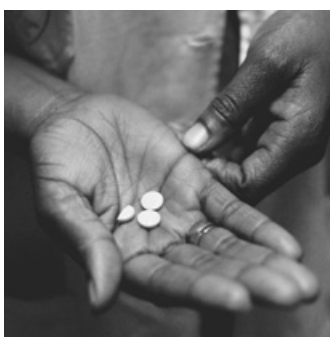
AN INNOVATIVE APPROACH
TO R&D FOR NEGLECTED PATIENTS

TEN YEARS OF EXPERIENCE & LESSONS LEARNED BY DND*i*



JANUARY 2014

DND*i*
Drugs for Neglected Diseases *initiative*

OVER THE PAST DECADE

Just a little over a decade ago, research and development (R&D) for neglected diseases was stagnant. A seminal publication in 2001 showed that only 1.1% of new drugs were approved specifically for neglected diseases over a period of 25 years (1974 to 1999), despite the fact that these diseases represented 12% of the global disease burden[1]. The report provided the evidence needed to advocate for action and change, within and beyond the global health community. Coined as the 'fatal imbalance', the report was part of a movement that triggered the emergence of new approaches and alternative R&D models to address market and policy failures[2], notably by Médecins Sans Frontières (MSF).

A DECADE AGO, NEGLECTED DISEASE R&D WAS STAGNANT.

Over the past decade, the R&D landscape for neglected diseases has evolved significantly: New R&D initiatives have been launched by a broad range of actors, including academic groups, pharmaceutical companies, governments from emerging economies, and others. One of the results of this evolution was the not-for-profit product development partnerships (PDPs), such as the Drugs for Neglected Diseases initiative (DND*i*), which aimed to fill R&D gaps and catalyse new scientific projects to address the needs of neglected patients.

DND*i*, an independent, international not-for-profit R&D organization, was established in 2003. Within 10 years and with a budget of approximately EUR 182.5 million, the initiative has delivered six new treatments for neglected diseases and established a solid drug development pipeline, including 12 new chemical entities (NCEs) in preclinical and clinical development. Over 350 collaborations in 43 countries, including nearly 20 pharmaceutical and biotechnology companies, and over 50 universities and research institutes have been put into action. North-South and South-South technology transfer projects and three disease-specific clinical research platforms were formed to strengthen research capacity in neglected disease-endemic countries. With its partners, DND*i* has conducted 25 clinical studies from Phase I to Phase IV implementation/pharmacovigilance studies, enrolling over 33,000 patients. The studies were carried out in compliance with international standards and often in very remote and unstable areas. This has all been possible through the diligent work and engagement of DND*i*'s approximately 125-member staff in eight offices around the world (Switzerland, Brazil, India, Kenya, Democratic Republic of the Congo, Malaysia, Japan, and the USA) with a balance of professional backgrounds from the private, academic, and non-governmental sectors.

OVER 350 COLLABORATIONS IN 43 COUNTRIES AND A 125-MEMBER STAFF IN EIGHT OFFICES WORLDWIDE WERE BUILT.

With the experiences and lessons of a decade of R&D for neglected diseases, it was considered vital to contribute to the current global discussions about new approaches to foster innovation for diseases that predominantly or exclusively affect people in low- and middle-income countries. DND*i* has taken the initiative, through this paper, to document its practices, and assess its strengths and weaknesses. The lessons learned are open to debate, and may be applicable to other diseases and product types.

(1) 'Drugs for neglected diseases: a failure of the market and a public health failure?' By Trouiller P, Torreele E, Olliaro P, White N, Foster S, Wirth D, Pecoul B. *Trop Med Int Health.* 2001 Nov;6(11):945-51.
(2) Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases. MSF Campaign for Access to Essential Medicines and Drugs for Neglected Diseases Working Group. Geneva, 2001.

FOUR PILLARS OF AN ALTERNATIVE R&D MODEL DESIGNED TO ADDRESS UNMET PATIENTS' NEEDS

DND*i* was launched in 2003 by several key institutions, following the recommendations of the Drugs for Neglected Diseases (DND) Working Group, an international 'think tank' set up by Médecins Sans Frontières (MSF) to analyse the causes of the R&D crisis for neglected diseases. The working group suggested innovative strategies to ensure the development of new and affordable medicines for neglected patients. Based on its recommendations, seven founding partners joined forces to create DND*i*: five publicly-funded research organizations – the Malaysian Ministry of Health, the Kenya Medical Research Institute, the Indian Council of Medical Research, the Oswaldo Cruz Foundation (Fiocruz) Brazil, and the Institut Pasteur, France; an international humanitarian organization, MSF; and the UNICEF/UNDP/World Bank/WHO's Special Programme for Research and Training in Tropical Diseases (TDR) as a permanent observer.

DND*i* 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.

The objective was and is unambiguous: deliver new treatments to patients suffering from the most neglected communicable diseases by developing new drugs or new formulations of existing drugs. In doing this, the aim was to build R&D networks to develop sustainable research capacity in disease-endemic countries and advocate for public responsibility globally.

Taking into consideration the diseases affecting the most neglected patients, including socio-economic contexts and health systems, DND*i*'s primary focus was the development of treatments for a small group of neglected tropical diseases with particularly high mortality rates. This group of severe neglected diseases, called 'kinetoplastid diseases', is comprised of human African trypanosomiasis (sleeping sickness), visceral leishmaniasis (kala-azar), and American trypanosomiasis (Chagas disease). DND*i* also considered engagement in R&D projects for other neglected diseases for which there were glaring gaps unaddressed by other actors. It is for this reason, for example, that DND*i* engaged with partners to develop two specific malaria treatments.

In 2011, while maintaining the core focus on the most neglected kinetoplastid diseases, DND*i* responded to calls from international organizations and partners, including MSF and the World Health Organization (WHO), to address additional, specific, urgent patient needs, notably the need for adapted antiretrovirals (ARVs) for children born with HIV (and those co-infected with tuberculosis), and for a macrofilaricide (drug that kills adult worms) for patients infected with three specific filarial (worm) infections: lymphatic filariasis (elephantiasis), onchocerciasis (river blindness), and loiasis (*Loa loa*, or African eye-worm).

Several distinctive features characterize DND*i*'s not-for-profit drug research and development model, which stimulates innovation by exploring non-conventional pathways for drug development. These features, or pillars, include: a concretely patient-centred, needs-driven approach; a commitment to both equitable access to treatment for patients and open access to knowledge; financial and scientific independence; and the leveraging of existing knowledge and expertise by building solid alliances with public and private partners.

PATIENTS' NEEDS AT THE CENTRE OF THE R&D PROCESS

Therapeutic impact is the constant, most important driving force of DND*i*'s work. This patient-centred approach is not an empty slogan, it is a fundamental and distinct part of daily practice within the organization: from the selection of target diseases, to the definition of ideal target product profiles, to key decision- and policy-making platforms. Beginning with the end in mind, and keeping it in mind until patient needs are addressed appropriately, is ingrained in the way the organizational model is designed.

Disease-specific target product profiles (TPPs), guide and determine all R&D activities. The TPP is a succinct description of the ideal specifications needed for a treatment, considering the needs of the patients and the main characteristics of the related health system. These TPPs are developed with leading experts from endemic countries, researchers, clinicians, disease control programme managers, WHO, and, most importantly, patient representatives whenever possible. This is one of the ways in which implementation of new technologies, once registered, is facilitated. TPPs are reviewed and, if necessary, updated annually in order to keep pace with the latest available scientific evidence.

Essential elements of a needs-driven Target Product Profile (TPP)

Indications: Which disease(s)?

Population: Which type of patients and where?

Clinical Efficacy: Does it treat the infection effectively?

Safety and Tolerability: What level of acceptability for adverse events?

Stability: How long is the shelf-life of the drug(s) and what are the storage conditions?

Route of Administration: What is an acceptable way to administer the treatment to the patient population?

Dosing Frequency and Treatment Duration: How often and how long must it be given?

Cost: Will it be affordable to the target population or health system?

Keeping abreast of patients' needs is also one of the key contributions of DND*i*'s founding partners from endemic countries (Brazil, India, Kenya, and Malaysia) and MSF, especially considering their historical involvement and expertise in infectious diseases. These founding partners play a crucial role in anchoring the organization in the urgency and reality of neglected patients in the field. At the highest level of governance, notably the Board of Directors, two patient representatives (currently from Ghana and Bangladesh) participate actively to ensure that all levels of the organization remain cognizant of the complex socio-economic, political, and research environments in which DND*i* operates. At the operational level, expert groups, including field practitioners, are involved in defining DND*i*'s scientific strategy, which is an additional guarantee of patient-centricity in decision-making. MSF has been particularly instrumental in devising a short-term strategy designed to address immediate patient needs through improving existing treatments and new drug formulations (see below for further details), and in placing unmet R&D gaps, for example in the field of paediatric HIV, on the list of priorities for DND*i*.

All of these factors are part of the patient-centred approach to R&D and help to increase impact for patients when new treatments reach the end of the pipeline.

ACCESS TO KNOWLEDGE AND ACCESS TO TREATMENTS

At inception, DND*i* adopted an intellectual property (IP) policy based on two critical guiding principles: the need to ensure that drugs are affordable and accessible in an equitable manner to patients who need them; and the desire to develop drugs as public goods wherever and whenever possible. These principles have been the basis of contract negotiations undertaken by DND*i* from the outset, particularly with a view to obtaining the best possible conditions to facilitate access to treatments. In practice, DND*i* aims at securing licensing terms which ensure that research itself and the outputs of research are considered public goods that lead to the advancement of health.

Specifically, DND*i* negotiates terms with partners that safeguard against the use of IP in a manner that impedes equitable and affordable access to the products of the research, or that impedes additional or follow-on research by DND*i*, its partners and other researchers, especially those undertaking research on neglected diseases. Access to knowledge and data, and the need to share newly generated knowledge to facilitate advancement of the science, are key to enabling and promoting R&D for diseases related to poverty.

Contractual provisions aim also at de-linking the cost of R&D from the price of the final product, which is essential to affordable and equitable access for patients, particularly in low- and middle-income countries. This is reinforced by the fact that DND*i* does not finance its research or operations through IP rent revenues[3].

Promoting and encouraging open access to new research knowledge generated by DND*i* activities, the data emanating from DND*i* projects are presented and published in a timely manner, primarily in open access journals and publicly accessible databases. Examples of the latter include the ChEMBL Neglected Tropical Disease archive[4], an open access repository for primary screening and medicinal chemistry data directed at neglected diseases; and WIPO Re:Search, created in 2011 to provide access to intellectual property for pharmaceutical compounds, technologies, and – most importantly – know-how and data available for research and development for a specific set of neglected tropical diseases, tuberculosis, and malaria.

Towards 'gold standard' licensing terms

After several years of experience in negotiations with pharmaceutical companies and other partners, DND*i* has come to define what is deemed the 'gold standard' of licensing terms to ensure equitable and affordable access to treatments, which can be summarized as follows:

- Perpetual royalty-free, non-exclusive, sub-licensable licenses in the specific disease areas determined in the contract;
- Worldwide research and manufacturing rights;
- Commitment to make the final product available at cost, plus a minimal margin, in all endemic countries, regardless of their income level;
- Non-exclusivity, enabling technology transfer and local production to multiply sources of production and decrease cost of product.

(3) DND*i* IP Policy http://www.dndi.org/images/stories/pdf_aboutDND*i*/ip%20policy.pdf
(4) https://www.ebi.ac.uk/chemblntd

DND*i* also encourages initiatives aiming to facilitate access to IP deemed necessary or useful to develop its products, such as the Medicines Patent Pool (MPP) for HIV. The licenses the MPP negotiates with patent holders facilitate the initiative's work on paediatric HIV, enabling the development of new child-adapted ARV formulations without IP obstacles and under affordable conditions.

FINANCIAL AND SCIENTIFIC INDEPENDENCE

Acting in the interest of public health, every effort is made to ensure DND*i* remains fully independent in its decision-making processes. Independence is particularly important in building and managing the project portfolio; prioritizing R&D projects; and in assessing significant unmet patient needs, R&D opportunities, potential partners, and potential sources of funding. A direct result of this independence, for example, is the power to decide to launch or terminate a project based on its capacity to fulfil the TPP criteria (see page 3).

One of the most important ways in which DND*i* secures this independence is through diversification of funding to prevent unhealthy influence by or dependence upon any single donor. This is why DND*i*'s funding policy, as established by its founding partners in 2003, in addition to diversifying funding sources, also seeks to maintain a balance of public and private support, to minimize as much as possible earmarked donations, and to ensure that no one donor contributes more than 25% of the overall budget.

Since 2003, DND*i* has raised EUR 277 million and has received support from a wide range of donors, including: governments, such as those of the United Kingdom, the Netherlands, France, Spain, Switzerland, Germany, EU/EDCTP, and Brazil; MSF as a founding partner; private philanthropic organizations, including the Bill & Melinda Gates Foundation and the Wellcome Trust; and also through innovative financing mechanisms such as UNITAID.

Three types of funding from 2003 to 2018

Core Funding (59%)
- United Kingdom – DFID (€72.9M)
- Médecins Sans Frontières (€65.8M)
- Spain – AECID (€12M)
- Switzerland – SDC (€10.4M)
- Other Private Foundations - Rockefeller, Slim, Starr (€3M)

Portfolio Funding (15%)
- Netherlands – DGIS (€17M)
- France – AFD & MAEE (€14.3M)
- Germany – KFW & GTZ (€9M)
- Brazil – MoH (€0.4M)

Project Funding (26%)
- Bill & Melinda Gates Foundation (€44.1M)
- UNITAID (€13.1M)
- Wellcome Trust (€4.3M)
- European Union – FP5,6,7 & EDCTP (€4.4M)
- Medicor Foundation (€2.3M)
- USA – NIH/NIAID (€1.8M)
- Switzerland – Republic and Canton of Geneva (€1.7M)
- The Global Fund – AMFm (€0.5M)

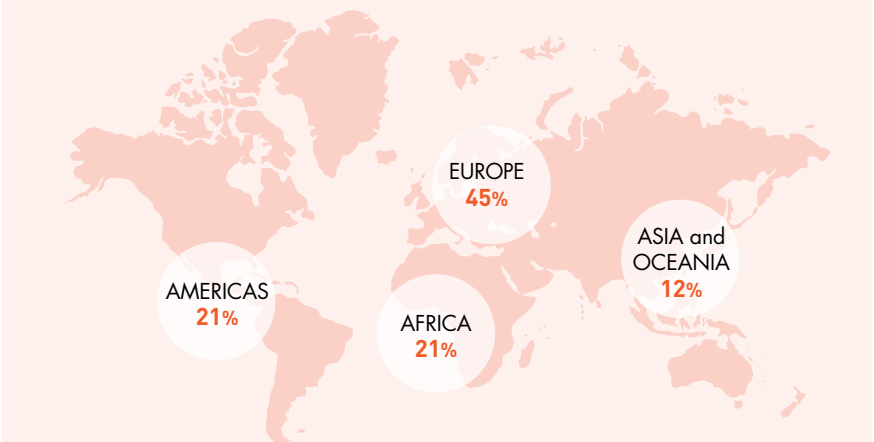
* November 2013

BUILDING AND SUSTAINING SOLID ALLIANCES

As with most of the new R&D initiatives set up over the last decade, DND*i* does not have its own laboratories or manufacturing facilities, and consequently cannot function without the engagement of public and private partners. Acting as a 'conductor of a virtual orchestra, DND*i* leverages partners' specific assets, capacities, and expertise to implement projects at all stages of the R&D process, integrating capabilities from: academia; public-sector research institutions, particularly in neglected disease-endemic countries; pharmaceutical and biotechnology companies; non-governmental organizations including other PDPs; and governments worldwide. In this way, DND*i* manages every phase of the drug development process – from drug discovery and pre-clinical research, to clinical trials and large-scale implementation studies – by articulating multiple alliances, thus ensuring the best possible alignment of partners in fulfilling the objectives set in the TPP. In so doing, DND*i* serves as a conduit of information between and among partners, and has been instrumental in strengthening cross-sector networks.

The past 10 years of experience have shown that a virtual R&D model can be successful in a strategy that seeks, in parallel, relatively rapid health impact for populations in need and a longer-term sustainable solution, which necessitates an integrated model for the management of North-South and South-South collaboration. This requires two essential components: constant and strong involvement of authorities and partners in neglected disease-endemic countries to help define priorities and facilitate implementation of new tools, on the one hand; and innovative alliances with pharmaceutical and biotechnology companies and academia through innovative IP licensing to access sources of knowledge in order to identify potential new compounds and ultimately reduce the cost of development, on the other hand (see various case studies on cost of development, pages 8-9; 11; 19; 21).

Main R&D partners & service providers per continent (2012)



TWO-PRONGED APPROACH TO R&D: ADDRESSING URGENT NEEDS AND DEVELOPING ENTIRELY NEW TREATMENTS

According to the DND*i* 2011-2018 Business Plan[5], the primary objective of the initiative is to deliver 11 to 13 new treatments for neglected patients by 2018 – including the six treatments already delivered – by developing new formulations or associations of existing drugs, and by building a robust pipeline with new drugs that will dramatically improve upon existing treatment options, potentially changing the way health systems deal with these diseases.

Early on in the initiative's existence, a thorough and global analysis of scientific portfolios and R&D opportunities for DND*i*'s priority diseases was carried out along with an assessment of the urgency to respond to existing R&D gaps and unmet patient needs. Based on that analysis, which determined medical needs and scientific opportunities, a two-pronged R&D strategy was adopted:

- Short-term approach (+/- 5 years): based on the optimization of existing drugs, to address the most urgent patient needs;
- Long-term approach (+/- 6 to 15 years): aimed at the development of completely new treatments, which would have the potential to change the future medical management of these diseases and to support sustainable control or elimination programmes for certain neglected diseases. These can be entirely new chemical entities (NCEs) or other innovative solutions to the health problems at hand.

In the early stages of the R&D process (i.e. discovery activities covering screening, hit-to-lead, lead optimization, and pre-clinical activities), DND*i* identifies the best scientific opportunities and the most effective organizations and institutions, bringing them together, often in consortia, to work towards highly focused targets and milestones under the supervision of its project leaders. In the later stages of the R&D process (i.e. clinical development), DND*i* staff work closely with partners, particularly within clinical research networks or 'platforms', to carry out clinical studies in often difficult settings and to pave the way for registration and implementation.

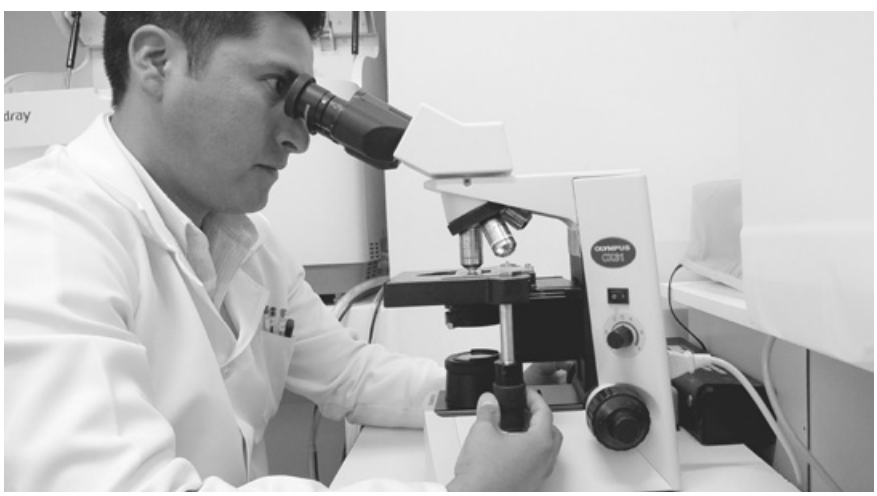
THREE ILLUSTRATIONS OF SHORT-TERM APPROACHES TO ADDRESS IMMEDIATE NEEDS

While investing in longer-term drug discovery for new chemical entities (NCEs), the imperative to respond to urgent patient needs guides the short-term strategy, focusing on improving existing treatments. This strategy aims to deliver innovations to neglected populations as quickly as possible, notably opportunities that others are unable or unwilling to seize.

This short-term strategy has led to improvements in terms of safety, reduction of treatment duration, decrease in number of injections, combining existing drugs to make treatment implementation easier for patients and clinicians, and doing away with the use of old and toxic treatments (e.g. use of melarsoprol for sleeping sickness). In general, this strategy, which is less risky in terms of scientific development and less expensive than developing NCEs, requires minimal pre-clinical studies if any, followed by clinical development, and finally the development or extension of a regulatory dossier.

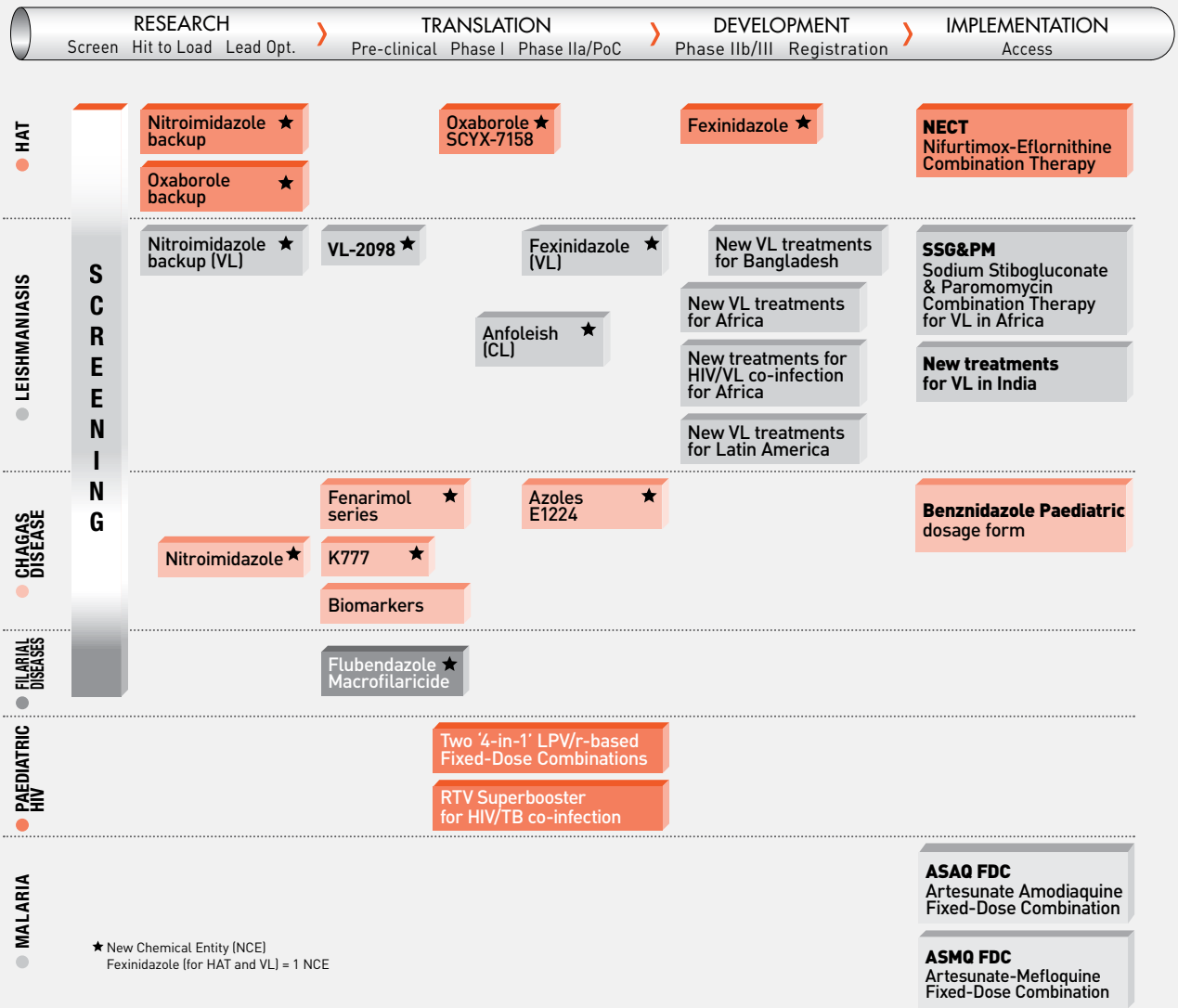
This was one of the major failures of the predominant market-driven pharmaceutical model, which has failed to invest in repurposing or combining existing treatments because of the lack of return on investment and less focus on real patients' needs, despite the relatively low cost of development. Since 2003, thanks to the long experience and extensive field expertise of the founding partners, DND*i* has delivered health innovations with concrete medical benefits for patients and health systems in general.

While all six treatments currently being implemented illustrate this, three of these are detailed here: the registration and implementation of the artesunate and amodiaquine fixed-dose combination therapy (ASAQ) for malaria; nifurtimox-eflornithine combination therapy (NECT) for sleeping sickness; and sodium stibogluconate and paromomycin combination therapy (SSG&PM) for kala-azar in East Africa.



(5) Every four years, DND*i*'s business plan is revised. The last business plan was adopted in 2011 for the period 2011-2018: http://www.dndi.org/images/stories/pdf_aboutDNDi/BusinessPlanWebSmall.pdf

Portfolio 2013



ASAQ: An easy-to-use, quality treatment realized through an innovative partnership

In 2001, in response to the increasing failure of existing malaria treatments with chloroquine due to drug resistance, and to contain and control the spread of drug resistance in malaria-endemic regions, the World Health Organization recommended worldwide abandonment of chloroquine and the use of artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated *P. falciparum* malaria.

ASAQ Winthrop, the fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), was the first treatment delivered by DND*i* in 2007 through an innovative partnership with Sanofi-Aventis (now Sanofi), led by the FACT consortium, including universities, biotechnology companies, and other non-for-profit organizations. ASAQ was an important breakthrough for patients, as it offers a more simple dosing regimen of one tablet per day (compared with one-and-a-half to four) for three days for infants, children, and adolescents and two tablets once a day (compared with eight tablets) for three days for adults. In addition, ASAQ is especially suited to the needs of children, the primary victims of malaria. To optimize dosing for each age range, and to avoid over- and under-dosing, four different presentations were made available for infants, young children, children, and adults. Colour-coding helps to identify the different dosages, which can also be easily crushed to be given with liquids or semi-liquid food if necessary. Available at less than USD 0.5 for children and USD 1 for adults, ASAQ has been developed as a non-patented public good. This facilitated a technology transfer to an Africa manufacturer in Tanzania, aimed at securing a second source of treatments and increasing competition for price reduction.

Continued on p.9

CASE STUDY N°1

ASAQ FDC

EUR 12 MILLION TO DEVELOP AND MONITOR IMPLEMENTATION OF A FIXED-DOSE COMBINATION THERAPY FOR MALARIA

ASAQ Winthrop, a fixed-dose combination of artesunate (AS) and amodiaquine (AQ) was the first treatment developed by DND*i* in 2007. ASAQ resulted from an innovative partnership between DND*i* and Sanofi conducted through the FACT consortium, initiated in 2002. To date, over 250 million treatments have been distributed throughout Africa.

- **2001-2002.** WHO guidelines recommend the use of four artemisinin-based combination therapies (ACTs), including the combination of AS+AQ for the treatment of uncomplicated *P. falciparum* malaria.
The FACT (Fixed-dose Artesunate Combination Therapy) consortium is set up in 2002, initially under the patronage of the MSF Access Campaign, later DND*i*, in coordination with WHO/TDR, with the objective to develop a fixed-dose combination of AS+AQ to improve compliance and be made available to all countries where resistance to amodiaquine is low.
- **2003-2004.** Pharmaceutical and clinical development involves several academic groups in Europe, Africa, and Asia, biotechnology companies in Europe, MSF, and TDR. A pivotal clinical study is carried out through a field-based Phase III trial in Burkina Faso to evaluate efficacy and tolerability (750 children <5 years of age).
- **2005.** Collaboration agreement signed with Sanofi (then Sanofi-Aventis) to develop ASAQ with four package-adapted weight dosages, based on the original formulation developed by DND*i*. The FDC combines two active ingredients in a single tablet. Sanofi, in charge of industrial development and implementation, commits to sell the product at cost (less than 1 USD for adults and USD 0.5 for children in the public sector). Other provisions include, for example, that ASAQ would not be patented.
- **2007.** First registration is obtained in Morocco, where the product is manufactured at the Sanofi plant.
- **2008-2010.** ASAQ is prequalified by WHO in 2008, facilitating implementation through Global Fund and other international tenders. In 2010, ASAQ obtains WHO authorization for its three-year shelf-life, giving the product the longest shelf-life of any prequalified FDC artemisinin-based treatment available for malaria.
- **2010-2011.** Over 80 million treatments are distributed by the end of 2010 in 30 African countries with an annual production capacity of up to 50 million. In partnership with Sanofi, MMV, and National Malaria Control Programmes, high-quality data on ASAQ effectiveness and safety in the field is collected as part of the first Risk Management Plan submitted to the WHO, and the first ever to be set up entirely in Africa. DND*i*, in collaboration with MSF and Epicentre, manages two sites in Liberia.
- **2011-2013.** DND*i* evaluates and begins working towards a transfer of technology to a second manufacturer in Africa, Zenufa, based in Tanzania, in order to secure a second source of ASAQ.
- **November 2013.** Over 250 million treatments are distributed in 31 African countries.

DEVELOPMENT — Phase III — Prequalification › IMPLEMENTATION — Access and technology transfer

2003 / 2008

DND*i*'s role:
- Pharmaceutical development including Phase III study (700 patients, Burkina Faso)
- Preparation dossier for registration
- Preparation of WHO Prequalification dossier

Main Partners and Service providers:
WHO/TDR; MSF; KEMRI (Kenya); University of Oxford (UK) / Mahidol University (Thailand); TROPIVAL, Univ. Bordeaux (France); Cardinal Health (France); Ellipse Pharma (France); University Sains Malaysia (USM) (Malaysia); Rottendorf Pharma (Germany); Créapharm (France); CNRFP (Burkina Faso); Sanofi (France); Bertin Pharma (France)

€7 M

2009 / 2014

DND*i*'s role:
- Support for implementation & access in countries
- Post-registration including Phase IV study, 1,300 patients in total in Liberia within risk management plan (led by Sanofi and MMV)

Main Partners and Service providers:
Sanofi (France); Medicines for Malaria Venture (MMV) (Switzerland); National Malaria Control Programmes of African countries; ICMR (India); Institut de Recherche pour le Développement (IRD) (Senegal); MSF & Epicentre; KATH & AMFm (implementation survey of ASAQ in Ghana)

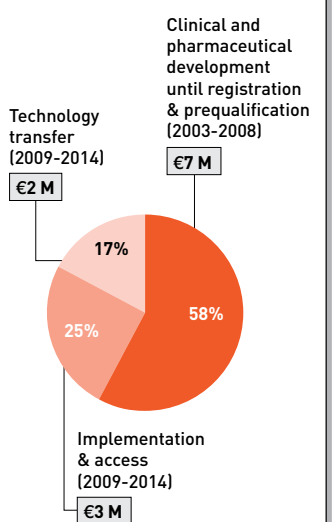
€3 M

DND*i*'s role:
- Support for transfer of technology in Africa
- Implementation & access

Main Partners and Service providers:
Zenufa (Tanzania); AEDES (Belgium); Bertin Pharma (France); OTECI (France); Sanofi (France)

€2 M

ASAQ COSTS 2003-2014



CASE STUDY N°2

NECT **EUR 6.8 MILLION** TO DEVELOP AN IMPROVED TREATMENT OPTION FOR SLEEPING SICKNESS

In 2009, Nifurtimox-Eflornithine Combination Therapy (NECT) was added to the WHO Essential Medicines List. NECT was the first improved treatment option developed in 25 years for the advanced stage of sleeping sickness. The development of NECT is the result of strong partnerships over a period of six years, notably among HAT Platform members.

• **2003-2008.** NECT project starts in 2003 as a single-centre study by MSF and Epicentre in the Republic of Congo (Brazzaville), based on the efficacy of eflornithine developed in 1981 for sleeping sickness and the addition of nifurtimox previously developed for Chagas disease. The study is extended in 2004 to additional sites in the Democratic Republic of the Congo (DRC) by DND*i*, in collaboration with the DRC national HAT control programme (PNLTHA) and MSF, as a multi-centre clinical study, enrolling 287 patients. The study is completed in 2008.

• **2009.** WHO includes NECT on the Essential Medicines List (EML) and affirms that NECT can be used to treat late-stage HAT patients, and provides an opportunity to improve the management of HAT cases. NECT proves to be as effective and safe as the former standard eflornithine monotherapy, but easier to use, with a reduced number

of intravenous infusions of eflornithine (14 instead of 56) and a shorter treatment period (10 days instead of 14). It is also proven to be far safer than melarsoprol, the previously used but highly toxic, arsenic-based drug that kills 5% of treated patients, which is still used in 50% of patients in 2008. During this same year, DRC orders the first NECT kits to treat patients. Meanwhile, DND*i* starts the 'NECT Field' study (Phase IV) to document the safety and ease of use of NECT in real-life conditions, in specific populations such as children, and pregnant and breast-feeding women (a total of 630 patients are included).

• **2011-2012.** Twelve African countries, accounting for 99% of reported HAT cases add NECT to their national essential medicines lists (Angola, Cameroon, Central African Republic, Chad, DRC, Republic of the Congo, Equatorial Guinea, Guinea Conakry, Gabon, Ivory Coast, South Sudan, and Uganda). By the end of 2012, 96% of late-stage *T.b. gambiense* HAT patients in endemic countries are treated with NECT, thus virtually eliminating use of melarsoprol for this type of HAT.

DEVELOPMENT Phase III › Recommendation › IMPLEMENTATION Access & effectiveness

2003 / 2008

DND*i*'s role & HAT Platform:
- Organize a multi-centre Phase III study, including 18 month follow-up (three clinical sites in DRC, 287 patients)
- Support HAT Platform activities

Partners and Service providers:
HAT Platform: TMRI Sudan, ICCT Angola, COCTU Uganda, National HAT Control Programmes of DRC, Republic of Congo, Central Africa Republic, Tchad, South Sudan; MSF; Epicentre; Swiss TPH; WHO NTD Department; Sanofi and Bayer

€3.6 M

2009 / 2013

DND*i*'s role & HAT Platform:
- Preparation of WHO EML submission
- Organization of the NECT Field study (630 patients)
- Implementation of NECT in countries

Partners and Service providers:
HAT Patform (see list to the left); RCTS (Data management) National HAT Control Programmes of DRC; Swiss TPH; Sanofi and Bayer

€3.2 M

The overall cost of development of NECT, including the Phase III study (2003-2008) and the NECT Field study (2009-2013) was EUR 6.8 million (as per December 2013) covering all clinical trials. The breakdown is as follows: the clinical development costs for initial NECT study amounted to EUR 3.6 million, including support activities from the HAT Platform. The implementation activities, including NECT Field, amounted to EUR 3.2 million. In addition, DND*i* refurbished and equipped the three clinical sites to ensure compliance with international Good Clinical Practice (GCP) standards.

These costs of development do not include in-kind contributions from partners, in particular the initial study conducted by MSF in 2003 and 2004 in the Republic of the Congo and their support for clinical trials, nor do they include the drug donations by Sanofi and Bayer through the WHO NTD department.

NECT: An improved treatment to do away with an arsenic-based drug

Added to the WHO Essential Medicines List in 2009, nifurtimox-eflornithine combination therapy (NECT) was the first new treatment in 25 years against sleeping sickness. The combination therapy consists of a simplified co-administration of two existing drugs, oral nifurtimox and injectible eflornithine, reducing the total number of intravenous infusions of eflornithine from 56 to 14, and shortening hospitalization from 14 days to 10 days. With two infusions a day, administered during the daytime (instead of four times, one every six hours), NECT was immediately easier to use and made the new treatment far more suitable for patients and healthcare workers in the remote and resource-poor settings where the disease occurs.

In addition, this improved treatment rapidly came to replace the arsenic-based and toxic drug that was widely used: melarsoprol. The latter killed an estimated 5% of the patients it was meant to cure, and until recently was still used for 50% of late-stage HAT patients. It also decreased the total cost of treatment from EUR 554 to EUR 288, although this has a lower genuine impact on access since the treatment is currently donated through the WHO[6].

(6) 'Update on field use of the available drugs for the chemotherapy of human African trypanosomiasis.' By P. P. Simarro *et al. Parasitology*, Volume 139, Issue 07, June 2012, pp 842-846, DOI: http://dx.doi.org/10.1017/S0031182012000169.

The 'ready-to-use' NECT treatment kit has been designed and is distributed by WHO in collaboration with MSF Logistique, with donations of the two drugs by Bayer and Sanofi, and with funding for distribution from Sanofi. NECT is thus free of charge to patients. The kit comprises the medicines and materials needed for the proper administration of NECT, with four full treatments in a 36 kg package, as opposed to two full treatments per kit with eflornithine used in monotherapy.
Despite the major improvements brought by NECT, it should be mentioned that it is still far from optimal in terms of making treatment highly accessible in very remote settings.

SSG&PM: Recommended by WHO as first-line treatment of kala-azar (visceral leishmaniasis, VL) in East Africa

Due to various limitations such as toxicity, difficulty of use, and the high cost of existing drugs, kala-azar is complicated to treat in Africa. Sodium stibogluconate (SSG), a relatively toxic drug requiring a daily regimen of painful injections over 30 days, was the treatment mainstay in East Africa for decades. Other drugs, such as paromomycin (PM) and miltefosine, were neither registered nor available in the region. In 2004, DND*i* and the Leishmaniasis East Africa Platform (LEAP) embarked on a clinical research programme with two objectives: geographically extend all currently available kala-azar treatments; and develop one to two new combination therapies. In 2010, the first combination therapy reached fruition through this clinical research: SSG&PM. The study involved over 1,100 patients and showed that a short-course combination of PM (15mg/kg/day) and SSG (20mg/kg/day) had a similar safety and efficacy profile as the standard SSG monotherapy treatment for 30 days. In 2010, the WHO Expert Committee on the Control of Leishmaniases recommended SSG&PM as first-line treatment for the disease in East Africa. This was a major advancement in prolonging the use of both drugs in the region and in reducing treatment costs and duration.

CRITICAL ROLE OF ENDEMIC COUNTRY LEADERSHIP

Many experts and several key reports[7] have confirmed that the sustainability of essential health R&D critically depends on the engagement and leadership of developing countries where neglected diseases occur. These countries have a critical role to play in defining needs and setting R&D priorities, as well as in conducting research and designing adequate national policies to ensure treatment access for their populations.

> THESE EXPERIMENTS ARE FRAGILE, BUT ARE PAVING THE WAY TO OWNERSHIP.

One key component of the DND*i* model has been the commitment to utilize and strengthen local research capacities in disease-endemic countries, rather than 'parachuting' in expertise from high-resource countries. By establishing regional clinical research platforms, and harnessing existing capacities in the affected countries, DND*i* has aimed at supporting and increasing endemic-country ownership in the health R&D field.
One disease-specific research platform per 'core' (kinetoplastid) disease has been put in place to support clinical development activities. These platforms bring together key actors in each region to carry out the clinical activities required to reach registration and adoption by country stakeholders.
The platforms work to define patient needs, train clinical researchers, conduct clinical trials, facilitate registration, and expedite implementation. They have achieved important milestones, for example, the rapid delivery of SSG&PM for kala-azar in East Africa thanks to the Leishmaniasis East Africa Platform (see box below, and case study page 11). The Chagas Clinical Research Platform participated in three important clinical studies for Chagas disease in Argentina and Bolivia. The HAT Platform, set up in 2005, was instrumental in developing NECT treatment and, under the leadership of WHO, promoting its implementation. Today, members of the HAT Platform play a central role in conducting clinical studies for a new drug candidate against sleeping sickness.
These experiments, based on alliances between partners, platforms, and different regional networks, are still fragile due to limited human resources and sustainable funding. Nonetheless, they are certainly paving the way to a greater level of ownership and responsibility, and increasing the role that experts and partners from endemic countries play in overcoming the challenges of conducting clinical trials in remote areas and in designing strategies to ensure rapid medical benefit for patients.

CHALLENGES OF CONDUCTING CLINICAL TRIALS IN REMOTE AREAS

Since 2003, DND*i*, the clinical research platforms, and other partners have together conducted 25 clinical studies in five disease areas (malaria, visceral leishmaniasis (kala-azar) and cutaneous leishmaniasis, sleeping sickness, Chagas disease, and paediatric HIV) with a recent average of 10 clinical trials simultaneously ongoing at any given time.

Continued on p.12

Clinical research 'platforms' to strengthen sustainable R&D capacity

DND*i* has helped to establish three clinical research platforms: the Leishmaniasis East Africa Platform (LEAP) in Kenya, Ethiopia, Sudan, and Uganda; the Human African Trypanosomiasis (HAT) Platform in the Democratic Republic of the Congo, Angola, Central African Republic, Chad, Republic of the Congo, Sudan, South Sudan, and Uganda; and the Chagas Clinical Research Platform in Brazil, Bolivia, Argentina, Mexico, and many others. These platforms bring together clinical researchers, ministries of health, disease control programmes, NGOs, and WHO through regional networks that help strengthen research capacity and treatment implementation in endemic countries. DND*i* has offices in Kinshasa (DRC), Nairobi (Kenya), and Rio de Janeiro (Brazil) that support existing platforms.

DND*i*-supported capacity strengthening activities may include the building and renovation of hospital wards, clinics, and health posts; renovation and re-equipping of clinical laboratories; and training of health service personnel with particular emphasis on building expertise in clinical trial methodology and conduct, good clinical practice and ethics, patient treatment and evaluation, accurate diagnosis and parasitological follow-up, and safety.

(7) As an example: Macroeconomics and health: investing in health for economic development. Report of the Commission on Macro-economics and Health. WHO, 2001.

CASE STUDY N°3

SSG&PM

EUR 11.5 MILLION TO DEVELOP A NEW COMBINATION THERAPY FOR KALA-AZAR IN AFRICA WITH THE LEISHMANIASIS EAST AFRICA PLATFORM (LEAP)

Created in 2003 in Khartoum, Sudan, LEAP is a medical research, regional collaboration platform focused on visceral leishmaniasis (kala-azar) in East Africa. The platform is jointly hosted by the Kenya Medical Research Institute (KEMRI); the Faculty of Medicine, Addis Ababa University, Ethiopia; the Institute of Endemic Diseases, University of Khartoum, Sudan; Makerere University, Kampala, Uganda; DND*i*; Médecins Sans Frontières (MSF), and other partners working in kala-azar in Eastern Africa. The LEAP secretariat is coordinated by the DND*i* Africa regional office in Nairobi, Kenya.

Today, LEAP is composed of approximately 60 individual members, representing over 20 institutions covering the spectrum of clinical research and disease control organizations working in leishmaniasis-endemic countries in East Africa. LEAP partners hold twice-yearly meetings in each member country on a rotational basis, to review the status of ongoing clinical trials and discuss patients' needs and the regional kala-azar control strategy.

The platform's objectives are to: strengthen local clinical research capacities; serve as a base for ongoing educational collaboration between countries in East Africa, as well as for standardization of procedures and practices within the boundaries of local regulations; and evaluate, validate, and facilitate implementation of new treatments for kala-azar in the region.

Overall, within ten years, LEAP has contributed to the enrolment of over 1,500 patients in clinical trials, the treatment of close to 3,000 patients outside clinical trials, and the follow-up of 3,000 patients in pharmacovigilance Phase IV studies.

- **Strengthening capacity**

Given the lack of facilities and knowledge in the region when trials commenced in 2004, there was a significant need for capacity building in order for studies to be carried out effectively. DND*i* and LEAP built 24-bed Leishmaniasis Research and Treatment Centres (LTRC) at two hospitals in Ethiopia, which are dedicated to treating patients with kala-azar and conducting clinical trials. They include laboratory space for diagnostic tests and are also used for teaching medical students. Existing facilities were rehabilitated at three sites in Uganda, Kenya, and Sudan. Between July 2004 and June 2011, a total of 442 personnel benefited from training sessions, including courses on GCP and GLP standards, trial and data management, clinical monitoring, pharmacovigilance, and audiometry. A further 14 people have undertaken graduate studies or higher degrees at local or international institutions.

The DND*i*/LEAP Data Centre was established in 2004, when the first clinical trial was set up in the region. The Data Centre is responsible for the creation and maintenance of data management and statistical analyses, which meet ICH GCP standards. Analyses are carried out in collaboration with the London School of Hygiene and Tropical Medicine.

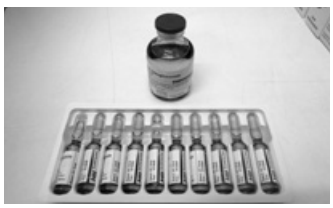
- **Clinical trials**

LEAP's major achievement is the launch of SSG&PM, a new, improved treatment option for kala-azar, which was recommended as first-line treatment for patients in East Africa by the WHO Expert Committee on the Control of Leishmaniases and included in the national guidelines of Sudan, South Sudan, Kenya, Uganda, and Ethiopia.

- **2003.** Due to various limitations such as toxicity, difficulty of use, and the high cost of existing drugs, kala-azar is complex to treat in Africa. SSG, a relatively toxic drug requiring a daily regimen of painful injections over 30 days, is the mainstay of treatment at this time. Other drugs, such as paromomycin (PM) and miltefosine, are neither registered nor available in the region at this stage.
- **2004.** DND*i* and LEAP set up a clinical research programme, based on experience of MSF in treating kala-azar patients with a combination of SSG and PM. This project is initiated to register paromomycin in East African countries and evaluate its use alone and in a shorter-course combination with SSG as an improved treatment for kala-azar.
- **2005-2006.** Failure of paromomycin at the initial dosage tested in monotherapy. Dosing study conducted to determine the dosage to be used to resume original study.
- **2008.** Return to Phase II with augmented dosage of paromomycin for monotherapy and continuance of combination study.
- **2010.** LEAP completes this multi-centre, multi-country clinical trial sponsored by DND*i* in Kenya, Ethiopia, Sudan, and Uganda. The study recruits over 1,100 kala-azar patients and shows that a short-course combination of PM (15mg/kg/day) and SSG (20mg/kg/day) has a similar safety and efficacy profile (efficacy at 6 months follow-up post-treatment >90%) as the standard monotherapy treatment with SSG for 30 days. Paromomycin as monotherapy is no longer pursued.

The WHO Expert Committee on the Control of Leishmaniases recommends SSG&PM as first-line treatment for kala-azar in East Africa. Sudan is the first country to apply the recommendation and implement SSG&PM to treat patients.

- **2011.** A pharmacovigilance study to monitor safety and effectiveness of SSG&PM is initiated with the ministries of health of LEAP countries and MSF in 2011 and completed in 2013.



DEVELOPMENT & RECOMMENDATION (Phase II, Phase III) › IMPLEMENTATION (Access)

2003 / 2010

DND*i*'s role & LEAP:

- Conduct multi-centre Phase II and Phase III studies in four African countries
- Support LEAP activities
- Prepare and rehabilitate clinical trial centres

Partners and Service providers:

WHO/TDR; MSF; KEMRI; University of Oxford / Mahidol University (Thailand); Tropival of Univ Bordeaux (France); Cardinal Health (France); Ellipse Pharma (France);University Sains Malaysia (USM) (Malaysia); Rottendorf Pharma (Germany); Créapharm (France); Institut de Recherche pour le Développement (IRD) (Senegal); CNRFP (Burkina Faso); Sanofi (France); Bertin Pharma (France)

€9.3 M

2011 / 2013

DND*i*'s role & LEAP:

- Organize Phase IV implementation study in four countries

Partners and Service providers:

LEAP, KEMRI, Kenya; IEND, University of Khartoum, Sudan; University of Makerere, Uganda; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Slotervaart Hospital, The Netherlands Cancer Institute, The Netherlands; KIT, The Netherlands; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; MSF; i+ solutions, The Netherlands; OWH/PATH, USA; Gilead; IDA Foundation, The Netherlands; Torkke & Dreyer, Switzerland

€2.2 M

To date, over 33,000 patients have been enrolled in clinical and pharmacovigilance studies in or directly linked to DND*i* projects[8]. Due to the often remote location of the clinical sites, DND*i* supports improvements in clinical research infrastructure and other renovations so that patients can access clinical trial facilities close to where they live. These clinical research capacities in remote settings have resulted in increased numbers of patients who access treatments: A total of 7,700 patients that could not be included in the trials due to strict inclusion criteria, received the best possible treatment for their disease as an indirect result of the trial[9]. Extensive training on the conduct and ethics of clinical trials is performed for medical staff through the clinical research platforms. Only regional investigators and medical field-oriented organizations have the expertise to contribute to clinical development in the field conditions in which DND*i*'s target diseases are most prevalent. For example, a Phase II, double-blind, randomized, controlled trial evaluating the safety and efficacy of the oral drug candidate E1224 against Chagas disease, the first ever such trial conducted in Bolivia, exemplified the strengthening of research capacity and conduct of an international standard clinical trial in a resource-limited, developing-country setting (see box, page 15).

All DND*i*-sponsored trials comply with international ethical and quality standards and are conducted in neglected disease-endemic regions (except for Phase I studies) in collaboration with local partners, as well as with support from international groups such as MSF.

WHAT HAS BEEN THE **IMPACT FOR NEGLECTED PATIENTS?**

ASAQ for malaria, delivered in 2007:

- Fixed-dose combination of artesunate (AS) and amodiaquine (AQ) that simplifies dosing and is more affordable than comparable drugs due to generic production
- Developed and implemented in partnership with Sanofi and FACT consortium
- Registered in 31 countries in Africa plus India, Bangladesh, and Colombia
- Prequalified by the World Health Organization (WHO) in 2008

Over **250 million treatments** distributed

ASMQ for malaria, delivered in 2008:

- Fixed-dose combination of artesunate (AS) and mefloquine (MQ), with same convenient dosing and cost benefits as ASAQ
- Prequalified by the World Health Organization (WHO) in 2012
- Registered in Brazil in 2008 and technology successfully transferred from Farmanghuinos to Cipla Ltd, generic Indian company, followed by registration in India, Malaysia, and Myanmar
- First-line treatment in a number of South-East Asian countries

Over **500,000 treatments** distributed

NECT for sleeping sickness, delivered in 2009:

- Nifurtimox-eflornithine combination therapy (NECT), first new treatment for sleeping sickness in over 25 years
- Simplifies treatment in the field and replaces the toxic drug melarsoprol
- Available in the 12 African countries where 99% of cases occur
- In 2012, NECT is used to treat 96% of late-stage sleeping sickness cases in endemic countries

Over **13,000 treatments** distributed

SSG&PM for kala-azar in Africa, delivered in 2010:

- Sodium stibogluconate (SSG) and paromomycin (PM) combination therapy reduces treatment duration by nearly half and decreases total cost, compared with SSG alone
- SSG&PM is recommended for first-line treatment of kala-azar in East Africa
- Approximately 10,000 patients treated in South Sudan
- Available in Ethiopia, Kenya, Sudan, South Sudan, and Uganda

23,000 patients treated in East Africa since 2010

Set of combination treatments for kala-azar in Asia, launched in 2011:

- Simplified treatment options available in India, Bangladesh, and Nepal
- Four-year pharmacovigilance study in India and Bangladesh

Over **6,000 patients** in pharmaco-vigilance study

(8) Over 3,000 patients were included in kala-azar clinical trials, plus 2,000 in an ongoing pharmacovigilance study; over 1,000 patients were enrolled in sleeping sickness studies; approximately 500 in Chagas disease studies; nearly 4,000 in malaria studies, in addition to 23,000 in a large pharmacovigilance study in Brazil; and 80 enrolled in cutaneous leishmaniasis studies.
(9) Close to 3,000 for kala-azar in East Africa; 150 for kala-azar in India; nearly 500 for Chagas disease in Bolivia; over 150 for sleeping sickness; and close to 4,000 for malaria.

THE LONG ROAD TO 'BREAKTHROUGH' MEDICINES FOR NEGLECTED DISEASES

The short-term strategy described has delivered relatively rapid, tangible benefits for patients. However, to radically change the course of its target diseases and, in some cases, to support sustainable control or elimination of certain neglected tropical diseases as per the WHO 2020 Roadmap[10], DND*i* has invested significantly – EUR 51 million since 2003, which covers screening activities and lead optimization – to discover entirely new and more adapted drugs, for example an oral drug that would only need to be taken once a day for a week or less.

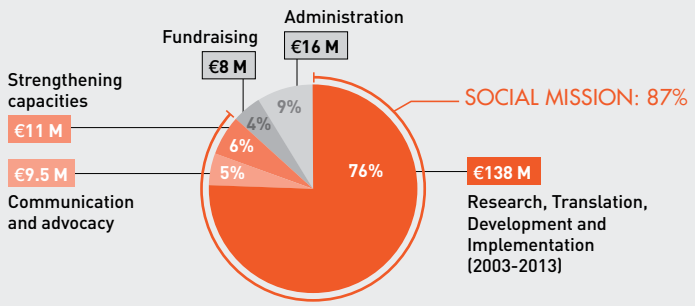
> THE MAIN CHALLENGE WAS TO GAIN ACCESS TO COMPOUND LIBRARIES TO IDENTIFY NEW HITS.

Such 'breakthrough therapies' – ideally implemented at the primary healthcare and/or community level in combination with a simple diagnostic tool – have the potential to fundamentally transform how patients are treated for their disease, supporting optimal individual case management and, potentially, large-scale disease elimination strategies. In addition, such treatments would relieve the burden placed on healthcare workers and lower the cost to health systems. For instance, for sleeping sickness, the current 'toolbox' to diagnose and treat patients has substantial limitations. The complex use of most diagnostic and therapeutic tools – even with NECT, which is already an improved treatment option – limits their decentralization in rural health centres. However, new diagnostics and drugs in clinical development could dramatically improve the diagnostic and treatment capacities of rural healthcare services. One diagnostic test and one oral treatment to 'test and treat' this disease would mean a revolution for the health system, healthcare professionals, and patients.

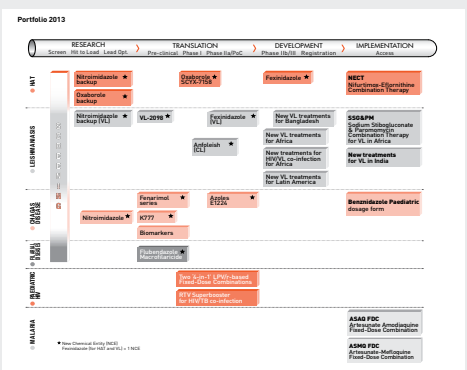
Nonetheless, the road to delivering such breakthroughs is a long one, notably because R&D for infectious diseases is subject to attrition, meaning that for every 1,000 'hits' only one will become a registered drug (see figure, page 20).

Operating 'virtually', the main challenge a decade ago was to gain access to good compound libraries, knowledge, and data from public and private partners to expedite early stage innovation and identify new hits and/or interesting classes of compounds. The idea was straightforward: combine DND*i*'s expertise in parasitology and kinetoplastid diseases with industry's prominent drug discovery and development capabilities, and collaborate with leading academic drug discovery groups to identify a large number of

DND*i* expenses from 2003-2013: EUR 182.5 Million
(including direct and indirect costs)



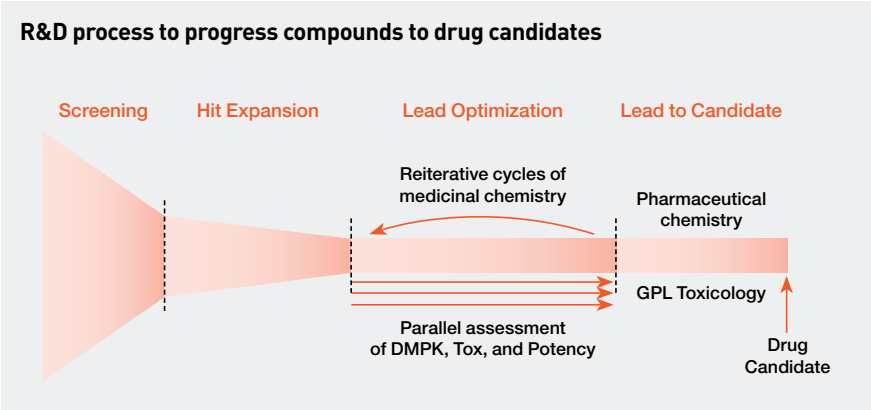
DND*i* portfolio: Costs per stage of R&D
(including direct and indirect costs)



RESEARCH €51 M | TRANSLATION €33 M | DEVELOPMENT €31 M | IMPLEMENTATION €23 M | = TOTAL €138 M

(10) Accelerating work to overcome the global impact of neglected tropical diseases: A roadmap for implementation. WHO, January 2012.
(11) Drugs for Neglected Diseases initiative model of drug development for neglected diseases: current status and future challenges. By J.R Ioset and S. Chang. *Future Med. Chem.* (2011) 3(11), 1361–1371.

top quality pre-clinical candidates by pooling resources and avoiding duplication of efforts. With 12 NCEs today in the pipeline and two entirely new drugs entering clinical development, DND*i* has achieved important milestones built on solid partnerships[11].
Based on the target product profile for each envisaged treatment, DND*i* implements three different strategies to actively source new drugs at different stages of maturity, described here below.



INTENSIVE COMPOUND LIBRARY SCREENING

Initially, DND*i* built its kinetoplastid portfolio primarily by relying on opportunities arising from academic and biotechnology collaborations, which were identified through networking interactions and calls for proposals within the scientific community. This approach revealed a major lack of high quality 'hits' and 'leads', a high attrition rate, and limited capacity for compound evaluation in DND*i*'s targeted disease areas. A more pragmatic approach was then taken with a more structured discovery strategy that required, in particular, additional capacity for target identification, assay development, high-throughput screening, drug candidate selection, and access to quality compound libraries with relevant chemical diversity.
Collaborations were set up with institutions such as Institut Pasteur Korea and the University of Dundee (UK) to increase high-throughput screening (HTS) of large libraries of pharmaceutical companies. For screening, the Swiss Tropical and Public Health Institute (Swiss TPH), the University of Antwerp, and the London School of Hygiene & Tropical Medicine (LSHTM) conducted this work for several years, and still serve as reference screening centres. Recently, DND*i* has set up a new project in an endemic and emerging country, Brazil: LOLA (Lead Optimization Latin America), which aims to build upon and enhance the research and development potential in the region.
As a result of these investments, since 2006 the virtual drug-discovery research apparatus of DND*i* has screened over 1 million compounds in three screening assays and identified 3,000 hits.
Most hits fail on rescreen because of lack of reproducibility, lack of chemical tractability or toxicity. On average, DND*i* progresses 10 to 20 hits per disease, per year to 'hit-to-lead' chemistry with a failure rate of around 80-90%. Of the successes, an anticipated 20-30% will move through lead optimization to become pre-clinical candidates. To date, three NCEs have been identified as pre-clinical candidates, VL-2098, SCYX-7158 and BS967/1246 for leishmaniasis, African trypanosomiasis and Chagas disease, respectively. The Chagas disease candidate failed during pre-clinical development and the remaining two are still in development. SCYX-7158 is based on new boron chemistry for drug discovery licensed from a USA-based biotechnology company, Anacor, and is in late Phase I development. VL-2098 was identified in collaboration with the University of Auckland (New Zealand) and the Global Alliance for TB Drug Development. If ongoing pre-clinical studies are successful, it will enter clinical trials in 2014. Several promising new series are currently in lead optimization for these diseases. Finally, other leads have been provided to research groups such as the University of Dundee to leverage additional research and research funding for neglected diseases.
DND*i*'s early screening efforts focus on well-annotated compound libraries from pharmaceutical and biotechnology companies. Gaining access to classes of compounds with drug-like characteristics from companies is vital as it also offers access to knowledge and know-how associated with compound series to ensure more efficient drug development. Several agreements with major pharmaceutical companies have been signed to gain such access to compound libraries and other assets, on increasingly favorable terms (see page 4).

COMPOUND-MINING

Promising drug candidates have also been found by revisiting the wealth of past drug discovery efforts, often driven by academia, and re-assessing promising lines of research that were not developed because of commercial or other strategic reasons. Here is an example: DND*i*'s assessment, beginning in 2005, of nitroimidazoles, a well-known class of anti-infectives developed by Hoechst, led to the re-discovery of fexinidazole (see page 19) and the revival of nitroimidazoles as a promising class of anti-infectives throughout DND*i*'s portfolio.

Proactive acquisition and investigation of compounds from selected series with a significant level of available information (biological activity, pre-clinical dossier, published data, safety profile), ideally ready to enter into pre-clinical or later stage development without the need for additional investment in optimization, has shown to be a successful way to address patient needs in a cost-effective way.

DND*i* has expanded its compound-mining strategy with further collaborations, particularly with pharmaceutical partners and PDPs, for example: with Sanofi by re-assessing a collection of 300 marketed drugs and clinical candidates; with GlaxoSmithKline by accessing collections of marketed drug sets; and with the TB Alliance, to develop nitroimidazoles for leishmaniasis through collaboration. The latter partnership not only strengthens the impact of investments in R&D for neglected diseases, but also demonstrates the goodwill among PDPs to create 'critical paths' by reducing repetition in research.

Another example is the development of a macrofilaricide to address unmet treatment needs of patients suffering from onchocerciasis and lymphatic filariasis, as well as areas where either of the two occurs in co-infection with loiasis. Several partnerships have been established with animal health companies and human health pharmaceutical companies to evaluate products initially developed for animals.

THERAPEUTIC SWITCHING OF CLINICAL CANDIDATES

DND*i* has also explored the potential of other drug candidates such as the antifungal drug E1224 for Chagas disease. Therapeutic switching, in which existing drugs previously developed or abandoned during clinical development for other indications are re-oriented or developed for a different indication, has already proved to be a successful approach to generate promising new drugs for leishmaniasis or trypanosomiasis.

In particular, the therapeutic areas of anti-fungals, anti-bacterials, and anti-malarials provide promising drug sources for therapeutic switching. DND*i* continuously monitors developments in these areas with the aim of either co-developing such drugs with partners (including with PDPs) or in-licensing them and developing them for DND*i*'s specific target disease indications.

Trial for therapeutic switching for Chagas disease: Mixed results lead to new directions for future research

The E1224 compound is a pro-drug of ravuconazole, an anti-fungal drug candidate. Ravuconazole was discovered and developed by the Japanese company Eisai Co. Ltd for another indication and showed potent *in vitro* and *in vivo* activity against the parasite causing Chagas disease. DND*i* and Eisai entered into a collaboration agreement in 2009, under which DND*i* was responsible for the clinical development of E1224 in patients with Chagas disease within endemic countries, with supplies of the drug by Eisai at no cost. Eisai contributed specific scientific expertise in clinical development.

The E1224 trial completed the Phase II/ proof-of-concept study in Bolivia, evaluating the safety and efficacy of different dose regimens for the treatment of adult patients with the chronic indeterminate form of Chagas disease.

While results showed limited to no sustained efficacy of E1224 in monotherapy, the study pointed towards new, immediate, and potential strategies to improve patient treatment: trial data showed that the current treatment regimen with benznidazole is efficacious but still has safety issues, and pointed to the need to further investigate potential combination therapy utilizing the two drugs as well as considering shorter duration benznidazole regimens.

LESSONS LEARNED & CHALLENGES: MOVING FROM INITIAL SUCCESSES TO SUSTAINABLE R&D

After a decade of existence, DND*i* can be viewed as a successful model that has both built a robust pipeline of game-changing drug candidates and delivered life-improving and live-saving treatments to millions of patients. While the number of treatments developed and delivered is measurable (see box, page 12), the socio-economic, cost-effectiveness, and public health impacts have yet to be appropriately measured. There are also weaknesses in the model and areas of uncertainty that should be addressed.

Ten years on, several key challenges loom:

- Overcoming regulatory barriers;
- Transforming regulatory approval to country adoption and implementation;
- Ensuring sustainable production of treatments for neglected diseases;
- Securing an enabling policy environment including clear global norms on IP management;
- Ensuring sustainable financing;
- Creating new incentives, which de-link the cost of R&D from the price of products, to ensure affordability.

The following points explore some of these challenges.

STRENGTHENING AND HARMONIZATION OF REGULATORY MECHANISMS TO MEET ESSENTIAL STANDARDS

With the development of six treatments for various diseases on different continents, DND*i* has gained a greater understanding of the regulatory environment, which is a major component of pharmaceutical innovation. A DND*i*-commissioned report on the regulatory environment in the African context showed that new regulatory pathways are needed to expedite research, registration, and ultimately patient access to new health tools[12].

Obtaining necessary approvals by regulatory authorities in many developing countries is a long and difficult process that ranges from acquiring ethics approval for clinical trials to the full registration of the product. Any delays along this chain can considerably delay patient access. The example of SSG&PM is telling: even though this new treatment for kala-azar was recommended by WHO as first-line treatment in East Africa, the lack of a harmonized regulatory environment in the region results in various, and sometimes different, regulatory processes in each country to include the treatment in essential medicines lists and in national treatment protocols, and to register notably one of two components of the treatment.

In addressing developing countries' health needs, the argument that 'stringent' (FDA or EMA) regulatory authorities are the only qualified institutions to evaluate the quality, safety, and efficacy of medicines has been challenged, in particular in terms of assessing the risks and benefits of health products for diseases predominant in developing countries, for which therapeutic options are often severely limited.

In the past decade, the role of WHO's Prequalification Programme has been critical in reviewing regulatory dossiers for HIV/AIDS, tuberculosis, and malaria and should be extended to other neglected diseases and serve as a guide for national regulatory authorities in low- and middle-income countries with weak regulatory capacity. Ultimately, it is necessary to strengthen capacities of poorly-resourced regulatory bodies in endemic countries, notably through enhanced formal collaboration with regu-

DND*i*'s experience with innovative regulatory pathways

DND*i* has used various strategies to jointly involve regulators from endemic countries – who have the best knowledge of the diseases and patients' needs as well as the responsibility to assess the benefit/risks for their own populations – and regulators from developed countries, who have experience in the approval of new drugs. For example:

- A DND*i* regulatory file was offered as a case study in a training of the WHO Prequalification Programme. The ASAQ dossier was reviewed for a virtual approval by participants from developing countries, with support from WHO and European Medicines Agency (EMA) experts.
- DND*i*'s ASMQ regulatory file was jointly assessed by a group of regulators from ASEAN (Association of Southeast Asian Nations) countries.
- Following review by WHO, the eligibility of fexinidazole (new drug candidate for sleeping sickness) for an evaluation through Article 58 of the EMA has been confirmed. In 2011, DND*i* and Sanofi received joint scientific advice from the EMA and FDA on the clinical development plan. In 2012, DND*i*, with administrative support from WHO, organized an international ethics workshop with representatives from endemic countries in Africa and a French Ethics Committee to review its pivotal clinical study of fexinidazole for late-stage sleeping sickness.
- In the case of the paediatric dosage form of benznidazole, DND*i* is working to have the new formulation registered in endemic countries based on the first registration in 2011 by the Brazilian regulatory agency, Anvisa. In addition, DND*i* and the Mundo Sano Foundation are working together on a regulatory strategy to provide greater access to the new second source of benznidazole to fill current treatment gaps for children and adults.

(12) Registering New Drugs: The African Context. By M. Moran et al., 2010. http://www.dndi.org/advocacy/regulatory.html

latory bodies of well-resourced and experienced endemic countries or of 'stringent' regulatory authorities, in partnership with WHO.
It is essential to promote and stimulate support for regional initiatives and harmonization that aim to accelerate scientific risk/benefit-adjusted reviews and rationalize mutual recognition of regulatory policies within regional zones where disease prevalence is similar).

ENSURING SUSTAINABLE PRODUCTION AND DELIVERING AFFORDABLE TREATMENTS

Even if DND*i* succeeds in developing new treatments for sleeping sickness, kala-azar, or Chagas disease, identifying a solid and committed industrial partner for the most neglected diseases is not a given. Since little or no profits can be made on sales of neglected disease products, other types of incentives or assets need to be identified to secure long-term commitment to production. The scenario of products with a dual market (e.g. the price for malaria treatments in the public market are limited due to international tenders, which is not the case for the private market) is not always applicable. Among the vital products that form the treatment arsenal today, many of these are produced by a sole manufacturer. Their sustainable supply is thus extremely fragile.
It is important to seek and support new types of incentives or other policy instruments that can ensure sustainable production at the lowest possible cost to the patient. Here again, governments and international organizations have a role to play in creating a more favourable framework: supporting adequate demand forecasts; pooling procurement mechanisms; ensuring enabling IP frameworks; and securing advance purchase commitments, to name but a few.

LEVERAGING STRONGER PARTNERSHIPS ROOTED IN MORE OPEN MODELS FOR INNOVATION

DND*i* has learned over the last decade that no one single organization can remedy the 'fatal imbalance', or the crisis of neglected disease R&D. DND*i* has developed the ability to engage a wide range of partners from the private, public, and non-profit sectors, through various mechanisms. However, as essential as this is, the sustainability of such partnerships cannot be considered acquired. Stronger research capacities in endemic countries as well as stronger political leadership from these countries are an absolute priority to identify unmet medical needs, strengthen research capacities, facilitate technology transfer, and increase local accountability to ensure medical innovations are accessible to the poorest populations.
The contribution of the private sector (pharmaceutical companies, generic companies, biotechnology companies) also needs to increase, and the London Declaration of 2012 may have marked an interesting turning point for private-sector engagement in neglected tropical disease (NTD) R&D in particular. This must also be reflected in emerging economies where pharmaceutical capacities are growing and where the public health burden of neglected diseases is high, for example in India, Argentina, Brazil, and China. Despite improvements over recent years, the resources invested in drug discovery and development for neglected diseases still fails to meet the huge need for innovation.

> STRONGER RESEARCH CAPACITIES IN ENDEMIC COUNTRIES AND POLITICAL LEADERSHIP ARE REQUIRED.

Open models of innovation and meaningful open access initiatives that maximize the sharing of quality research knowledge and reduce duplication in research efforts, may reduce overall R&D costs and therefore augment efficiency. With the Open Source Drug Discovery consortium in India, ChEMBL-NTD, WIPO Re:Search, the Medicines for Malaria Venture's Malaria Box, GSK's Open Lab, and the Medicines Patent Pool, open models aimed at boosting innovation are flourishing.
While it may be too early to evaluate their impact, such initiatives are part of a trend towards open approaches. These initiatives need to be critically monitored, analysed, and evaluated to identify what components are required to genuinely spur innovation and ensure affordable and equitable access to new health technologies for neglected populations.
In addition, all possible efforts should be made, including at DND*i*, to ensure that results are placed and remain in the public domain, as stated in DND*i*'s IP policy. It is clear that preparing data for public release requires significant human resources, in particular to disseminate early drug discovery data generated by high throughput screens.

DEVELOPMENT COSTS FAVOUR A NEW PARADIGM FOR R&D

Over the past 10 years, DND*i* has shown that it is possible to develop and deliver quality treatments to neglected patients. To reach its objective of developing 11 to 13 new treatments in total by 2018, including at least one new chemical entity (NCE), and to continue to build a robust pipeline, DND*i* estimates that a total of EUR 400 million will be needed over 15 years. Currently, DND*i* estimates its costs of development to range from EUR 6-20 million for an improved treatment, and EUR 30-40 million for an NCE. However, it is important to note that applying the usual attrition rate in the field of infectious diseases (see figure, page 20), the cost to develop an improved treatment would be EUR 10-40 million and EUR 100-150 million for an NCE.

Continued on p.20

METHODOLOGY FOR DRUG DEVELOPMENT COSTS ASSESSMENT

Recognizing the different treatment categories

Segmentation of treatment categories is essential to better understand DND*i*'s cost structure and reflect the level of complexity of projects. Four main categories are described in the case studies:

- Combination therapy with existing drugs;
- New indication of an existing drug;
- Development of an existing compound or drug candidate;
- Development of a new chemical entity.

Financial data

The case studies contain three types of financial data:

- Real costs that describe past expenditures that have already occurred (known figures). They include direct costs of projects and indirect costs which are part of the DND*i* social mission and business model (R&D coordination, capacity strengthening, advocacy, fundraising, general management), based on overall breakdown of expenditures (which are also used for future estimated and projected costs);
- Estimated costs (for the treatments which are still in development), to assess the expenditures required to reach registration of the treatment (upon budgets and DND*i* experience with similar activities);
- Projected costs (only for projects still in development) factor in the risk of failure. They apply attrition rates to the real and estimated costs of development and provide a hypothetical figure of the overall cost of development, by using the DND*i* model, of a given treatment (for development of an existing compound or drug candidate, and development of a new chemical entity).

Types of collaboration

Service providers: As a virtual R&D organization, most activities are externalized to service providers and these costs are fully integrated in DND*i* expenditures (statement of accounts). Their roles and contribution, under the leadership and coordination of DND*i*, are described in the case studies. When their contribution went significantly beyond business terms, we attempt to render this as explicitly as possible. Basic business 'discounts' potentially resulting from negotiation or 'light goodwill' were not considered as specific *pro bono* services.

Partners: Beyond service providers, DND*i* works with partners who bring specific value to the projects under different forms:

- Free access to their assets (e.g. compound libraries);
- In-kind contributions (expertise, including from independent/retired experts; active pharmaceutical ingredient (API) or manufactured products for trials; delivery/funding of R&D process, e.g. pharmacokinetic/pharmacodynamics studies; registration)
- Operational role in downstream processes (manufacturing, distribution) as 'implementation partner'.

In-kind contributions are not included in the calculation of the development costs. Audited data show an average of 20% in-kind contributions per year. However, DND*i* is aware that partners' contributions are probably not calculated at a fair value.

Other methodological choices

Some expenditure initially allocated to project costs was considered as investment potentially serving other projects/objectives or being reusable for back-up projects. This has been discounted accordingly in the retained amount of real costs.

With respect to attrition, all past expenditures associated with other projects targeting the same objective and that failed underway were aggregated.

Costs have been calculated up to the registration/recommendation stage, and where possible access and implementation activities are included.

No cost of capital or opportunity costs were included.

CASE STUDY N°4

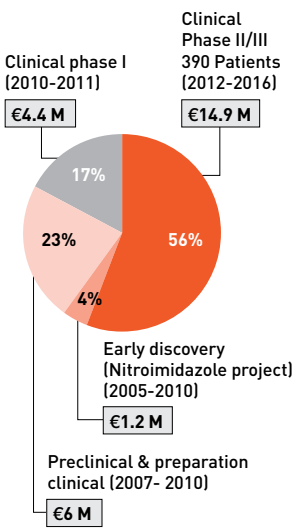
FEXINIDAZOLE

EUR 26.5 MILLION TO DEVELOP A REDISCOVERED NEW CHEMICAL ENTITY FOR SLEEPING SICKNESS

Nitroimidazoles are a well-known class of pharmacologically active compounds, among which several compounds have shown good activity against trypanosomes. Even though the development of some compounds of this chemical family had been abandoned because of toxicity, in particular mutagenicity, other members of this family were widely used as antibiotics, indicating that it was possible to select compounds with an acceptable activity/toxicity profile in this class.

- **2005-2007.** 'Compound mining' is undertaken by DND*i* to provide a systematic review and profiling of more than 700 nitroheterocyclic compounds (mostly nitroimidazoles) from 15 different sources in academia and industry, including an assessment of antiparasitic activity and mutagenic potential using state-of-the-art scientific methods, in particular through collaboration with the Swiss Tropical and Public Health Institute (Swiss TPH). These efforts lead to the identification of fexinidazole (previously known as Hoe 239), which had been in pre-clinical development as a broad-spectrum antiprotozoal drug by Hoechst AG (now Sanofi) in the 1970s and 1980s, but pulled out before entering clinical studies.
- **2007-2008.** Pre-clinical studies are conducted. Sanofi provides initial samples, data, and advice based on the previous Hoechst development programme on fexinidazole. DND*i* performs extensive regulatory toxicology studies, including safety pharmacology and animal studies, carried out by several contract research organizations. The pre-clinical profiling of fexinidazole is subcontracted to Accelera SpA (Italy) and Covance Ltd (UK), which also provide technical advice. The GMP manufacture of fexinidazole is subcontracted to Centipharm (France). Overall, fexinidazole is found to be well tolerated, with a good safety profile.
- **2009.** Partnership with Sanofi for development and manufacturing is formed. DND*i* and Sanofi enter into a collaboration agreement for the development, manufacturing, and distribution of fexinidazole. Under the terms of the agreement, DND*i* is responsible for preclinical, clinical, and pharmaceutical development. Sanofi is responsible for the industrial development, registration, and production of the drug at its manufacturing sites.
- **2010–2011.** DND*i* carries out three Phase I clinical trials, assessing the safety and pharmacokinetics of fexinidazole in human volunteers given in single and multiple doses. In early 2011, DND*i* and Sanofi request joint scientific advice from the FDA and the EMA (through Article 58), on the clinical development plan for fexinidazole. This leads to the development of a protocol for a single pivotal Phase II/III study to prove the safety and efficacy of fexinidazole, with NECT as the active comparator.
- **2012.** A Phase II/III pivotal clinical study in late-stage sleeping sickness patients is initiated in the Democratic Republic of the Congo and the Central African Republic, with DRC national control programme (PNLTHA) as principal investigator and in collaboration with various partners of the HAT Platform (selection and equipment of trial sites and training in Good Clinical Practice, GCP). Approvals are obtained in DRC and CAR, and from MSF, following review by an international (African and French) ethics working group convened by the Société Française et Francophone d'Ethique Médicale (SFFEM) with WHO support.

Costs for the development of an existing compound: rediscovery up to registration (Including actual and forecasted costs) (2005-2016)



TRANSLATION: Pre-clinical, Phase I › DEVELOPMENT: Phase II/III, Registration

2005 / 2010

DND*i*'s role:
- Initiate & develop compound mining
- Management of pre-clinical activities

Partners and Service providers:
Accelera; Covance; Centipharm; Swiss TPH; SCYNEXIS; Pace University

DND*i*'s role:
- Selection of the Phase I unit
- Design of Phase I clinical plan
- Dose selection for Phase II/III

Main partners and Service providers:
SGS Clinical Research Services; Phinc, Sanofi; Xcentipharm; Covance

€7.2 M

2010 / 2011

DND*i*'s role
- Conduct Phase I trial
- Selection & preparation of clinical sites in DRC and CAR
- Design of pivotal study and discussion (with partner) during joint EMA Article 58/ FDA Scientific Advice
- Organize an international ethics workshop to review the study protocol
- Submit the study protocol to ECs and NRAs in DRC and CAR (including MSF's EC).
- Select the monitoring partner

Main partners and Service providers:
SGS Clinical Research Services; Cardinal Systems; Cardiabase; Bertin; Aptuit; Sanofi; Swiss TPH; MSF; HAT Platform; National HAT Control Programmes; Qualilab; Epicentre

€4.4 M

2012 / 2016 (estimates)

DND*i*'s role
- Conduct of the Phase II/III in Africa
- Fund back-ups
- For late-stage, only 390 patients
- Additional studies (2014-2017) not included: Paediatric, early-stage disease, and *T.b. rhodesiense* HAT (+EUR 8 million)

Partners and Service providers:
Swiss TPH; MSF; HAT Platform; national HAT control programmes; FIND; Sanofi; WHO; IMT Antwerp; Theradis Pharma; INRB, DRC; PHINC; Vanga Hospital - CBCO; Cardinal Systems; Cardiabase; SGS Aster

€14.9 M

Costs of development for R&D projects only including DND*i*'s investments

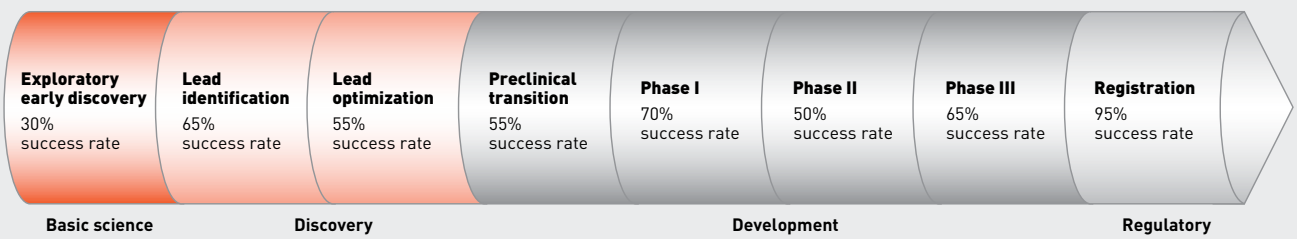
CATEGORY	SPECIFIC CASE	DRUG/ CLINICAL CANDIDATE	CLINICAL DEVELOPMENT TO REGISTRATION		ACCESS, IMPLEMENTATION AND/OR TECHNOLOGY TRANSFER	TOTAL COST
			Ph I /POC	Ph II/III		
For an improved treatment (Combination therapy with existing drugs) → **€ 6- 20 M**	**ASAQ** Fixed-dose combination therapy for Malaria	*Not relevant for this category of projects*		€7.0 M	€5.0 M	**€12.0 M**
	NECT: Improved treatment option for Sleeping sickness			€3.6 M	€3.2 M	**€6.8 M**
	SSG&PM a new combination therapy for kala-azar in Africa			€9.3 M	€2.2 M	**€11.5 M**
For a new chemical entity or an existing compound → **€ 30 - 40 M**	**SCYX-7158** new chemical entity for Sleeping sickness from discovery programmes	€22.1 M	€3.6 M	€12.6 M	*To be engaged upon partnership*	**€38.3 M**
	Fexinidazole rediscovered new chemical entity for late stage *T.b. gambiense* sleeping sickness	€7.2 M	€4.4 M	€14.9 M		**€26.5 M**

As a virtual R&D organization, most upstream activities are externalized to service providers and these costs are fully integrated in DND*i* expenditures. However, beyond service providers, DND*i* works with partners who bring specific value to the projects under different forms, such as free access to their assets (e.g. compound libraries), in-kind contributions through specific technical expertise, direct funding of some R&D activities, or a more operational role in downstream processes (e.g. manufacturing, distribution) as 'implementation partners'. Although it is difficult to compare costs of development between different business models, the first 10 years of DND*i*'s experience indicate that innovative R&D models can both deliver rapidly for patients and potentially be more efficient than the traditional pharmaceutical business model. This may be explained by the more open, collaborative *modus operandi*, the emphasis on leveraging expertise from a wide range of partners in a non-competitive way, and the fact that the short-term strategy capitalizes on low-hanging fruits.

However, deeper analysis of costs of R&D invested with support of donors should be conducted, notably to fairly quantify in-kind contributions of all partners, in order to estimate *in fine* the overall funding needed for neglected disease R&D and evaluate the presupposed cost effectiveness of these new models. By providing some financial components covering different projects along its R&D pipeline, DND*i* aims at transparency of the cost of its model to complete further global analyses when it comes to defining global health R&D priorities according to patients' needs.

DND*i* ESTIMATES EUR 6-20 MILLION FOR AN IMPROVED TREATMENT AND EUR 30-40 MILLION FOR AN NCE WITHOUT IN-KIND CONTRIBUTIONS FROM PARTNERS, BUT WITH ATTRITION THIS COULD BE EUR 10-40 MILLION FOR AN IMPROVED TREATMENT AND EUR 100-150 MILLION FOR AN NCE.

R&D attrition per stage and potential for success and failure



Source: 'Virtual drug discovery and development for neglected diseases through public–private partnerships'. By N. Solomon and R.G. Ridley, *Nature Reviews, Drug Discovery*, Volume 2, 919-928, Nov 2003, pp 5-15. doi:10.1038/nrd1230

CASE STUDY N°5

SCYX-7158 **EUR 38.3 MILLION** TO DEVELOP A NEW CHEMICAL ENTITY FOR SLEEPING SICKNESS FROM DISCOVERY PROGRAMMES

DND*i* and its partners have delivered a new chemical entity drug candidate within a short timeframe. Oxaborole will enter into pivotal Phase II/III in 2014. Regardless of attrition, DND*i* anticipates that an overall investment of approximately EUR 38.3 million will be needed to develop an entirely new chemical entity, in the specific context of human African trypanosomiasis (HAT, or sleeping sickness).

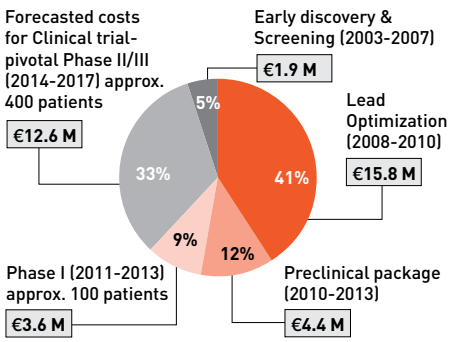
- **2003-2007.** DND*i* invests in screening and early discovery activities for sleeping sickness with various partners, in search of a new chemical entity for sleeping sickness. These activities include investment and in-kind contributions from several individual partner institutions worldwide. During this period, no successful candidates are identified.
- **2007-2008.** DND*i* sets up the HAT Lead Optimization Consortium aimed at optimizing new classes of compounds more efficiently with SCYNEXIS, a US-based drug discovery and development company, and Pace University in New York, with Professor Cyrus Bacchi, who is responsible for the discovery of eflornithine for the treatment of sleeping sickness. This consortium progresses a number of series identified from the screening campaigns into lead optimization.
- **2008.** DND*i* is approached by Anacor (USA-based biotechnology company) with a promising new chemical series (oxaboroles), already screened with the Sandler Center at the University of California, San Francisco (UCSF) and active against sleeping sickness. Given the lack of an economically viable market for the disease, Anacor approaches DND*i* as a licensee to optimize this series for treatment of sleeping sickness. Anacor serves as a technical advisor to the DND*i*/SCYNEXIS/Pace University team and grants DND*i* a no-cost license to develop the leads from this series. At the end of 2009, DND*i* decides to advance one particular candidate into pre-clinical development (SCYX-7158).
- **2010.** Advinus Therapeutics (India) is contracted to conduct safety/toxicity studies. SCYNEXIS, Penn Pharma, Drugabilis, and Patheon are contracted to develop, manufacture, and formulate SCYX-7158.
- **2011.** DND*i* enters Phase I in-human clinical trials. Approval for the study is obtained from a French Ethics Committee (Comité de Protection des Personnes) and the French regulators.
- **2012-2013.** Phase I trial starts. This randomized, double-blind, placebo-controlled study assesses the safety, tolerability, pharmacokinetics, and pharmacodynamics of SCYX-7158 in healthy volunteers. The trial is conducted at a Phase I unit in Paris, SGS Aster, and then at Eurofins Optimed in Grenoble, France. The trial is completed in 2013.
- **2014-2017.** The drug is prepared to enter into pivotal Phase II/III clinical trials in 2014 with registration projected for 2017. DND*i* anticipates collaborating with national control programmes and other partners such as MSF and Swiss TPH for clinical trials, and with a pharmaceutical company for industrial development, registration, and distribution.

This case calculates the cost of development of a drug candidate for sleeping sickness from earliest hit-to-lead phase to a Phase I candidate at approximately EUR 21 million, and extrapolates upon the development experience with other DND*i* projects to build the case for a registered new chemical entity (NCE).

At the current stage of development of the project, it is not possible to provide accurate information on the overall cost of development of a new chemical entity for sleeping sickness. DND*i* will publish its real financial data once effective registration of an NCE is reached. Today, it is only possible to provide a tentative cost estimate, based on the DND*i* model. It is anticipated that an overall investment of approximately EUR 38.3 million will be needed to develop an entirely new chemical entity, in the specific context of sleeping sickness.

With the hypothesis of 25% probability of success from drug candidate to Phase I, and of 45% from Phase II/III to registration, the projected overall cost for DND*i* to develop an NCE for sleeping sickness could reach approximately EUR 130 million. This figure is highly sensitive to attrition hypotheses, however, and should be taken strictly as a projected figure, not as a financially audited figure, nor as a direct derivation resulting from DND*i* experience. The figures lack statistical depth to provide consensual attrition data. However, as DND*i* has insight into its cost structures, and if assumed attrition rate is correct, it is likely that these estimates are realistic.

Costs for the development of a new chemical entity from screening up to registration (Including actual ad forecatsed costs) 2003-2018



RESEARCH (Hit to Lead, Lead Opt.) › TRANSLATION (Pre-clinical, Phase I) › DEVELOPMENT (Phase II/III, Registration)

2003 / 2007

DND*i*'s role
- Project design, monitoring and control since inception

Partners and Service providers:
Anacor; UCSF-Sandler Center; Swiss TPH

2008

DND*i*'s role
- Consortium-building and management

Partners and Service providers:
Anacor; SCYNEXIS; Pace University

€17.7 M

2010 / 2012

DND*i*'s role
- Contract research organization (CRO) selection
- Regulatory dossier

Main partners and Service providers:
SCYNEXIS; Drugabilis; PhinC; Advinus; Accelera Therapeutics; Patheon; Penn Pharma; Greenwich University; Absorption System

€4.4 M

2012 / 2013

DND*i*'s role
- Phase I clinical trial, France

Main partners and Service providers:
SGS Aster; Eurofins Optimed; Bertin Pharma; Cardiabase

€3.6 M

2014 / 2018 (estimates)

DND*i*'s role
- Phase II-III trial in Africa

Main partners and Service providers:
Swiss TPH; MSF; HAT Platform; national HAT control programmes; FIND; pharmaceutical partner; WHO; IMT Antwerp; Theradis Pharma; INRB, DRC; PHINC; Vanga Hospital - CBCO; Cardinal Systems; Cardiabase; SGS Aster

€12.6 M

CONCLUSION

Innovative R&D models that have emerged over the past decade have been an important part of the positive evolution of the neglected disease R&D landscape. However, despite the promise of initial successes, with the first deliverables reaching patients today, initiatives such as PDPs do not, should not, and cannot constitute the sole solution to the systemic lack of R&D to address the needs of patients who have no purchasing power. In a study published by DND*i* and other researchers in November 2013,[13] a persistent deficiency in truly new therapeutics for neglected diseases was reported, despite nominal progress and acceleration in R&D efforts. Of the 850 new drugs and vaccines approved for all diseases, 4% (37) were for neglected diseases, which represent more than 11% of the global burden of disease (WHO source). Most newly developed therapeutic products were new formulations of existing drugs and of the 336 new chemical entities approved for all diseases from 2000 to 2011, only 1% (4) were for neglected diseases. Again, of the nearly 150,000 registered clinical trials for new therapeutic products in development as of December 2011, only 1% were for neglected diseases. This highlights the persistence of the 'fatal imbalance', described over a decade ago, between global disease burden – and thus patients' needs – and therapeutic product development for neglected diseases.

DND*i* and others' experience over the past ten years has shown that it is possible to address the needs of the poorest populations by developing quality, adapted, and affordable new health technologies. However, these efforts will not be transformed into sustainable change if the foundations for a new global framework that stimulates essential health R&D are not laid.
This is what is really at stake today and for the future.

> IT IS POSSIBLE TO ADDRESS THE NEEDS OF THE POOREST POPULATIONS BY DEVELOPING QUALITY, ADAPTED, AND AFFORDABLE NEW HEALTH TECHNOLOGIES.

To generate public health breakthroughs it is mandatory to consolidate sustainable public and private partnerships, notably with partners from endemic countries. In addition, to ensure further development and advance promising technologies through the global R&D pipeline for neglected diseases, increased and innovative funding as well as new incentives are needed.

After ten years of experience and lessons learned, DND*i* has identified key components for success, which could serve as perspectives for the next decade to address global health needs in developing countries:

- **put the specific needs of patients in developing countries upfront, at the start of the innovation process;**
- **break the link between the cost of R&D and the price of products;**
- **ensure that the fruits of innovation are accessible and affordable;**
- **integrate global health R&D monitoring, coordination, and financing;**
- **strengthen and harmonize regulatory capacities in endemic regions to facilitate implementation of new health technologies.**

After over ten years of negotiations and expert reports, WHO and its member states have the unique opportunity to establish a multilateral framework of principles and rules regulating R&D that will ensure patient needs are at the core of R&D efforts and maximize global health impact.
While DND*i* has evoked its own lessons learned, we hope that this report will be a starting point for further analysis to ensure that the future will bear the fruits of the past decade's efforts for neglected patients.

(13) 'The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment'. By Pedrique B, Strub-Wourgaft N, Some C, Olliaro P, Trouiller P, Ford N, Pécoul B, and Bradol J-H. *The Lancet Global Health.* 24 October 2013. doi:10.1016/S2214-109X(13)70078-0

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