacities in developing countries aim to:
- build networks around specific projects between researchers from developing and developed countries;
- establish working partnerships, including technology transfers, with public and private institutions, and researchers from developing and developed countries; and
- invest in sustainable capacity and leadership in developing countries at all stages of research and development.

8. ADVOCACY, FUNDRAISING, AND GENERAL & ADMINISTRATION EXPENSES

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Human resources</td>
<td>370,462</td>
<td>333,670</td>
<td>504,588</td>
<td>274,468</td>
<td>790,591</td>
<td>837,653</td>
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<tr>
<td>Office charges</td>
<td>38,975</td>
<td>13,909</td>
<td>52,146</td>
<td>14,256</td>
<td>97,291</td>
<td>110,055</td>
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<tr>
<td>Travel expenses</td>
<td>52,961</td>
<td>41,660</td>
<td>31,812</td>
<td>23,052</td>
<td>97,291</td>
<td>110,055</td>
</tr>
<tr>
<td>Administration</td>
<td>76,350</td>
<td>62,217</td>
<td>43,781</td>
<td>23,946</td>
<td>90,274</td>
<td>145,376</td>
</tr>
<tr>
<td>IT &amp; telecommunications</td>
<td>42,496</td>
<td>25,590</td>
<td>28,484</td>
<td>19,454</td>
<td>88,755</td>
<td>63,311</td>
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<tr>
<td>Communication</td>
<td>268,525</td>
<td>173,894</td>
<td>24,479</td>
<td>3,902</td>
<td>65,718</td>
<td>44,427</td>
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<tr>
<td>Depreciation</td>
<td>14,240</td>
<td>5,608</td>
<td>9,197</td>
<td>4,006</td>
<td>24,208</td>
<td>9,133</td>
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<tr>
<td>Exceptional expenses</td>
<td>0</td>
<td>1,032</td>
<td>0</td>
<td>0</td>
<td>18,504</td>
<td>8,264</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>864,009</strong></td>
<td><strong>657,580</strong></td>
<td><strong>694,486</strong></td>
<td><strong>363,084</strong></td>
<td><strong>1,246,694</strong></td>
<td><strong>1,251,076</strong></td>
</tr>
</tbody>
</table>

*Including Business Development in 2007

9. INDEMNITIES & REMUNERATIONS GIVEN TO DIRECTORS

All members of the Board are volunteers. The Board members did not receive any remuneration for their mandate in 2008, or in 2007.
10. VALUATION OF IN-KIND CONTRIBUTIONS

The Drugs for Neglected Diseases initiative (DNDi), as an independent needs-driven not-for-profit organisation, is developing drugs for people suffering from the most neglected diseases around the world. Its operations and activities are funded through financial donations. In addition to funding, generous partners, companies, and individuals provide DNDi with goods or services at zero cost, as gifts-in-kind.

> Gifts-in-kind evaluated in Euros for the year 2008 per category and per project

<table>
<thead>
<tr>
<th></th>
<th>Staff scientific</th>
<th>Staff non-scientific</th>
<th>R&amp;D services</th>
<th>Office, furniture &amp; admin.</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT</td>
<td>120,000</td>
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<td>120,000</td>
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<tr>
<td>Natural Substances</td>
<td>10,031</td>
<td>5,261</td>
<td>750</td>
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<td>16,042</td>
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<tr>
<td>Institut Pasteur Korea IPK</td>
<td>145,888</td>
<td></td>
<td></td>
<td></td>
<td>145,888</td>
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<tr>
<td>Kitasato Institut</td>
<td>47,712</td>
<td></td>
<td></td>
<td></td>
<td>47,712</td>
</tr>
<tr>
<td>Regional Support Offices</td>
<td>78,431</td>
<td>6,667</td>
<td>13,128</td>
<td></td>
<td>159,673</td>
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<tr>
<td>General Management</td>
<td>6,000</td>
<td></td>
<td></td>
<td></td>
<td>6,000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>402,062</strong></td>
<td><strong>17,928</strong></td>
<td><strong>13,128</strong></td>
<td><strong>62,197</strong></td>
<td><strong>495,315</strong></td>
</tr>
</tbody>
</table>

Main in-kind contributors: Experts J.-R. Kiechel, France and C. Brünger, Japan; Volunteers for administrative work in Geneva and Tokyo; ICMR, India; KEMRI, Kenya; Sains University, Malaysia; Institut Pasteur, Korea (IPK); Kitasato Institute, Japan.

11. ASSETS PLEDGED AS GUARANTEE FOR COMMITMENTS

At year-end, a bank of the Foundation provided a rental letter of guarantee for CHF 70,000 (EUR 46,942) in favour of a third party. Cash for an equivalent amount is pledged at the corresponding bank.
REPORT OF THE STATUTORY AUDITOR

To the Board of
Drugs for Neglected Diseases initiative (DNDi), Geneva

Report on the financial statements
As statutory auditor, we have audited the financial statements of Drugs for Neglected Diseases initiative (DNDi), which comprise the balance sheet, statement of operations, funds flow statement, statement of changes in capital and notes, presented on pages 51 to 62, for the year ended December 31, 2008. In accordance with Swiss GAAP RPC 21, the content of the performance report presented on pages 45 to 50 is not audited.

Board’s Responsibility
The Board is responsible for the preparation of the financial statements in accordance with the requirements of Swiss GAAP RPC and the requirements of Swiss law as well as with the charter of foundation and regulations. This responsibility includes designing, implementing and maintaining an internal control system relevant to the preparation of financial statements that are free from material misstatement, whether due to fraud or error. The Board is further responsible for selecting and applying appropriate accounting policies and making accounting estimates that are reasonable in the circumstances.

Auditor’s Responsibility
Our responsibility is to express an opinion on these financial statements based on our audit. We conducted our audit in accordance with Swiss law and Swiss Auditing Standards. Those standards require that we plan and perform the audit to obtain reasonable assurance whether the financial statements are free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statements. The procedures selected depend on the auditor’s judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error. In making those risk assessments, the auditor considers the internal control system relevant to the entity’s preparation of the financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity’s internal control system. An audit also includes evaluating the appropriateness of the accounting policies used and the reasonableness of accounting estimates made, as well as evaluating the overall presentation of the financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

Opinion
In our opinion, the financial statements for the year ended give a true and fair view of the financial position, the results of operations and the cash flows in accordance with Swiss GAAP RPC and comply with Swiss law as well as with the charter of foundation and regulations.
Report on Other Legal Requirements

We confirm that we meet the legal requirements on licensing according to the Auditor Oversight Act (AOA) and independence (articles 83b paragraph 3 CC and 728 CO) and that there are no circumstances incompatible with our independence.

In accordance with articles 83b paragraph 3 CC and 728a paragraph 1 item 3 CO and Swiss Auditing Standard 890, we confirm that an internal control system exists, which has been designed for the preparation of financial statements according to the instructions of the Board.

We recommend that the financial statements submitted to you be approved.

DELOITTE SA

[Signatures]

Peter Quigley
Licensed audit expert
Auditor in charge

Jurg Gehring
Licensed audit expert

May 26, 2009
Photos credits: All photos are DNDi’s apart from 5: Médecins Sans Frontières (MSF), Institut Pasteur Korea (IPK); 6: Edmundo Caetano; 14: Eskitis; 15: IPK; 21: WHO; MSF; 26: Anna Surinyac (MSF); 28: Anna Surinyac (MSF); 29: C. Zuniga, National Chagas and Leishmaniasis Control Program of Honduras; 30: MSF; 31: James Gathany (CDC); Shoklo Malaria Research Unit (SMRU); 64: Edmundo Caetano; Acre, Amazon, Brazil.

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Best science for the most neglected

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