Drugs for Neglected Diseases initiative; Best Science for the Most Neglected

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Introduction

The Drugs for Neglected Diseases *initiative* (DND*i*) is an independent not-for-profit product development partnership working to research and develop new and improved treatments for neglected diseases. With the objective of addressing unmet patient needs—particularly for human African trypanosomiasis, leishmaniasis, Chagas disease, and malaria—DND*i* was founded in 2003 by Brazil's Oswaldo Cruz Foundation, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia, the Pasteur Institute in France, and Médecins Sans Frontières/Doctors Without Borders (MSF), with the Word Health Organization/TDR as a permanent observer. The creation of DND*i* is the result of years of campaigning by MSF for more and better resources for the world's most neglected diseases.

Working in partnership with industry, non-governmental organizations, and academia, DND*i* has established the largest ever R&D portfolio for kinetoplastid diseases such as sleeping sickness, leishmaniasis, and Chagas disease. Since 2007, DND*i* has delivered three products: "ASAQ" and "ASMQ", both fixed-dose artemisinin combination therapies for malaria, and NECT (nifurtimox-eflornithine combination therapy) to treat the advanced stage of sleeping sickness.

DND*i*'s Objectives by 2014

Primary:

- Deliver 6-8 new treatments by 2014 for Chagas disease, sleeping sickness, leishmaniasis, and malaria
- Establish a robust portfolio for a new generation of treatments

Secondary:

- Use and strengthen existing drug R&D capacity in disease-endemic countries
- Advocate for increased prioritization and funding for R&D for neglected diseases

Breaking the cycle of poverty

In wealthy countries, scientific advances over the past 30 years have produced substantial gains in life expectancy and unparalleled medical care. Yet deadly tropical diseases – many of which are preventable, treatable, and curable – continue to ravage poor communities across the developing world, largely due to market and public policy failures.

Of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4% of the global disease burden. Despite progress made in the basic knowledge of many tropical diseases, this research is not being translated into practical applications, such as the development of new treatments.

Over one billion people are infected with one of the diseases defined by the World Health Organization (WHO) as neglected tropical diseases (NTDs). These diseases are the world's sixth leading cause of disability-adjusted life years (DALYs)[1]. They are the most common infections in the 2.5 billion people who live on less than 2US$[2] a day, people who are often marginalised or forgotten by their governments, and left to suffer in silence. The majority of people suffering from these diseases are too poor to afford any kind of treatment. NTDs are diverse, but all cause severe disability or death, and create a major economic burden for endemic countries.

Despite the devastating impact of NTDs, they fall outside the scope of the drug industry's research and development (R&D) efforts because they do not represent a profitable market. As a consequence there is a considerable lack of appropriate treatments. For some neglected diseases, such as Chagas, visceral leishmaniasis, and sleeping sickness, available treatments are largely archaic, toxic, ineffective, or unaffordable. The lack of suitable drugs represents a major barrier to social and economic progress in the developing world. Without better prevention, treatment, and control of neglected diseases, vulnerable populations will never be able to break the cycle of poverty. New lifesaving drugs are a critical priority. Significant investments in drug research and development (R&D) are urgently needed to develop safe, effective, and affordable medicines for neglected tropical diseases.

For all of these NTDs, however, there are existing health tools—and these need to be implemented immediately. But specific gaps in R&D remain, and increased resources are required to develop innovative tools to support the treatment, sustainable control, and even the elimination of these diseases.

An innovative and cost effective model to boost R& D for neglected diseases

Since 2003, DND*i* has been working with the following mission and 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 by ensuring equitable access to new and field-relevant health tools.
- To act in the public interest and bridge existing R&D gaps 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.

DND*i*'s collaborative approach is focused, cost-effective, and driven by the needs of patients and healthcare workers in disease endemic countries.

Building a robust portfolio

As DND*i* does not have its own laboratories or clinics, the organisation relies on partners to help develop improved treatments for patients with neglected diseases. DND*i* seeks to maximise existing resources and available expertise so as to minimise costs, overlaps, and risks of attrition.

DND*i*'s portfolio is a mix of projects in-sourced at any stage of the development process, from early discovery through post-registration, with the objective of bringing to market new treatments that are safe, efficacious, and field-adapted, while also balancing the urgent needs for incrementally improved treatments that offer meaningful improvements. The portfolio consists of a mix 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.

Discovery is the first step of drug research and development to bring forward a new generation of medicines that are more efficient than current therapies. It is a three-stage process consisting of screening, lead selection, and lead optimization.

DND*i* has initiated a number of different partnerships so as to have access to a broad chemical diversity. To this end, a number of agreements with major pharmaceutical and biotechnology companies have been signed, with, for example, Pfizer, sanofi-aventis, GlaxoSmithKline, Novartis, and Anacor.

DND*i* has set up a dedicated lead optimisation consortium for each of its core diseases to obtain optimized leads by progressing compounds with a good safety and efficacy profile into preclinical development.

For all diseases, DND*i* is currently conducting more than 10 clinical projects, all of which include clinical trials activities at various stages. These trials mostly take place in remote and poor settings.

Currently DND*i* has 4 projects in preclinical development and 6 in clinical development, including 1 new drug candidate entered into phase 1 of clinical development for sleeping sickness.

Worldwide DND*i* works with more than 200 public and private partners in R&D to find best solutions for the most neglected patients.

Achievements up to 2010

Key achievements in a nutshell:

10 ongoing clinical trials in Latin America, Asia, and Africa
3 new treatments developed for malaria and sleeping sickness
3 regional clinical trial platforms set up to endorse projects
1 new drug candidate entering clinical trial for sleeping sickness
3 lead optimization consortia (groups of different organizations and institutions working for R&D)

Three new affordable and field-adapted treatments have been registered and implemented as public goods since 2007.

NECT (2009)

Nifurtimox-eflornithine combination therapy (NECT) is a new combination treatment developed by DND*i* and its partners (MSF, Epicentre and the HAT Platform). It is a new improved treatment option for the advanced stage of human African trypanosomniasis (HAT) or sleeping sickness. NECT consists of a simplified coadminsitration of nifurtimox, which is given orally, and eflornithine, which is given intravenously. In May 2009 NECT was added to the WHO Essential Medicines List. The treatment has been available since September 2009, and the first NECT kits with treatments arrived in the Democratic Republic of Congo in November 2009.

ASMQ (2008)

ASMQ is a new combination treatment for uncomplicated falciparum malaria in South America and **Southeast Asia**. This fixed-dose combination therapy of artesunate and mefloquine (ASMQ) is a **simple regimen consisting of** a single daily dose of one tablet (for children) or two tablets (for adults) over three days. ASMQ was **successfully registered in Brazil** in March 2008 in collaboration with the Brazilian pharmaceutical company Farmanguinhos/Fiocruz .

ASAQ (2007)

ASAQ is a combination treatment for uncomplicated falciparum malaria in Africa. The combination therapy of artesunate and amodiaquine (ASAQ) is a non-patented fixed-dose combination treatment for malaria that has been prequalified by the WHO. It consists of a single dose regimen with one tablet a day for three days for infants and two tablets once a day for three days for adults. ASAQ is a treatment for malaria strains found in sub-Saharan Africa, and by December 2009 had been registered in 25 countries in collaboration with the French pharmaceutical company sanofi-aventis. At the end of 2009, more than 25 million treatments had been made available.

Strengthening existing research capacities in endemic regions

As an integral part of its mission, DND*i* uses and strengthens existing research capacities in endemic countries. DND*i* helps to build additional capacity through technology transfer in affected countries and by transferring ownership of the solutions and responsibility to affected countries. DND*i* helps to build additional capacities. To help define patient needs, DND*i* created platforms for HAT and visceral leishmaniasis-networks of representatives from the health and NGO sectors of the most affected countries. These platforms also bring together experts to assist R&D as well as to implement access to treatments in endemic regions. These platforms furthermore help to conduct clinical development projects and facilitate regulatory approval processes.

- **The HAT platform** is a network of representatives from the seven sub-Saharan countries most affected by sleeping sickness (Sudan, Democratic Republic of the Congo, Republic of the Congo, Angola, Uganda, Chad, Central African Republic). Partners are working to build up local clinical research capacity and improve treatment options across the region, and have conducted gap assessments and numerous training sessions.
- **The LEAP platform** (Leishmaniasis East Africa Platform) is a regional network consisting of Ugandan, Kenyan, Sudanese, and Ethiopian partners and was established to strengthen local clinical research capacity and improve treatment options for visceral leishmaniasis in the region. The network facilitated the start of seven clinical trial sites and has conducted numerous training sessions. Through this network, more than 1,000 patients have been included in a clinical trial in select hospitals since 2004. The objective of this trial is to register an improved treatment at low cost for visceral leishmaniasis.
- **The Chagas platform** was launched in 2009 at Uberaba in Brazil to bring together partners, experts, and stakeholders in a network that will provide support to the successful evaluation and development of new treatments for Chagas disease. The main objectives of the platform are to facilitate clinical research by creating a forum for technical discussions, to develop a critical mass of expertise, and to strengthen institutional research capacities.

Political leadership needed

In the past decade, changes in the field of R&D have opened up new opportunities to collaborate with different actors to advance basic health needs around the globe. DND*i* advocates for change and furthermore calls for innovative and sustainable financing mechanisms.

Recognising the importance of fostering a supportive environment for research for NTDs, DND*i*, since its inception, has worked on raising awareness on the critical issue of the need for strong political leadership to create a more enabling environment and to mobilise public and private resources to meet the needs of the world’s most neglected patients. Political leadership is also crucial in defining global health priorities, stimulating R&D, building

sustainable financial support, and ensuring equitable access to essential medicines.

Public leadership is needed to implement new policies that will support the development of new essential health tools (treatments and diagnostic tools) to ensure equitable access to treatment for affected populations. They would also contribute to the development of innovative needs-based measures such as intellectual property management policies to encourage needs-driven R&D, technology transfer, and strengthening of research capacities in developing countries.

Despite the existence of product development partnerships such as DND*i*, much remains to be done. New commitments from public and private donors, new initiatives from pharmaceutical companies and developing countries, funding for scientific and medical innovation for diseases that affect the developing world disproportionately, remain inadequate.

In 2008 the global funding for R&D for neglected diseases (including malaria, tuberculosis, and HIV/AIDS) amounted to US$ 3 billion. Of this only 4.9 percent was spent on the kinetoplastid diseases (sleeping sickness, leishmaniasis, and Chagas disease).

New and innovative funding mechanisms and incentives are required to ensure that, in the future, R&D for neglected diseases becomes sustainable in order to ensure better access to new products.

By February 2010, DND*i* had secured €130 million in funding. However, DND*i* still needs another €100 million to achieve its business plan objectives until 2014. DND*i* seeks to ensure balanced financial support from public and private sectors, allowing the organisation more flexibility and sustainability, while also preserving its independence.

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[1] One DALY can be thought of as one lost year of “healthy” life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability.

[2] Poverty data: A supplement to World Development indicators 2008