



**BEST SCIENCE**  
FOR THE MOST  
NEGLECTED

# 15 YEARS OF NEEDS-DRIVEN INNOVATION FOR ACCESS

Key lessons, challenges, and  
opportunities for the future

**DND*i***

Drugs for Neglected Diseases *initiative*

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# INTRODUCTION

The Drugs for Neglected Diseases *initiative* (DNDi) was created as a response to the frustration of clinicians and the desperation of patients faced with medicines that were ineffective, highly toxic, unavailable, unaffordable – or that had never been developed at all.

DNDi was launched in 2003 when the Indian Council of Medical Research (ICMR), the Oswaldo Cruz Foundation in Brazil, the Kenyan Medical Research Institute (KEMRI), the Malaysian Ministry of Health, and the Institut Pasteur of France, with the participation of the World Health Organization Special Programme on Research and Training in Tropical Diseases (WHO/TDR), teamed up with Médecins Sans Frontières (MSF), after MSF dedicated a portion of its 1999 Nobel Peace Prize award to exploring a new, alternative, not-for-profit model for developing drugs for neglected populations.



## The fatal imbalance

At the time of DNDi's creation, MSF and partners found that of the 1,393 new drugs brought to market globally between 1975–1999, only 1.1% were for neglected diseases, although these represented 12% of the global disease burden.<sup>1</sup> This situation was a result of both market failure, as investments in R&D were guided by market considerations, leaving the needs of those with little to no purchasing power unaddressed, and public policy failure, as governments had not intervened to correct for this failure of the market.<sup>2</sup>

Just over ten years later, a follow-up analysis was conducted. While some limited progress had been made, during the period of 2000–2010, of the 850 new drugs and vaccines approved for all diseases, just 4% were for neglected diseases, and most of these were repurposed versions of existing drugs. Just 1% of the 336 new chemical entities (NCEs) approved were for neglected diseases.<sup>3</sup>



**Just 1.1%** of the 1,393 new drugs brought to market between 1975 and 1999 were for neglected diseases, although these made up 12% of the global disease burden

1 Trouiller et al. Drug development for neglected diseases: A deficient market and public-health policy failure. *Lancet* 2002;359:2188–2194. DOI: 10.1016/S0140-6736(02)09096-7

2 MSF and the DND Working Group. *Fatal Imbalance: The Crisis in R&D for Neglected Diseases*. Médecins Sans Frontières, 2001. Available at: <https://msfaccess.org/fatal-imbalance-crisis-research-and-development-drugs-neglected-diseases>

3 Pedrique et al. The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment. *Lancet Global Health* 2013;1:e371–79. 2013. Available at: [http://dx.doi.org/10.1016/S2214-109X\(13\)70078-0](http://dx.doi.org/10.1016/S2214-109X(13)70078-0)

Today, there is widespread recognition that the market has failed to deliver across the innovation lifecycle and for a much broader range of disease areas and countries. Historically, the crisis in R&D was understood to affect primarily, or even exclusively, 'diseases of poverty' in 'developing countries'. Today there is an emerging consensus that the dominant market-based model for financing and incentivizing health technology R&D has become increasingly problematic:

- *For both innovation and for access to the fruits of scientific research*, with the crisis in innovation not solely related to lack of investment in R&D but also to unaffordable medicine prices;
- *Regardless of disease area*, with, for example, the limited pipeline for new antibiotics, and the drug pricing crisis for hepatitis C and non-communicable diseases such as cancer; and
- *Regardless of country income level*, affecting not just low- and middle-income countries (LMICs), but also high-income countries (HICs), with publicly financed health systems destabilized by the high prices of medicines, and privatized systems under severe strain, leading to public outcry, intense media attention, and pressure on companies, payers, and governments to take action.

In response to this changing landscape, DNDi has continuously adapted its approach to respond to evolving R&D needs and gaps. DNDi has taken on new disease areas or projects when specific neglected populations are affected, even when the broader research environment is robust, such as paediatric HIV; when transformative innovations have been developed by the traditional R&D system, but high prices keep them out of reach, such as hepatitis C virus (HCV); and when there has been a global market failure affecting all countries, regardless of income level, such as with antimicrobial resistance (AMR).

This report documents the 15 years of experience that DNDi has now accumulated discovering, developing, and delivering new and improved treatments for neglected patients. It highlights both achievements and challenges, and aims to contribute to the current global discussions about how to foster and sustain alternative approaches to innovation in the public interest. It is hoped that the lessons described here can spark debate, inform policy-making, and ultimately improve the ability of health and R&D systems to deliver necessary treatments for neglected patients while offering ideas for a more effective and equitable approach to biomedical innovation that may be applicable to other diseases and product types.



# EVOLUTION OF THE DNDi MODEL, 15 YEARS ON



DNDi seeks to address identified gaps in the R&D process that lead to serious unmet medical needs.

DNDi is one of several product development partnerships (PDPs) founded in the late 1990s or early 2000s as not-for-profit entities to conduct and coordinate R&D for new drugs, diagnostics, or vaccines to address pressing health needs in resource-limited settings.

Yet when DNDi was founded, many were sceptical that a not-for-profit approach to R&D could succeed. DNDi has been an 'experiment in innovation', both in *what* it does – develop urgently needed treatments for neglected populations – and *how* it does so: testing an alternative virtual R&D model, based not on profit maximization but on patient needs, which aims to promote the broadest possible sharing of research knowledge and data through a collaborative approach, and which seeks to ensure both innovation and affordable access to new and improved treatments with the desire to develop drugs as public goods wherever and whenever possible.

DNDi seeks to address identified gaps in the R&D process that cause serious unmet medical needs. This has meant developing an 'end-to-end' approach to drug R&D, with the capacity to bring brand new chemical compounds from the laboratory bench to the patients' bedside.

So how has the DNDi model fared over the past 15 years? In what ways has it evolved or changed? What have been the critical achievements, lessons learned, and challenges or dilemmas faced?

There are several distinctive features of DNDi's alternative, not-for-profit R&D model. These revolve around six central tenets:

- 1 Needs-driven** [page 9](#)  
Putting patients – not profits – at the heart of R&D
- 2 Independent** [page 11](#)  
Ensuring financial and scientific independence to guarantee a needs-based approach to priority-setting and decision-making
- 3 Collaborative, open, and transparent** [page 13](#)  
Harnessing the public, private, academic, non-profit, and philanthropic sectors to bring the best science to the most neglected and drive knowledge creation through open drug discovery, and aiming to share research data, knowledge, and costs
- 4 Globally networked** [page 21](#)  
Facilitating scientific exchange, utilising and strengthening research capacity, and nourishing innovation ecosystems and networks, particularly in low- and middle-income countries
- 5 Access-oriented** [page 24](#)  
Making sure treatments are affordable, available, and adapted to the communities who need them most
- 6 Transformative** [page 28](#)  
Piloting and incubating new approaches to innovation that promote public health-driven R&D, fostering public leadership, and engaging as an informed advocate for a more effective and equitable biomedical R&D system

# DNDi AT 15

As DNDi marks its 15-year anniversary as a not-for-profit R&D organization, several important scientific and organizational milestones have been reached.

## TREATMENTS DELIVERED



**8** field-adapted and affordable treatments delivered

including fexinidazole, the first all-oral treatment for sleeping sickness and DNDi's first new chemical entity (NCE)

**7-8** additional treatments anticipated in 2020-2023

## BROAD GLOBAL NETWORK



**Over 180** partners in more than **40** countries

**More than 1/3** of collaborating institutions are based in LMICs

reflecting DNDi's ambition to be grounded in the reality of communities affected by its target diseases



## LONG-TERM INVESTMENTS IN DISCOVERY CONTRIBUTING TO A ROBUST PIPELINE

**4m+**



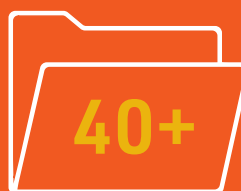
**Over 4 million** compounds screened

as part of various drug discovery efforts, including screening of pharmaceutical company compound libraries, compound-mining, and open and collaborative drug discovery initiatives

**More than 20** NCEs



in DNDi's portfolio, a number of which are now at an advanced stage of clinical development



**Upwards of 40** R&D projects across seven disease areas

## CLINICAL RESEARCH EXPERTISE IN LMICs



### An average of 20 clinical studies from Phase I to Phase IV

are ongoing at any given time, with many more in the planning stages

Five disease-specific clinical research 'platforms' created in Africa and Latin America



### Over 2,500 patients enrolled in active clinical trials at any given time

with studies following international ethical and quality standards, even in very remote and unstable areas

## INCUBATION AND CREATION OF A NEW ORGANIZATION ON AMR

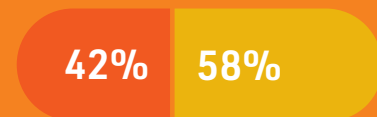
In 2016, in response to the dry pipeline for new antibiotics, DNDi joined forces with the World Health Organization (WHO) to create the Global Antibiotic R&D Partnership (GARDP). GARDP was successfully incubated within DNDi and then launched as an independent organization in 2019 with four R&D programmes for serious drug-resistant infections already underway.



## LONG-TERM DONOR SUPPORT CRITICAL TO SUCCESS

For over 15 years, DNDi has successfully partnered with public and private institutions to secure over €550 million for its mission, with a cumulative target of €730 million for the period 2003–2023. DNDi has, since its inception, been keen to ensure public leadership for neglected disease R&D, including the conduct and funding of such R&D.

### Public vs private contributions (2003–2023)

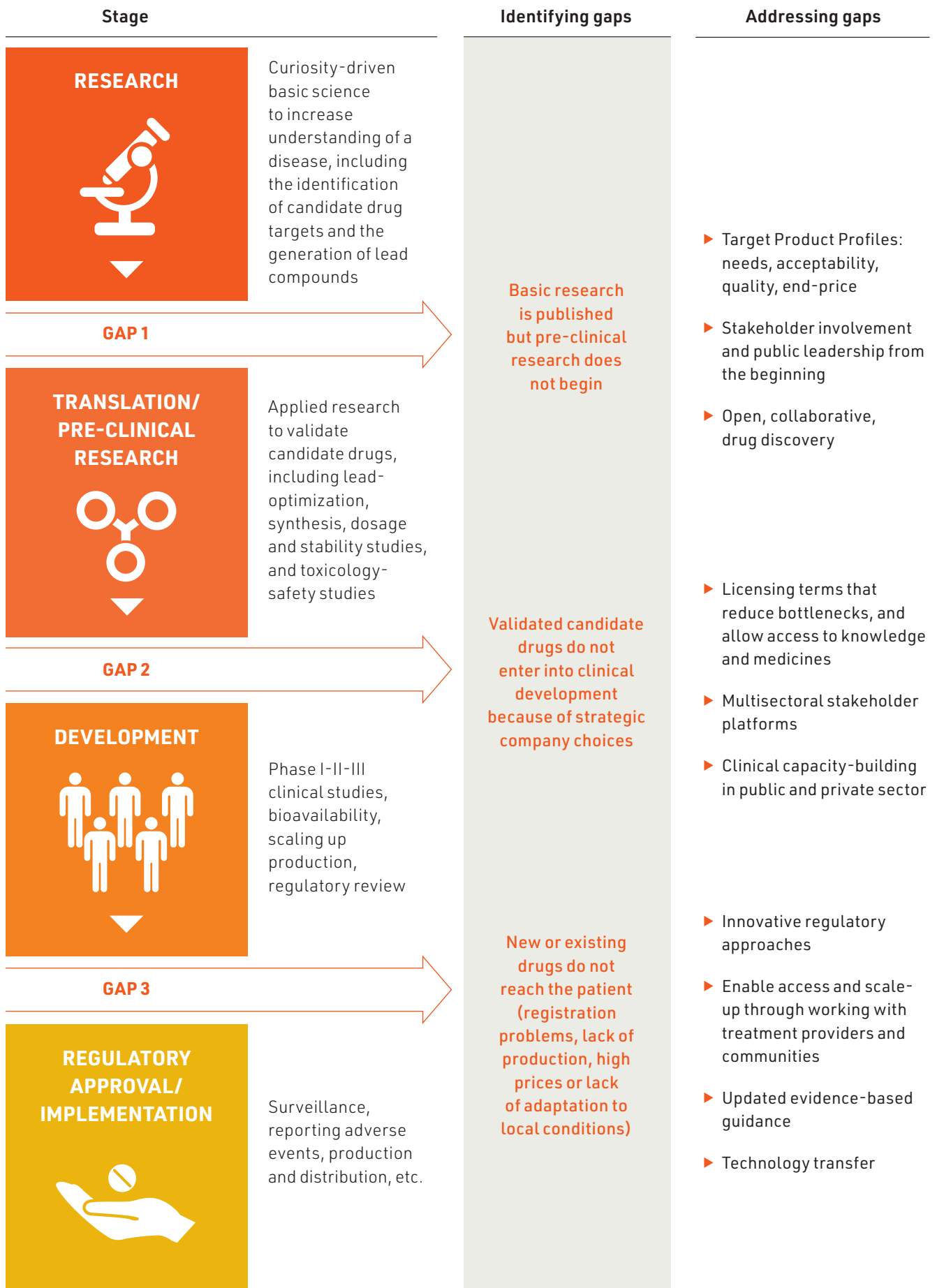


- Private funds
- Public funds

The bulk of DNDi's support (58% in its first 15 years) was therefore secured from the public sector by rallying support from high-income countries, primarily from overseas development assistance, as well as support from middle-income governments. Brazil, Colombia, France, Germany, Malaysia, the Netherlands, Norway, Spain, Switzerland, Thailand, the UK, the US, as well as the European Union and innovative financing mechanisms such as Unitaid and the Global Health Innovative Technology Fund (GHIT), have all mobilized resources for DNDi's mission. Significant support has also come from nongovernmental and philanthropic partners, namely MSF, the Bill & Melinda Gates Foundation (BMGF), and the Wellcome Trust, as well as other foundations and generous individuals.

For a list of major DNDi donors since 2003, see page 39.

## Gaps in the drug development process and how DNDi addresses them





# Needs-driven



## Key take-aways

- Proximity to local treatment providers and close engagement with key stakeholders such as WHO, MSF, and affected communities are essential to ensure R&D efforts remain rooted in the medical needs of neglected populations and the contexts in which they live.
- Public-interest Target Product Profiles developed with experts and partners are critical tools to ensure that products developed are both affordable for and specifically adapted to the needs of the people affected and the health systems that serve them.
- A dynamic approach to managing an R&D portfolio can allow product developers to adapt to new, emerging, and persistent R&D needs and gaps, and respond to evolving epidemiological trends.

In the traditional biomedical R&D system, innovation is driven mostly by market and financial interests, and there are limited national or global processes to define the public health priorities and public interest principles that ought to drive R&D for health. While WHO member states have underscored that “health research and development should be needs-driven and evidence-based and be guided by the following core principles: affordability, effectiveness, efficiency, and equity; and that it should be considered a shared responsibility”,<sup>4</sup> the mechanisms to make this possible are not yet in place. DNDi has advocated for formal priority-setting mechanisms and principles to be developed, but as an experiment in innovation has also designed its own needs-driven approach.

## Therapeutic impact as driving force

Therapeutic impact is the driving force of DNDi’s R&D activities. This means focusing on delivering improved treatments that can be rolled out as part of new treatment guidelines, and not only on new individual products or drugs.

Critical to this needs-driven approach is the ability of DNDi to source and implement projects with partners at any stage in the R&D process. DNDi has adopted a three-pronged approach:

- **Short-term projects (1–3 years)**  
Focused on delivering important and immediate benefits for patients, for example, by completing registration dossiers or geographic extensions of existing treatments.
- **Medium-term projects (3–5 years)**  
Aimed at improving therapeutic options for patients within a short timeframe through optimization of existing drugs, such as new formulations or new combinations of existing drugs, or new indications for existing drugs (therapeutic switching).
- **Long-term projects (6–15 years)**  
With the goal of developing completely new treatments, including NCEs, which have the potential to transform individual patient care, disease management, and in some cases may lend themselves to supporting the sustainable elimination of certain diseases.



<sup>4</sup> WHO. Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. World Health Organization, 2016. Available at: [http://apps.who.int/gb/ebwha/pdf\\_files/WHA69/A69\\_R23-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_R23-en.pdf)

**Public-interest Target Product Profiles (TPPs)** serve to ensure that all products are designed from the start for the people and places that need them. While TPPs are a standard industry practice, public-interest TPPs describe the ideal specifications needed for a treatment, considering the needs of the patients and the main characteristics of the health systems that serve them. They are developed with leading experts, including from countries with high burdens of the target disease, researchers, clinicians, disease control programme managers, WHO, and representatives of affected communities whenever possible. They also include affordability concerns. These TPPs then guide and determine all R&D activities, and are reviewed and updated when necessary in order to account for the latest scientific or epidemiological evidence.

Public-interest TPPs are now widely recognized as a critical step to help guide and inform public health-driven R&D. In May 2019, WHO/TDR launched the Health Product Profile Directory,<sup>5</sup> a freely available, online searchable database, which aims to promote R&D for neglected diseases, AMR, diseases with pandemic potential, and other diseases of public health importance. DNDi contributed several TPPs to the Directory.

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### Essential elements of a public-interest Target Product Profile

Indications	Which disease(s)?
Population	Which type(s) of patients, and where and in what conditions do they live?
Clinical efficacy	What is the level of efficacy required and how will it be measured?
Safety and tolerability	What level of acceptability is there for adverse events (i.e., side effects)?
Stability	How long is the shelf-life of the drug(s) and what are the storage conditions (i.e., does it require refrigeration)?
Route of administration	What is an acceptable way to administer the treatment to the patient population (e.g., oral, injectable)?
Dosing frequency and treatment duration	How often and how long must it be given?
Price	Will it be affordable to the target population or health system?

### Neglected diseases and neglected patients

DNDi was created as a result of an MSF-initiated working group that analysed the crisis in drug R&D for neglected diseases. In 2015, a more dynamic approach to the evolution of DNDi's portfolio was adopted, allowing the organization to build on its collaborative R&D model while retaining the core focus on some of the most neglected diseases, and providing the flexibility to have multiple modes of operation and variable levels of investment in different disease areas. Concretely, this led to DNDi taking on paediatric HIV in direct response to treatment needs identified by MSF, as well as a broadening of DNDi's mission to move beyond the initial concept of 'neglected diseases' to 'neglected patients' – enabling, for example, the inclusion of hepatitis C in the portfolio and the incubation of GARDP, a new initiative focused on the global challenge of AMR.

**Sleeping sickness (HAT)**  
**Leishmaniasis**  
**Chagas disease**  
**Filarial diseases**  
**Mycetoma**  
**Paediatric HIV**  
**Hepatitis C virus (HCV)**

<sup>5</sup> World Health Organization. Smarter Research & Development to Tackle Global Health Priorities. July 2019. Available at: <https://www.who.int/news-room/detail/15-05-2019-smarter-research-development-to-tackle-global-health-priorities>

# Independent



## Key take-aways

- Scientific independence is critical to identifying target diseases, setting R&D priorities, and driving decision-making during the drug development process.
- A deliberate funding policy that safeguards independence is most effective when it ensures a balance of public and private support, maximizes unrestricted support from key donors, and guarantees that no single donor contributes more than 25% of overall funding.

DNDi safeguards its independence in several ways to ensure that every decision in building and managing the portfolio, together with partners, is driven exclusively by science and the imperative of patient needs.

Scientific and financial independence support DNDi's strategic ability to select priority areas of engagement, as well as partners, to support the advancement of its portfolio. DNDi strives to keep itself accountable, by ensuring that the selection of portfolio priorities is informed by broad consultations with stakeholders in affected regions, including ministries of health, national disease control programmes, researchers, clinicians, and patient and civil society groups, and through the representation of public-interest institutions on the DNDi Board of Directors.



## Scientific independence

DNDi's scientific independence – its ability to drive its portfolio development based on strict scientific evidence – is grounded in the organization's governance structure:

- DNDi directs and oversees all projects, while all scientific portfolio decisions are taken by the Board of Directors and based on the review and recommendations of DNDi's Scientific Advisory Committee (SAC).
- The SAC operates independently of the Board of Directors and the Executive Team. SAC members are prominent scientists with drug discovery and development expertise, and/or medical and public health experts with disease-specific expertise or expertise with specific neglected populations (e.g. children). They are tasked with providing independent and exclusively evidence-driven recommendations to the Board of Directors.

**DNDi's scientific independence is grounded in the organization's governance structure.**

## Financial independence

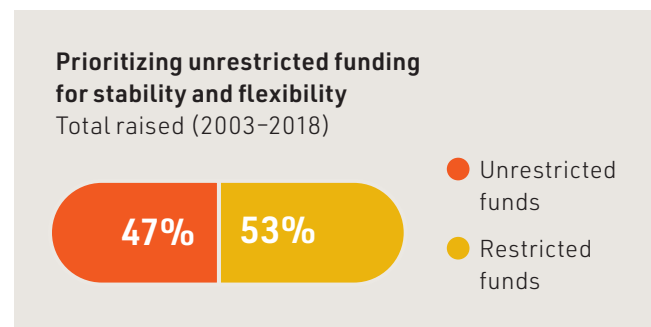
One of the most important ways in which DNDi's independence is maintained is through an ambitious and purposeful funding policy.

A critical aspect of this policy is the insistence on diversification of funding sources, maintaining a healthy balance of public and private support, and ensuring that no single donor contributes more than 25% of DNDi's overall budget.

A second important aspect is the focus on securing significant non-earmarked support, or "core funding", which gives DNDi the ability to manage its scientific portfolio in a dynamic and flexible manner, steer investments to ensure alignment with ever-changing R&D priorities in a way that reflects project attrition and unforeseen opportunities, and enable the selection of projects for extremely neglected or underfunded diseases, such as *T.b. rhodesiense* sleeping sickness and mycetoma.

Over the last 15 years these ambitions were met: unrestricted contributions represented 47% of income, while 34% was partly restricted (attributed to a portfolio of projects), and 19% was more strictly restricted at a programme or project level. This high ratio of unrestricted income, rare in similar PDPs, was achieved thanks to the sustained support from DNDi founding partner MSF, and from strategic public partners such as Germany, the Netherlands, Spain, Switzerland, and the UK.

The Gates Foundation and more recently the Wellcome Trust provide significant funding, which although relatively restricted to specific priorities, acts as a critical catalyst to trigger additional support, not least by de-risking the investment of other potential donors.



Finally, and importantly, DNDi's funding model does not require the organization to recoup R&D investments or finance its future research through the sale of products or revenues generated by intellectual property (IP – see page 29). Public and private contributions pay for the cost of R&D up front, allowing DNDi to identify needs, gaps, priorities, and opportunities based on patient needs, not commercial imperatives. As such, the DNDi model is a practical illustration – provided it is sufficiently financed – of how R&D can be conducted in the public interest when an approach that de-links the financing of R&D from pricing (or volume-based sales) is implemented.

**Public and private contributions pay for the cost of R&D up front, allowing DNDi to identify needs, gaps, priorities, and opportunities based on patient needs.**

## Perspectives for the future

Despite remarkable developments in the funding landscape over the past 15 years, the long-term future of the financing of global health R&D remains fragile. In addition, as DNDi and other PDPs' portfolios mature, additional needs are emerging around the financing of access and delivery of new health technologies.

Whether public donors continue to mobilize resources, and whether they allow for flexibility in how programmes are managed, will strengthen or challenge DNDi's independence in the future. New or continued support from innovative funding mechanisms such as GHIT, Unitaid, the European and Developing Countries Clinical Trials Partnership (EDCTP), and the Right Fund, and development of new ones to attract additional support are needed. Commitments and engagement from new potential funding partners, including governments in emerging economies and MICs as well as the philanthropic community, will also need to be developed.

# Collaborative, open & transparent



## Key take-aways

- Collaborative R&D organizations act as 'conductors of a virtual orchestra' and cannot function effectively without the engagement of public and private partners sharing a common vision to implement projects at all stages of the R&D process.
- More collaborative and open approaches to R&D, particularly drug discovery, can attract additional researchers to a neglected field, accelerate the R&D process by reducing duplication and generating a greater volume of hits or leads, and make R&D activities more efficient and less expensive. Innovative approaches to discovery can also contribute to unlocking capacity in LMICs in particular.
- More open research collaborations could be facilitated, and duplication reduced, if public and private research funders developed clear policies to encourage openness and sharing of data, knowledge, and costs at each stage of the R&D process.
- Global health R&D actors should be encouraged to sign the WHO Joint Statement on Public Disclosure of Results from Clinical Trials and commit to registering all trials in a publicly available register, promptly reporting trial results 12 months after completion of the trial, and publishing findings in open access journals.

DNDi has forged a diverse range of partnerships, alliances, and research collaborations. DNDi does not have its own laboratories or manufacturing facilities, and consequently cannot carry out its work without the engagement of public and private partners.

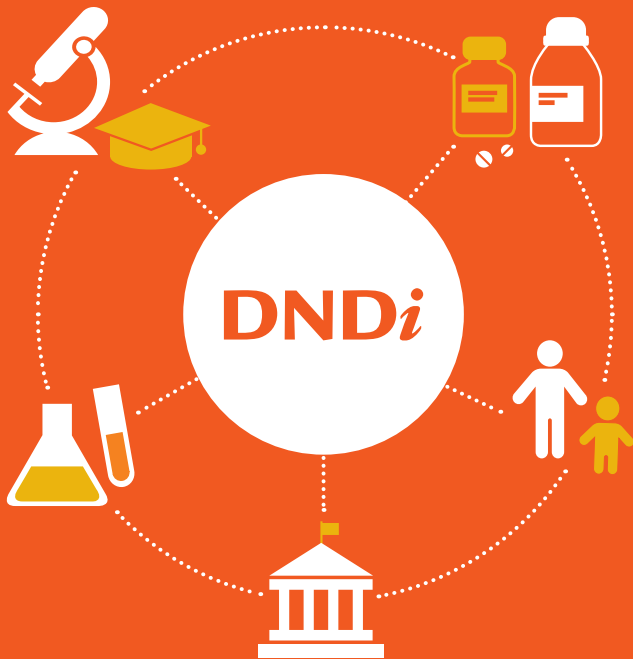
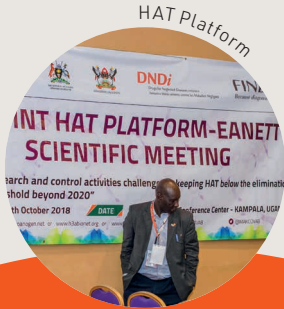
Acting as a 'conductor of a virtual orchestra,' DNDi leverages partners' specific assets, capacities, and expertise, integrating capabilities from all actors. Collaboration is therefore an essential part of DNDi's model.

At every phase of the R&D process – from drug discovery and pre-clinical research to clinical trials and large-scale implementation studies – DNDi manages the process, creating multiple alliances, strengthening cross-sector networks, and working in close partnership with a broad range of different actors.

With over 180 partners in more than 40 countries, giving an exhaustive list is impossible here, but the range of different partners includes:

- **Pharmaceutical and biotechnology companies**, including generic companies. Notable examples include AbbVie, Astellas, AstraZeneca, Bayer, Celgene, Cipla, Daiichi Sankyo, Eisai, Elea, Farmanguinhos, GSK, Insud, Lafepe, Merck, Novartis, Pfizer, Pharco, Pharmaniaga, Sanofi, Shionogi, and Takeda.
- **Health ministries**, particularly in countries where DNDi's target diseases are endemic. Examples include Argentina, Bangladesh, Bolivia, Brazil, Colombia, DRC, Ethiopia, Guatemala, India, Kenya, Malaysia, Nepal, South Africa, Sudan, Thailand, and Uganda.
- **Academia and public sector research institutions**. Notable examples include Addis Ababa University, BHU Varanasi, University of Gondar, iccdr,b, ISGlobal, Imperial College, Institut Pasteur Korea, French National Research Institute (IRD), ITM Antwerp, KEMRI, IED University of Khartoum, Liverpool School of Tropical Medicine, London School of Tropical Medicine and Hygiene, Mahidol University, Makerere University, the Mycetoma Research Centre Khartoum, RMRIMS India, SSGCID, Stellenbosch, Swiss TPH, University of São Paulo, UNICAMP, US NIH, the DDU at the University of Dundee, and Witwatersrand.
- **Other PDPs** including the Foundation for Innovative New Diagnostics, the Medicines for Malaria Venture, and the TB Alliance.
- **NGOs**, including civil society organizations. Examples include MSF, CEADES Bolivia, Clinton Health Access Initiative, Elizabeth Glaser Pediatric AIDS Foundation, Fundación Mundo Sano, ICAP at Columbia University, Knowledge Ecology International, Malaysian Aids Council, Third World Network and Treatment Action Group.

# A global network of 180 partners



## Open and transparent

Over the past 15 years, a number of new initiatives and new policies have favoured the sharing of data and IP and a greater diffusion of knowledge, a movement which has impacted global health – through, for example, the creation the Medicines Patent Pool – as well as multiple other sectors. DNDi is committed to exploring the potential contributions of open and collaborative science. This is because the organization considers that publicly or philanthropically funded R&D ought to be carried out in the public interest, be as transparent as possible, and shared as broadly and equitably as possible.

DNDi also believes in the intrinsic advantages of sharing and collaborating, which can attract additional researchers to a neglected field, enable more and different results, and potentially accelerate the R&D process by reducing duplication as well as make R&D activities more efficient and less expensive. DNDi's approach is focused on areas where bottlenecks exist, and where openness and collaboration could have the greatest impact for neglected patients.

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### Open and collaborative approaches to drug discovery

The **NTD Drug Discovery Booster** is a collaborative project which aims to speed up the process and cut the cost of finding new treatments for leishmaniasis and Chagas disease. Thanks to the participation of eight pharmaceutical companies (AbbVie, Astellas, AstraZeneca, Celgene, Eisai, Merck, Shionogi, and Takeda), DNDi can simultaneously screen millions of unique compounds generated over decades of research. This will significantly reduce the time to find new promising treatment leads and also potentially reduce attrition. Since its creation in 2015, the Booster has released 13 hit series, of which six have progressed to *in vivo* proof-of-concept studies for Chagas disease or leishmaniasis.

The **Open Synthesis Network (OSN)** aims to engage students of medicinal chemistry in research for neglected diseases. DNDi shares data on an active research project with participating universities, along with a list of "wanted" chemical compounds. Students then carry out, as part of their lab training, the synthesis for one or more of these compounds, which DNDi will then test for anti-parasitic activity. All work generated by OSN will be published in the public domain in real time and remain free of IP.

Launched in 2015, the OSN has now attracted over 20 participating institutions around the world, in Europe, the US, India, Australia, and Latin America.<sup>6</sup>

The **Mycetoma Open Source project (MycetOS)** uses a radically open approach (first tried with a similar project called Open Source Malaria) to identify new drug candidates. Launched with partners in 2018, the project will progress discovery efforts through community-driven, in-kind scientific contributions. All ideas and results will be published immediately in real time to an open-access database. The MycetOS community communicates via Twitter and uses a dedicated subreddit forum for transparent discussions, and github for sharing data and key project files.

DNDi also contributes to the **Pathogen Box** launched by Medicines for Malaria Venture (MMV), which seeks to accelerate the discovery of new treatments by providing researchers free access to 400 compounds active against bacteria, viruses or fungi. In 2019, DNDi and MMV launched a second project along the same lines, the **Pandemic Response Box**. Each Box is available free of charge, and in return researchers are expected to share in the public domain any generated data within two years.

<sup>6</sup> University of Sao Paolo, UFRJ (Brazil); University of Munster (Germany); University of Ghana (Ghana); IIT Gandhinagar, NMIMS Mumbai (India); University of Geneva (Switzerland); Imperial College London, De Montford, University of Nottingham, University of Birmingham, University of Dundee (UK); Northeastern University, Pace University, Haverford College, Miami University, University of Washington Tacoma, Williams College, Montclair State University, Illinois Mathematics and Science Academy, Augusta University (USA)

## Leveraging partnerships

As a virtual R&D organization, DNDi leverages its partners to carry out many of its research activities. The number of full-time equivalent (FTE) positions created in partner organizations and working on DNDi activities has been tracked in recent years.

In 2018, there were over 1,000 FTEs in partner organizations for 215 FTEs at DNDi and GARDP. That every DNDi FTE generates five FTEs supporting DNDi research activities is a measure of how central partnership is to the DNDi model.

## Sharing knowledge

DNDi recognizes the importance of contributing to scientific knowledge by sharing data – whether positive or negative – collected through its clinical trials, in order to improve the lives of neglected patients whose needs are often overlooked in research.

In May 2017, DNDi adopted a policy on the Sharing of Clinical Trial Data<sup>7</sup> and signed on to the WHO Joint Statement on Public Disclosure of Results from Clinical Trials.<sup>8</sup> DNDi has also committed itself to registering all trials in a publicly available register, such as the US National Institutes of Health (NIH) [clinicaltrials.gov](https://clinicaltrials.gov) or the Pan-African Clinical Trials Registry, promptly reporting trial results 12 months after completion of the trial, and publishing findings in open access journals.

Various policies now push for scientific findings to be openly accessible, from the 2008 US NIH Public Access Policy,<sup>9</sup> to the Plan S initiative launched in 2018 in Europe, with backing from numerous funding bodies, calling for free access to all scientific papers at the point of publication.<sup>10</sup> DNDi commits to contributing to public databases and open-access journals, to “support the timely communication of all research it sponsors (discovery, pre-clinical, clinical), and facilitate the rapid and accurate communication of DNDi-sponsored research and clinical trial results to the wider scientific and medical communities”.<sup>11</sup> In 2018, 85% of the 26 peer-reviewed scientific articles published by DNDi authors were open-access.

## Pooling clinical data to overcome the fragmentation of research

Pooling and standardizing the data generated by different trials allows for improved understanding of clinical outcomes and can guide the design of future trials. The Infectious Diseases Data Observatory (IDDO) seeks to assemble global clinical, laboratory and epidemiological data on a collaborative platform that can be shared across the research and humanitarian communities.

DNDi collaborates with IDDO by sharing fully anonymized data from its visceral leishmaniasis trials in a data platform launched in 2017. In 2019, IDDO and DNDi created a Chagas Clinical Data Sharing Platform to collate and standardize data, enabling comparisons of efficacy between drugs, regimens and regions, which is almost impossible from publications.



- 7 DNDi. Guiding Principles on the Sharing of Clinical Trial Data. 2017. Available at: [https://www.dndi.org/wp-content/uploads/2018/05/DNDi\\_Guiding\\_Principles\\_Sharing\\_of\\_Clinical\\_Trial\\_Data.pdf](https://www.dndi.org/wp-content/uploads/2018/05/DNDi_Guiding_Principles_Sharing_of_Clinical_Trial_Data.pdf)
- 8 WHO. Joint statement on public disclosure of results from clinical trials. 2017. Available at: <https://www.who.int/ictrp/results/jointstatement/en/>
- 9 NIH. NIH Public Access Policy Details. 2008. Available at: <https://publicaccess.nih.gov/policy.htm>
- 10 Coalition S. Plan S. Making full and immediate Open Access a reality. 2019. Available at: <https://www.coalition-s.org>
- 11 DNDi. Scientific and Clinical External Communications Policy. 2015. Available at: [https://www.dndi.org/wp-content/uploads/2018/03/DNDi\\_Scientific\\_Clinical\\_External\\_Communications\\_Policy.pdf](https://www.dndi.org/wp-content/uploads/2018/03/DNDi_Scientific_Clinical_External_Communications_Policy.pdf)



## R&D costs: how much does it cost DNDi to develop a drug?

DNDi's 15 years of experience is such that its data can credibly inform a review of drug research and development costs under its virtual, collaborative model. As part of its commitment to cost transparency, DNDi publishes this information periodically, based on its latest historical data set.

### Out-of-pocket costs

DNDi's historical out-of-pocket expenses for drug development projects (registration included) have ranged from around €4 million to approximately €60 million.

DNDi has led diverse R&D projects in the field of anti-infectives, from developing entirely new chemical

entities (NCEs) to developing combinations of existing drugs, in loose or fixed-dose combinations, with or without new formulations.

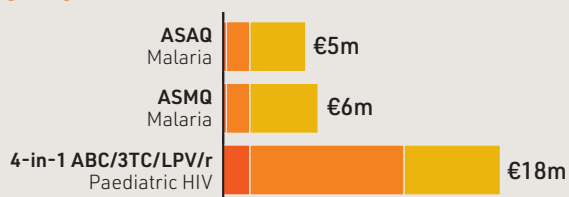
Figure 1 presents the direct out-of-pocket expenses per phase of development for eight such projects, seven of which are treatments that are already registered and the last is in late-stage development. Clear cost differences appear between different types of projects: NCEs require investments all the way from early discovery or, at best, lead optimization to registration, while drug repurposing or combinations can start as late as Phase III; projects involving new formulations are more costly.

**Figure 1: Out-of-pocket costs per stage of development for eight projects in DNDi's portfolio** (in millions of euros)

### Existing drugs without new formulation\*



### Existing drugs with new formulation\*



### New chemical entities



Drug   disease	Discovery and pre-clinical	Phase I	Phase II, III and registration	Total cost (rounded)
<b>Existing drugs without new formulation*</b>				
NECT   Sleeping sickness	-	-	€3.6m	€4m
SSG+PM   Visceral leishmaniasis	-	-	€9.5m	€10m
PAEDIATRIC BENZNIDAZOLE   Chagas disease	€0.1m	-	€3.3m	€3m
<b>Existing drugs with new formulation*</b>				
ASAQ   Malaria	€0.2m	€1.5m	€3.6m	€5m
ASMQ   Malaria	€0.2m	€1.5m	€4.4m	€6m
4-in-1 ABC/3TC/LPV/r   Paediatric HIV	€1.7m	€9.9m	€6.2m	€18m
<b>New chemical entities</b>				
FEXINIDAZOLE   Sleeping sickness	€7.2m	€4.4m	€43.8m	€55m
ACOZIBOROLE   Sleeping sickness	€22.6m	€5.2m	€30m**	€58m**

\* Combinations (as loose or fixed-dose combinations) or repurposing of existing drugs

\*\* Acoziborole is still under development. Late-stage costs are projections.

These full, actual costs exclude in-kind contributions from industry partners, where there are significant variations according to product, stage of development and the terms of the partnership. Audited data show that in-kind contributions from industry amounted to 12.5% of DNDi total expenditures. Ninety percent of this in-kind support was provided by five partners: Sanofi, Eisai, AbbVie, Johnson & Johnson, and Cipla.

### Costs with attrition

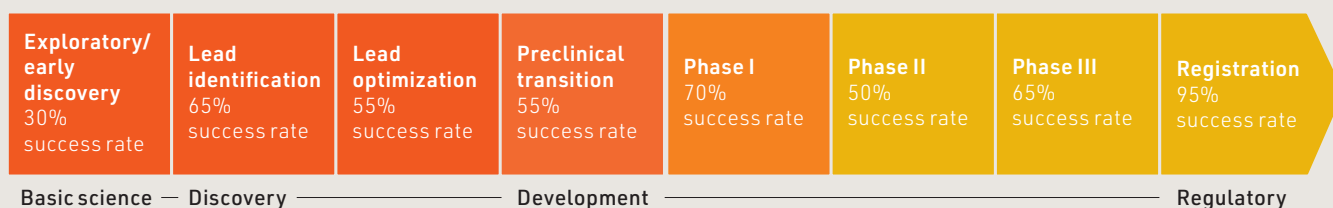
While out-of-pocket costs are a valuable marker of expenditure for any given drug development project, they can vary significantly according to the attrition encountered: the cost of failure that occurs at every stage of the discovery and development cycle.

The development of fexinidazole as a sleeping sickness NCE, for example, cost DNDi €55 million, thanks to a development which proved to be well below the anti-infective attrition average. In contrast, DNDi's leishmaniasis portfolio is so far experiencing closer to standard attrition.

Figure 2 illustrates the average attrition rates, for PDPs, per phase of development given in a 2003 study,<sup>12</sup> which estimated attrition in the field of anti-infectives ranging from 70% failure rates in early discovery to 5% at registration stage.

DNDi's historical data on eight of its drug development projects show out-of-pocket expenses ranged from €4 to €60 million per treatment developed, up to and including registration.

**Figure 2: Potential for success and failure at each stage of the R&D cycle, for PDPs, in the field of anti-infectives**



In figure 3, in order to estimate how much the development and registration by DNDi of a new drug may cost, the DNDi out-of-pocket costs given above have been adjusted to account for the cost of failure, by applying these average attrition rates per phase of development, for PDPs in the field of anti-infectives. This method allows DNDi to estimate that it can develop and register new treatments based on existing drugs at a cost of €4-32 million, and new chemical entities for €60-190 million, attrition included.

Adjusting these figures for average attrition costs per phase of development, DNDi estimates it can develop and register: new treatments that combine or repurpose existing drugs for €4-32 million; and a new chemical entity for €60-190 million. These figures do not include post-registration additional studies and access costs, nor in-kind contributions from pharmaceutical partners.



<sup>12</sup> S Nwaka & RG Ridley. Virtual drug discovery and development for neglected diseases through public-private partnerships. *Nature Reviews Drug Discovery*. 2003;2:919-928.

**Figure 3: Minimum and maximum costs from discovery to registration for projects in DNDi’s portfolio, given as out-of-pocket costs and adjusted for standard attrition** (in millions of euros, minimum and maximum costs per phase)

	Discovery & pre-clinical	Clinical development & registration		Total	Range of costs, with attrition
		Phase I	Phases II & III and registration		
Existing drugs without new formulation*	Not applicable		€4-10	€4-10	€4-12
Existing drugs with new formulation*	€1-2	€1-4	€3-7	€4-13	€5-32
New chemical entity	€10-20	€4-6	€30-45	€44-71	€60-190

\*Combinations (as loose or fixed-dose combinations) or repurposing of existing drugs

DNDi stresses the value of academic and public research centres as well as industry to the early research phase, but as the organization is often not engaged until the discovery phases (screening, hit to lead, lead optimization) or pre-clinical phases, it cannot place an exhaustive and reliable economic value on **early research costs**. Industry costing models often have a similar limitation, as costs incurred prior to lead optimization cannot be attributed to specific compounds, and industry studies<sup>13</sup> often aggregate data at this level to assess costs per drug for R&D incurred prior to human testing. In addition, industry cost models do not capture public investments at this early stage of research.

There is no “market price” methodology that can serve as a valuation benchmark to determine the **value of a compound at the discovery stage** secured from an industry partner. When DNDi secures the licence to a compound for a neglected indication, the economic value (defined as potential for financial returns, as distinct from the historical

cost) of that compound for that indication is considered as very limited or null. The only exception occurs when the compound development could lead to a Priority Review Voucher (PRV – see page 27). In such cases, the industry partner and DNDi negotiate a collaboration on the principle of fair distribution of possible economic benefits commensurate with investments, and past investments by the IP holder are factored into the equation.

**Post-registration additional studies and access costs** are not included here. DNDi investments in implementation vary widely from project to project depending on what is needed to secure wide access to a treatment developed (see page 24). It is therefore challenging to define average ranges of costs. Furthermore, while DNDi designs its development activities with access in mind from the outset, the full roll-out and implementation is a domain where DNDi more commonly looks to other organizations to co-lead.

### Validating and comparing DNDi costs

DNDi collaborated with WHO to assess the Portfolio-To-Impact (P2I) Model,<sup>14</sup> a novel tool developed by TDR and Duke University. The P2I Model estimates minimum funding needs to accelerate health product development from late-stage pre-clinical studies to Phase III clinical trials, and to visualize potential product launches over time, as part of a portfolio of products. There are some important differences between assumptions in the P21 methodology when compared with specific drug development costs, given the portfolio-based nature of the model, the exclusion of some cost

categories such as registration, and the aggregation of many datapoints. However, overall the methodology is within the range of DNDi’s real world experience.

To further validate and complement its costing model, DNDi solicited an independent review of this data by management consultants Arthur D. Little (ADL), who led interviews with industry and contract research organizations (CROs) and conducted literature reviews to provide benchmarking data to support evaluation of the full costs, including the quantification of in-kind contributions from partners, where possible.

13 DiMasi et al. Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics*. 2016;47C:20-33.

14 Terry et al. Funding global health product R&D: The Portfolio-To-Impact Model (P2I), a new tool for modelling the impact of different research portfolios. *Gates Open Res*. 2018 Jul 19;2:24. (doi: 10.12688/gatesopenres.12816.2.). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30234194>

ADL “found DNDi’s methodology and cost calculations to be robust and the resulting costs to be reasonable compared to benchmarks”, albeit “significantly lower than standard market estimates for general drug development”, referring here to Di Masi et al.<sup>15</sup> and the Office of Health Economics.<sup>16</sup>

Having compared DNDi costs with private sector CROs, often used by the pharmaceutical industry, ADL highlighted, “DNDi costs [are] largely in line with estimated CRO costs for similar drug candidates and development processes (small molecules, small trial sizes, etc.)”.

**Figure 4: NCE development costs, excluding discovery and including registration, in various models other than Di Masi et al.**

	DNDi	CRO benchmark	P2I model costs
<b>Phase I</b>	€1-6 million	€1.4-4.1 million	€2-6.4 million
<b>Phase II and III</b>	€30-45 million	€34-62 million	€34-37 million
<b>Model variations</b>	Range of costs for DNDi	Range of costs of contracting CROs for similar studies. Includes 15% commercial mark-up	Range of costs for simple and complex NCE in P2I model
<b>Costs not included</b>	No exclusion: Fully loaded costs for DNDi, including management and indirect costs	Excluded: R&D cycle management and indirect costs	Excluded: CMC and registration costs

Indeed, DNDi’s cost estimates align well with CRO benchmark costs for similar studies. They also generally align with or are below the P2I model, considering that the latter excludes CMC and registration costs, which are included in DNDi’s costs. On the other hand, the costs are significantly different from the industry benchmark published by Di Masi et al. in 2016, who reviewed new estimates of R&D costs in the pharmaceutical industry.

While comparing the costs of R&D between different business models and across a range of diseases is complex, a number of factors influence DNDi costs:

- Trial sizes and location:** As DNDi studies focus on diseases for which treatment options are usually limited, the number of patients and volume of studies required to show statistically significant improvements over the standard of care is lower than for many industry trials looking to show only incremental improvements over previously approved drugs. Furthermore, as DNDi patients are in LMICs, costs of clinical trials are usually lower than in HICs. However, logistics and trial coordination are more complex, and as part of its mission, DNDi invests 5% of its overall expenditures (2018 data) in strengthening existing clinical research capacities to increase the ability of neglected disease-endemic countries to respond to their own research needs. Finally, patient recruitment varies considerably (for a drug intended to facilitate the sustainable elimination of a disease, patient recruitment may require many sites, sometimes across several countries, whereas patient recruitment is easier for trials with sites in highly endemic areas) and this has a bearing on DNDi costs.

- Infrastructure costs:** DNDi is a cost-effective and widely networked organization: for each FTE working within DNDi, another four FTEs work in partner organizations around the world (see page 16). Furthermore, DNDi’s FTE costs are significantly below industry levels, by at least 50%.
- Attrition and therapeutic area:** A foremost factor of efficiency is that attrition is always only scientific in nature, as no project is ever dropped for marketing and financial reasons, unlike in the traditional profit-driven model. Attrition rates vary as well across therapeutic areas, a fact that is well documented in publications.<sup>17</sup> Duration of trials and success rates are more favourable in the field of anti-infectives than in other fields, and vary as well across indications.
- Regulatory requirements:** DNDi focuses on neglected populations, and its treatments fill an unmet medical need, sometimes allowing for fast-track reviews and lower fees for scientific consultation and regulatory submission under supportive provisions from various stringent regulatory authorities.
- Costs of capital:** Given DNDi’s public funding model, funded upfront by public sources rather than borrowing capital, costs of capital do not apply. In contrast, in the industry model designed by Tufts, the “opportunity cost” of capital invested along the development cycle is a key cost component accounting for more than half of total costs.
- For additional methodological considerations, please see [www.dndi.org/costs](http://www.dndi.org/costs)

<sup>15</sup> DiMasi et al. 2016. op.cit.

<sup>16</sup> Mestre-Ferrandiz J, Sussex J, and Towse A. The R&D Cost of a New Medicine. UK Office of Health Economics, 2012. Available at: <https://www.ohe.org/publications/rd-cost-new-medicine>

<sup>17</sup> Mestre-Ferrandiz, Sussex, and Towse op.cit.

# Globally networked



## Key take-aways

- A virtual, collaborative R&D organization can only succeed with strong partnerships and alliances and a global network. Leadership from the public sector, particularly in LMICs, is essential to ensuring sustainable innovation ecosystems.
- Proximity to the needs of affected communities and patients is critical and can only be achieved through building trusting and equal partnerships with local clinicians, scientists, and experts, as well as patient and community/civil society groups in affected countries.
- In LMICs, innovative partnerships throughout the R&D process leverage and strengthen existing research capacity, facilitate needs definition, promote scientific exchange, and enable access. In addition, targeted investments in training and health infrastructure improvements, including in remote settings, are critical for success.



## DNDi has a strong stake in low- and middle-income countries to ensure proximity to patients



34% of DNDi partners are in LMICs.

DNDi was created in part due to a strong impetus from a group of countries wishing to address the lack of R&D for diseases largely ignored by the market: four of DNDi's seven founding partners are public research institutes or health ministries from countries in Latin America, Africa, South and South-East Asia. Representatives from these institutions have, since DNDi's inception, been a part of the governing Board of Directors.

The close involvement of these founding partners has proved essential in the development of strong partnerships at the national level, allowing DNDi to leverage expertise and other technical investment from the countries concerned, and in the region. Examples include: the close collaboration with disease programmes in India and Bangladesh, which facilitated rapid introduction of new treatments to support leishmaniasis elimination in South Asia; partnership with the Colombian MoH, which, with DNDi support, boosted diagnosis and treatment for Chagas disease;<sup>18</sup> and the partnership with the Malaysian MoH, co-sponsoring clinical trials for new hepatitis C treatments, as a part of efforts to implement a public health approach to the disease.

As of 2018, 34% of DNDi partners are in LMICs, an illustration of the globally-networked nature of DNDi. DNDi's eight regional offices, six of which are based in LMICs, house half of DNDi staff, and ensure the organization remains rooted in neglected disease-endemic countries.

<sup>18</sup> DNDi. Chagas Access Programme achieves an increase of 1300% in the number of people screened. Press release. 20 June 2019. Available at: <https://www.dndi.org/2019/media-centre/press-releases/chagas-access-programme-achieves-an-increase-1300-percent-people-screened/>

## New innovation ecosystems

DNDi's ultimate objective is to contribute to new innovation ecosystems, driven by scientific leaders in LMICs that will fundamentally change how research priorities are defined and where end-to-end health R&D in the public interest is conducted. Initiatives to use and strengthen research capacities in LMICs and support networks of excellence to sustain the future of public-interest health R&D are central to the DNDi model.

For example, consortia to drive drug discovery have been established in Latin America and South Asia, enhancing and expanding national and regional resources by bringing together academia, government, and industry partners to collaborate on advancing drug candidates for diseases of relevance to the region. The aim of the Lead Optimization Latin America project (LOLA), for example, is to identify and develop new promising compounds for leishmaniasis and Chagas disease by harnessing the chemistry experience of Latin American academic partners, combined with DNDi's access to libraries of compounds owned by pharmaceutical and biotechnology partners, which also support the group by providing expertise in medicinal chemistry, and professional advice and training on drug discovery. This international collaborative approach has anchored DNDi's early-stage R&D activities in Latin America.

In addition, since 2003, five disease-specific clinical research platforms and networks have been created. By bringing together key actors, including health ministries, national disease control programmes, regulatory authorities, WHO, academia, civil society groups, as well as clinicians and health professionals, these 'knowledge hubs' promote scientific exchange, and facilitate access and delivery of new tools.

They also capitalize on and reinforce existing clinical capacity to ensure clinical trials can be conducted in accordance with Good Clinical Practice (GCP) and international ethical and scientific quality standards, no matter how remote or resource-limited the setting. Addressing this challenge has meant investing in improving health infrastructure through clinic and laboratory renovations, provision of essential equipment and supplies, and continuous training of health personnel, with almost 5,000 people trained since 2010.

Looking to the future, existing R&D capacity in LMICs, and the desire to support and enhance this potential, should be harnessed to address national, regional, and global health priorities while ensuring the needs of the most vulnerable are met. Achieving this goal will require the active participation of medical and scientific communities, civil society, as well as national and regional political leadership and financing.

### The DNDi model as an illustration of the Commons

In 2018, the Agence française du Développement conducted an analysis<sup>19</sup> of DNDi's model to evaluate whether the DNDi experience could be described as exemplifying the 'Commons' within the area of public health.

The report identified certain key characteristics of the Commons as they pertain to the DNDi-supported research platforms:

- A group of self-organized actors, grouped around a common goal and purpose;
- Agreed rules governing the production of results and products, as well as the sharing of benefits;
- A form of governance to oversee and arbitrate, and to decide when to improve or adapt the initial purpose as needed.



19 Coriat B et al. DNDi, a distinctive illustration of Commons in the area of public health. AFD Research Papers. 2019. Available at: <https://www.dndi.org/2019/advocacy/afd-research-paper-dndi-distinctive-illustration-commons-public-health/>

## Clinical research platforms

Clinical research platforms help identify patients' needs and R&D gaps; strengthen and sustain clinical research capacity; facilitate access to new treatments; and advocate for an enabling policy and regulatory environment for needs-driven R&D.

Below are some examples of the ways in which the platforms have contributed to DNDi's achievements in recent years, and how they create value for their members and help to meet patients' needs.

### Advocating for R&D for NTDs and for patients' needs: the Chagas Platform

In 2018, members of the Chagas Clinical Research Platform and the Global Chagas Disease Coalition published the Santa Cruz Letter,<sup>20</sup> calling on the governments of 21 endemic countries to intensify their efforts to control and eliminate Chagas disease as a public health problem by expanding access to diagnosis and treatment; increasing investment in research for new, safer, and more effective treatments; improving disease surveillance for better data and conducting a long-term patient cohort study to inform and guide research priorities; and establishing an International Day of People Affected by Chagas Disease on 14 April. At the World Health Assembly in Geneva in 2019, 14 April was named World Chagas Day.

### Creating a centre of excellence on leishmaniasis research in Ethiopia: the LEAP Platform

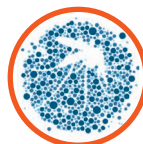
The Leishmaniasis Research and Treatment Centre at the Gondar University Hospital, Ethiopia was constructed with DNDi support in 2004 to strengthen its capacity to conduct clinical trials led by the LEAP Platform. The centre has grown to become a fully equipped modern laboratory with the construction of a new building and technicians trained in Good Clinical Practice and Good Clinical Laboratory Practice. Today, it is used as a reference laboratory for other health facilities in the catchment area and serves as a centre of excellence for leishmaniasis care and innovation in Ethiopia.



### Leishmaniasis East Africa Platform (LEAP)

Founded: 2003  
Khartoum, Sudan

60 members from more than 20 institutions



### RedeLEISH

Founded: 2014  
Rio de Janeiro, Brazil

162 members from 83 institutions



### HAT Platform

Founded: 2005  
Kinshasa, DRC

120 members from more than 20 institutions



### Chagas Clinical Platform

Founded: 2009  
Uberaba, Brazil

459 members from 150 institutions

### Filariasis Clinical Research Network

Founded: 2015  
Geneva, Switzerland

31 members, from more than 20 institutions

<sup>20</sup> Coalición Chagas. Carta de Santa Cruz – Reunión de la Plataforma y Coalición de Chagas. 19 Nov. 2018. Available at: [http://www.coalicionchagas.org/news-article/-/asset\\_publisher/hJnt8AyJM2Af/content/carta-de-santa-cruz](http://www.coalicionchagas.org/news-article/-/asset_publisher/hJnt8AyJM2Af/content/carta-de-santa-cruz)

# Access-oriented



## Key take-aways

- Even for R&D organizations, it is critical to work with partners and treatment implementers to overcome the considerable challenges related to introducing and ensuring access and delivery of new health technologies and tools.
- Access must be prioritized from the outset of any R&D project, not only at a late stage or after regulatory approval; R&D programmes should be developed with access in mind, and TPPs should include key elements to ensure affordability, availability, and field feasibility.
- Developing robust collaborations with industrial partners is essential to securing sustainable production, supply, and distribution, and engaging key stakeholders, including affected communities, is vital to ensuring public leadership and community support from the beginning.
- Critical to success is ensuring sustainability of production; in some instances, technology transfer can be key to assuring sustained affordability and access.

With its mission and vision directed primarily towards R&D, DNDi has neither the capacity nor expertise to act as a direct provider of treatments.<sup>21</sup>

However, from the very beginning of every R&D project, DNDi endeavours to define clearly how it will ensure that the treatments it develops will be affordable, available, and adapted to the needs of neglected patients and the health systems that serve them – three pillars that help guarantee access.

DNDi's commitment to access influences all aspects of the organization's work – from the design of TPPs, the approach to IP and licensing, and the selection of partners, to regulatory strategy and the involvement of DNDi in 'post-registration' efforts (such as large-scale implementation studies) to introduce and scale up access to treatments. This commitment starts at the conception phase of every project, not once a product is in late-stage clinical development or has received regulatory approval.

21 DNDi. DNDi Access Policy. 2009. Available at: [https://www.dndi.org/wp-content/uploads/2018/03/DNDi\\_Access\\_Policy.pdf](https://www.dndi.org/wp-content/uploads/2018/03/DNDi_Access_Policy.pdf)



## An evolving role

Over the past 15 years, DNDi has gained valuable experience in introducing and scaling up access to many of the eight treatments it has developed. While in some instances DNDi efforts have met with considerable success when it comes to guaranteeing wide-scale access for those in need, there have also been tremendous challenges. In response, DNDi's role in access has evolved.

It is important to note that DNDi activities are driven by a public-health, patient-needs mindset rather than being focused simply on promotion of a specific product. Hence, for example, DNDi's early efforts in the field of malaria were aimed at ensuring demand for and supply of *all* artemisinin-based combination therapies (ACTs) to meet patient needs, not only ASAQ or ASMQ, two drugs that DNDi delivered with partners. Similarly, for paediatric HIV, DNDi is driven by the imperative to improve treatment options broadly for the youngest children living with HIV, not solely the antiretroviral (ARV) '4-in-1' being developed by DNDi and Cipla, and for hepatitis C, DNDi strives to encourage access to all new-generation direct-acting antivirals (DAAs), rather than just the product DNDi is developing with its partners.

## Overcoming systemic challenges through partnership

There is no one-size-fits-all approach to access given the widely diverging epidemiological, demographic, geographic, infrastructure, and market dynamics of each specific disease.

Access challenges are more acute in many of the settings in which DNDi works – both because the people who stand to benefit most from DNDi treatments live predominantly in remote areas, where health systems may need strengthening, and because there are systemic failures in ensuring neglected populations benefit from innovation. Ensuring access to treatments for neglected diseases and populations therefore requires coordinated action from a broad variety of stakeholders and partners to overcome multiple systemic failures.

The solidity of partnerships requires a high degree of alignment – for example on access provisions in licensing agreements with industrial partners responsible for manufacturing, registration and distribution of any DNDi-developed products, and on adoption and uptake of treatments with WHO, health ministries, regulators, and community stakeholders.

### Strategies to overcome access challenges: Lessons from the DNDi experience

#### Malaria and sleeping sickness: when strong multisector partnerships lead to broader access

DNDi has met with the most success where 'systems' for treatment implementation have been functional to ensure the widest possible access to treatment.

More than 500 million treatments of artesunate-amodiaquine (ASAQ), developed with Sanofi, have now been delivered. This was possible because of many enabling factors. Clear international guidelines from WHO were unequivocal about the need for countries to transition to ACTs. Sanofi led on manufacturing, regulatory approval, and distribution, and committed at the outset to a price – on a no-profit no-loss basis – of less than US\$ 1 for adults and US\$ 0.50 for children, and a stipulation that the combination should be patent-free. (This price subsequently enabled a reduction in the price of other ACTs.)<sup>22</sup> A deliberate strategy to achieve inclusion in the WHO Essential Medicines Lists and WHO Prequalification (PQ) ensured ASAQ could be procured by major global health institutions such as the Global Fund to Fight AIDS, Tuberculosis and

Malaria. DNDi ensured sustainability of the project by handing over the malaria portfolio to the Medicines for Malaria Venture in 2015.

The roll-out of nifurtimox-eflornithine combination therapy (NECT) was coordinated by WHO. A deliberate strategy of working hand-in-hand with health ministries, national HAT control programmes, clinicians, and researchers in HAT-endemic countries was developed through the HAT Platform, a clinical research, training, and access-supporting network of over 20 member institutions and 120 individuals. The HAT Platform contributed to defining the TPP and carried out clinical trials, ensured acceptability at the clinician and community level, and facilitated adoption of NECT in national guidelines. An explicit strategy succeeded in ensuring NECT was added to the WHO Essential Medicines Lists. Industrial partners Sanofi and Bayer committed to supplying the eflornithine and nifurtimox, respectively, free of charge. And a centralized procurement and distribution mechanism through WHO and MSF Logistique facilitated distribution to all endemic

22 Moon et al. A win-win solution? A critical analysis of tiered pricing to improve access to medicines in developing countries. *Globalization and Health*. 2011;7:39. Available at: <http://www.globalizationandhealth.com/content/7/1/39>

countries (MSF packs NECT kits to treat patients with all necessary consumables, including water for infusion, IV tubes, catheters, gloves, disinfectant, etc. and WHO distributes to countries). NECT was delivered in 2009 and by 2012, 95% of patients with stage-2 disease were treated with NECT. The delivery of fexinidazole to all endemic countries is anticipated to build on this WHO-coordinated system.

### **Paediatric HIV: preparing for access by running implementation studies**

DNDi is working with Cipla to improve treatments for children living with HIV by developing a WHO-recommended '4-in-1' that contains all the ARVs a child needs. A dossier was submitted to the US FDA for review in October 2019.

In the meantime, DNDi has been working with countries to increase access to an interim solution. The '2-in-1' pellets developed by Cipla represent a major improvement for children, as they are more effective than many suboptimal regimens still prescribed in some countries and much easier for children to take and for caregivers to administer when compared to older liquid formulations of a more effective treatment that taste foul and require refrigeration. To increase access to the 2-in-1, DNDi has been running an implementation study known as the 'LIVING' study in Kenya, Tanzania, and Uganda. Interim results show very high levels of adherence and clinical improvement, with 83% of children having undetectable levels of HIV after 48 weeks of treatment. The study aims to facilitate in-country adoption of better paediatric formulations, which will ultimately help the transition to the 4-in-1, once it is available, and other long-awaited improved treatment options for children.

### **Hepatitis C: Innovative approaches to overcoming pricing and IP barriers**

New-generation treatments for hepatitis C virus (HCV) known as direct-acting antivirals (DAAs) are safe and effective; yet only 7% of patients are currently on treatment, largely due to high drug prices, but also because people are unaware of their infection and go untreated for years.<sup>23</sup>

While prices have come down in recent years, they still constitute a barrier to access to HCV diagnosis and treatment in many countries. An affordable regimen would benefit many, particularly in countries that are excluded from licensing agreements that enable access to generics, and

in which competition is not sufficiently robust to bring prices down. DNDi and the Malaysian Ministry of Health began collaborating on HCV in 2016, with Malaysia co-sponsoring clinical trials to study the safety and effectiveness of a potentially affordable combination using drug candidate ravidasvir (RDV) with the backbone of HCV treatment sofosbuvir (SOF). The partnership agreement also covered the transfer of the RDV manufacturing technology to enable local production. In 2017, Malaysia issued a 'government use' licence to source generic SOF, a move which has allowed it to accelerate access to affordable treatment in its public hospitals.

In addition to R&D, DNDi's HCV programme has a strong component to support countries in implementing a public health approach to the disease. In 2018, DNDi and FIND announced a partnership, in collaboration with the Ministry of Health in Malaysia, to support scale-up of diagnosis and treatment. The project decentralizes HCV screening, with people who screen positive and are subsequently confirmed to have HCV linked to DAA treatment in government hospitals or, on a voluntary basis, as part of a DNDi clinical trial. DNDi is also working with MSF to develop and implement simpler models of care in specific target populations in other countries.

### **Technology transfer: sustainable production, multiple sources, closer to patients**

DNDi has developed specific strategies to assure sustainability of production. Technology transfer has been pursued in some instances and has fostered both a second source of the anti-malarial ASAQ, with the Tanzanian manufacturer Zenufa now also producing, and the South-South technology transfer between Brazilian public laboratory Farmaguinhos and Indian generic company Cipla, allowing regional implementation of the anti-malarial ASMQ in South and South-East Asia.

### **DNDi has developed specific strategies to assure sustainability of production.**

Technology transfer is also a key part of the strategy for hepatitis C, with sharing of the manufacturing technology for hepatitis C treatment ravidasvir by Egyptian generic producer Pharco with Pharmaniaga in Malaysia, and potentially Grupo Insud in Argentina, which will enable local production and further transfer to additional generic producers to follow.

23 WHO. Progress report on access to hepatitis C treatment: Focus on overcoming barriers in low- and middle-income countries. World Health Organization: 2018. Available at: <https://www.who.int/hepatitis/publications/hep-c-access-report-2018/en/>

## US FDA priority review voucher and benznidazole for Chagas disease

In 2007, based on an idea originating from academics at Duke University,<sup>24</sup> the US Congress created a new incentive mechanism to stimulate R&D for neglected diseases, known as the priority review voucher (PRV).

A PRV is a voucher issued by the US Food and Drug Administration (FDA) to a sponsor that has received FDA approval for a specific new drug application addressing any disease on a list of neglected infectious diseases, rare paediatric diseases, or medical countermeasures. This voucher entitles its holder to either designate any other drug application for priority review by the FDA, thereby facilitating early access to market, or to sell its voucher to others. To date, more than 30 PRVs have been awarded and have sold for between US\$67-350 million.<sup>25</sup>

The PRV has proven to be important as an incentive for pharmaceutical companies to partner with DNDi on NTD projects. Key flaws in the mechanism's design have been criticized by DNDi, MSF, TB Alliance, and other public health, R&D, and academic groups. In order to ensure both innovation and access for the patients the PRV was designed to benefit, these groups have called on Congress to add an access requirement (to ensure the availability and affordability of the products for which companies are awarded PRVs) and a novelty test (to ensure PRVs are only awarded following actual investments in R&D that result in genuinely new health technologies).

**The PRV has proven to be important as an incentive for pharmaceutical companies to partner with DNDi on NTD projects.**

In 2016, DNDi and Argentinian non-profit Fundación Mundo Sano signed an agreement focused on technical collaboration in support of a regulatory submission to obtain FDA approval of benznidazole, with the goal of increasing access to treatment for Chagas patients. This led in 2017 to FDA approval of benznidazole for children 2 to 12 years (efforts to

expand the approval to include adults are ongoing) and to the award of a PRV to Chemo Group (now Insud Pharma), part of the same group as Mundo Sano.

As part of the collaboration agreement between Insud and DNDi, a substantial proportion of the revenues from the sale of the PRV are to be dedicated to increasing access to diagnosis, treatment and prevention throughout the Americas.<sup>26</sup> A Regional Access Framework for Chagas Disease, developed by DNDi and Mundo Sano, is now being implemented in collaboration with key governments and members of the Global Chagas Disease Coalition.

Funds from the PRV are already at work. Countries can look to efforts made by the Colombian Ministry of Health, which, with DNDi technical support, launched a pilot project to boost diagnosis and treatment. Initial results show a more than tenfold increase in the number of patients screened and a radical reduction in the wait for a confirmed diagnosis.<sup>27</sup> Similar projects in Brazil and Guatemala seek to replicate this success. DNDi is also working with US treatment providers and other stakeholders to improve screening, diagnosis, and treatment for the estimated 300,000 people with Chagas disease in the US.



24 Ridley DB, Grabowski HG, Moe JL. Developing Drugs for Developing Countries. *Health Affairs*. 2006;25:2. Available at: <http://content.healthaffairs.org/content/25/2/313.abstract>

25 Gaffney A, Mezher M, Brennan Z. Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers. *Regulatory Focus*. Regulatory Affairs Professionals Society: 30 September 2019. Available at: <https://www.raps.org/regulatory-focus/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fdas-priority-review-vouchers>

26 DNDi. US FDA approves Chemo Group's benznidazole to treat children with Chagas disease. Press release. *Drugs for Neglected Diseases initiative*: 2017. Available at: <https://www.dndi.org/2017/media-centre/press-releases/fda-approves-benznidazole-chagas-children/>

27 DNDi. Chagas Access Programme achieves an increase of 1300% in the number of people screened. Press release. *Drugs for Neglected Diseases initiative*: 2019. Available at: <https://www.dndi.org/2019/media-centre/press-releases/chagas-access-programme-achieves-an-increase-1300-percent-people-screened/>

# Transformative



## Key take-aways

- Establishing an intellectual property policy and making it publicly available can be fundamental to achieving 'gold standard' pro-access licensing terms in contractual agreements.
- Negotiations are more complex when operating in 'competitive' fields and/or when they begin at a later stage in the development process, but this does not prevent pro-access approaches when the pharmaceutical partner has a commitment to access and when countries are prepared to make use of TRIPS flexibilities. Nevertheless, it would be helpful if access provisions were included at an earlier stage in the R&D process when public or philanthropic funds are used.
- Regulatory bottlenecks remain a challenge, but regulatory strategies should aim to secure technical and scientific review that is rigorous in terms of quality and patient safety, appropriate to the public health context, and rapid.
- Important initiatives aimed at regional regulatory harmonization for optimizing review of dossiers should be supported.
- Public leadership and public policies to address market failures – including those that guarantee a public return on public investment in R&D and that enable the setting of R&D priorities by affected countries – are critical to create a more effective, equitable, and needs-driven global biomedical R&D system.

Since its inception in 2003, DNDi has had a three-fold mission: to develop new and improved treatments for neglected patients; to utilize and strengthen research capacity in low- and middle-income countries; and to promote public responsibility for neglected disease R&D by advocating for public policies that will enable a more needs-driven global biomedical R&D system.

This third pillar of the DNDi mission sets the organization apart from many other global health R&D actors and non-profit product developers and highlights the central importance of not only what DNDi does but how DNDi carries out its R&D activities. It also enables the organization to experiment with new approaches and models, and in some cases, to 'disrupt' the status quo.

Three areas where DNDi's experience and practice may have a transformative impact on the broader field of R&D include:

1. Managing intellectual property and licensing in the interest of public health
2. Facilitating access through innovative regulatory strategies
3. Advocating for a more effective, equitable, and needs-driven R&D system



## Managing intellectual property and licensing

It is widely recognized that IP rights can create roadblocks throughout the innovation cycle, limiting the possibility of collaboration, follow-on R&D, production, or equitable access to end-result products. The signature of the TRIPS agreement in 1995 enshrined IP-protected monopolies as the predominant way of funding and steering biomedical R&D. Licences that sought to enhance access to affordable medicines were therefore rare at the time DNDi was created.

### It is widely recognized that IP rights can create roadblocks throughout the innovation cycle.

To address these barriers, DNDi's IP policy<sup>28</sup> was developed with a group of experts in 2004. It is based on two guiding principles that inform all contract negotiations:

- 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 whenever possible.

DNDi's IP policy provides that 'DNDi will not accept projects in which IP is obviously going to be an insurmountable barrier to follow-up research on behalf of DNDi and/or equitable and affordable access'. In addition, where IP barriers exist, DNDi uses available TRIPS flexibilities for research purposes (e.g. experimental use and/or research exemptions) and supports the use of other TRIPS flexibilities by governments to enable production or importation of affordable medicines.

Over the past 15 years, DNDi negotiations have concerned compounds or technologies that are either already publicly available or that originate from a public or private partner. If the compound is publicly available, DNDi negotiates ownership of new IP generated through DNDi-supported activities, or a perpetual non-exclusive licence, to ensure full freedom to operate for DNDi and prevent any future use of such new IP that may impede equitable and affordable access to the product. If the compound comes from a partner, DNDi negotiates licence rights to any pre-existing IP related to the compound and owned by the partner, as well as to any new IP that will be generated through the collaboration.

If the partner is contributing and investing in compound development (either early or pre-clinical stage studies, Phase I studies, or pharmaceutical development),

DNDi has often agreed that the licensing rights granted to DNDi may be limited to what is necessary to perform the tasks covered by the collaboration. However, the partner must agree to extend the licence to DNDi allowing full freedom to operate if the partner withdraws from the project or is in default in delivering its own commitments (e.g., unmet demand or unaffordable pricing).

To ensure DNDi rights can be efficiently exercised after a collaboration agreement expires or if the partner withdraws from the collaboration earlier than planned, DNDi agreements also include clauses to ensure technology transfer of all necessary IP so that any related know-how is not lost and DNDi activities are minimally affected by a partner's change of business priorities.

"DNDi does not seek to finance its research and operations through IP rent revenues," and any patenting by DNDi would be the exception rather than the rule, given that associated costs are very likely to outweigh benefits.

#### 'Gold standard' licensing terms

- Perpetual royalty-free, non-exclusive, sub-licensable licences to DNDi in the contractually defined target disease(s);
- Worldwide research and manufacturing rights;
- Commitment to making the final product available at cost plus a minimal margin, in all endemic countries, regardless of income level;
- Non-exclusivity, enabling technology transfer and local production to multiply sources of production and decrease price of product.

Distribution under the licence is constrained to compliance with the principle of 'affordable basis', which is defined as "the pricing of a product at the lowest sustainable level that includes only: the amortization of R&D costs, excluding any such costs paid for with third party public or private grants or donations (i.e. funds not given for investment purposes); full production costs, as optimized without compromising the quality of the Product; and direct distribution costs, plus, a reasonable margin."

28 DNDi. DNDi Intellectual Property Policy. 2004. Available at: [https://www.dndi.org/wp-content/uploads/2018/03/DNDi\\_Intellectual\\_Property\\_Policy.pdf](https://www.dndi.org/wp-content/uploads/2018/03/DNDi_Intellectual_Property_Policy.pdf)

These 'gold standard' principles have been included in most DNDi agreements with some variations, depending on the stage of development and the partner's involvement. DNDi has agreed to a handful of exceptions to the principle of non-exclusivity as

an incentive to engage a partner in the field of neglected diseases. However, such exceptions are rare, and the partner is always bound by the obligation to ensure equitable and affordable access to any treatments developed.

## Putting principles into practice: two examples from DNDi's experience

### Early-stage drug discovery: The NTD Drug Discovery Booster

Initially, DNDi screened large collections of quality compounds through bilateral agreements with several pharmaceutical companies and other institutions, using new, medium- to high-throughput screening assays developed by DNDi.

In 2015, DNDi launched the NTD Drug Discovery Booster with eight pharmaceutical companies to significantly accelerate the discovery of validated hits through a multilateral cooperative mechanism (see page 15). Under this collaborative framework, the eight participating companies commit to not protecting the resulting hit if the 'seed' compound is in the public domain or belongs to DNDi. If it belongs to one of the participating companies, the commitment is to license any resulting hit series to DNDi on a non-exclusive basis for use and affordable distribution in the treatment of Chagas disease or leishmaniasis.

### Later-stage compounds: Hepatitis C

In the case of compounds more advanced in development, DNDi negotiations must consider the partner's investments prior to DNDi collaboration, and existing IP. In the case of ravidasvir for the treatment of hepatitis C, the compound had been developed up to a Phase III trial when DNDi negotiations started in 2015. DNDi negotiated a non-exclusive licence agreement from the patent owner, Presidio Pharmaceuticals, to further demonstrate the safety and efficacy of ravidasvir as a pan-genotypic treatment, used in combination with sofosbuvir, and make it available at an affordable price in LMICs. Development has been conducted in collaboration with the Egyptian company Pharco Pharmaceuticals.

Non-exclusivity was deemed essential to increase competition in the field and drive down the prices of hepatitis C treatments. However, the agreement includes, for the first time in DNDi history, the payment to Presidio of tiered royalties of 4 or 7% of net sales (based on gross national income) in the countries where Presidio holds patents on



ravidasvir. Such royalties will be borne by DNDi sub-licensees, namely the companies which will benefit from a technology transfer from DNDi and Pharco to sell ravidasvir.

The DNDi hepatitis C project was also innovative in its contribution to securing treatment access through its clinical trial co-sponsored by the Ministry of Health (MoH) of Malaysia. DAAs were not available in the Malaysian public health system when DNDi and the MoH agreed to study ravidasvir combined with sofosbuvir. Given that sofosbuvir was protected by patents in the country, DNDi and the MoH used an exception in the Malaysia Patent Act to import an affordable generic sofosbuvir for use in the clinical trial. Patent exceptions for scientific research are included in most patent laws, in accordance with the TRIPS Agreement. The government also issued a government use licence (a form of compulsory licensing) to overcome IP barriers to access to sofosbuvir in the national response to HCV.

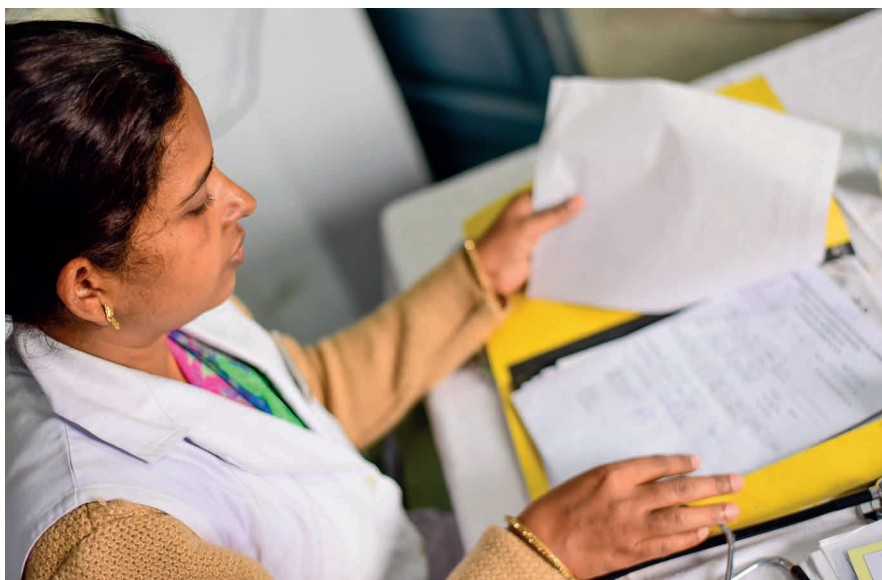
## Facilitating access through innovative regulatory strategies

Regulatory procedures have long led to serious bottlenecks for new health technologies that will be used primarily in LMICs, resulting in unequal or delayed access to the fruits of medical innovation. DNDi has used different regulatory strategies depending on the characteristics of the treatments (e.g. repurposed treatment, new combination of existing treatments, or NCE), the regulatory landscape, and the nature of alliances with industrial partners.

Regardless of the regulatory strategy used, DNDi's approach has always been guided by a desire to harness technical and scientific review that is rigorous in ensuring quality and patient safety; appropriate, in that it is able to evaluate the benefit/risk ratio in the public health context in which neglected patients will receive their treatments, with technical support as needed from so-called 'stringent regulatory authorities';<sup>29</sup> and fast, to enable rapid access to innovation for patients.

Over the past 15 years, DNDi has benefited from initiatives which have sought to increase regulatory harmonization, notably through intra- and inter-regional collaboration, converging requirements, and reducing duplication across countries, through the efforts of the African Medicines Regulatory Harmonization initiative,<sup>30</sup> for example. DNDi has also demonstrated the usefulness of mechanisms aiming to optimize the review of dossiers with the early participation of national medicines regulatory agencies (NMRAs) in endemic countries. The European Medicines Agency (EMA) Article 58 procedure, for instance, allows for an application for a 'scientific opinion' from the EMA Committee for Medicinal Products for Human Use (CHMP), in cooperation with WHO, on certain drugs intended exclusively for markets outside the EU.

New mechanisms and processes<sup>31</sup> are seeking to build information about the regulatory landscape, strengthen capacity, reduce duplication and develop solid regulatory networks within regional zones where disease prevalence is similar.<sup>32</sup>



Over the past 15 years, DNDi has benefited from initiatives which have sought to increase regulatory harmonization.

- 29 Moran M, Guzman J, McDonald A, Wu L, Omune B. Registering new drugs: the African Context. New tools for new times. The George Institute for International Health Marketing and Communications. 2010. Available at: <https://www.dndi.org/2010/advocacy/registering-new-drugs-african-context>
- 30 NEPAD. AUDA-NEPAD and WHO, joint secretariat of the African Medicines Regulatory Harmonisation Initiative. 18 Feb. 2019. Available at: <https://nepad.org/news/auda-nepad-and-who-joint-secretariat-african-medicines-regulatory-harmonisation>
- 31 Including, for example: WHO. WHO Global Benchmarking Tool for Evaluation of National Regulatory System of Medical Products. 2018. Available at: [https://www.who.int/medicines/areas/regulation/01\\_GBT\\_RS\\_RevVI.pdf?ua=1](https://www.who.int/medicines/areas/regulation/01_GBT_RS_RevVI.pdf?ua=1)
- 32 WHO. Global Benchmarking Tool for Evaluation of National Regulatory System of Medical Products. 2018. Available at: [https://www.who.int/medicines/areas/regulation/01\\_GBT\\_RS\\_RevVI.pdf?ua=1](https://www.who.int/medicines/areas/regulation/01_GBT_RS_RevVI.pdf?ua=1)

### Towards a new understanding of risk

More regulation does not necessarily mean better regulation. Raising regulatory standards above those essential for patient safety inevitably leads to increased investments, prices, timelines and inefficiency. This has led to calls for the establishment of 'essential regulatory standards'.<sup>33</sup> A process for agreeing such standards requires political as well as technical support.

### More regulation does not necessarily mean better regulation.

Equally, reducing existing regulations needs to be approached with care: while there is the potential to get fast access to treatments and to speed up the drug development process, there is a need to ensure that patient safety and public health needs, rather than commercial considerations, remain at the centre

of any review process and appropriate safeguards are in place. There are a number of existing and proposed processes such as priority reviews or conditional approvals designed to facilitate early access to priority medicines for people in need.

In 2013, the US FDA released a new guideline on a "Risk-based Monitoring Approach", significantly changing the previous approach of mandatory regular, costly monitoring visits, and opening the door to more flexible, risk-adjusted, technology-based pathways for sponsors to fulfil their monitoring obligations. The risk/benefit ratio of newer proposed regulatory mechanisms, such as adaptive pathways, have attracted controversy with concerns from academia, payers, and civil society that fast-track procedures, based on more limited initial safety data, could expose patients to unnecessary health risks and questions about how 'real-world data can be used after drug approval to allow drawing reliable conclusions on benefit and harm'.<sup>34</sup>

## Illustrations of DNDi's regulatory experience

### Combinations of existing medicines

Developed in partnership with Sanofi, ASAQ was first registered as a malaria treatment in Morocco in 2007. Morocco was chosen because the product was to be used mainly in Africa, because the NMRA had already approved an AS+AQ co-blister, and because artesunate was not registered in either the US or Europe. WHO PQ was later sought (and granted in 2008) to enable ASAQ's inclusion by countries in Global Fund tenders. In 2006, the ASAQ dossier was reviewed for virtual approval by participants from developing countries, with support from WHO and EMA experts, as a case study in a WHO training programme. ASAQ is registered today in more than 30 African countries.

### New chemical entities

In 2011, DNDi and Sanofi first had scientific advice meetings with the EMA and the US FDA to define the regulatory strategy for fexinidazole for sleeping sickness. Considering regulatory capacity in sleeping sickness-endemic countries, DNDi and Sanofi identified the EMA Article 58 procedure as the most appropriate and efficient pathway, in that it would subsequently facilitate access by ensuring participation of WHO and NMRAs. Throughout the review, the Democratic Republic of Congo (DRC) and Uganda regulatory representatives were involved, as well as the WHO NTD Department.

The protocol for the pivotal clinical trial initiated in 2012 in the DRC and Central African Republic was developed with recommendations from European regulators. In 2014, DNDi and Sanofi again requested scientific advice from the EMA to revise and update the clinical development plan. The regulatory dossier was submitted in 2017 and the positive opinion given by the EMA in November 2018, followed by registration in DRC just over a month later. This opens the way for distribution of the product by WHO to other countries. Fexinidazole was also prequalified by WHO and added to the WHO Essential Medicines List in 2019.

DNDi's clinical study in Sudan of fosravuconazole, a potential new treatment for mycetoma, will test an NCE versus a reference compound where previous experience in assessing NCEs is limited. In light of the efforts initiated by the African Medicines Regulatory Harmonization initiative to expand regulatory capacity on the continent, DNDi requested support from WHO to assist in the review of the clinical trial, ensuring participation of ethics committee (EC) and NMRA representatives from Sudan, Kenya, and Uganda. Following this positive experience, DNDi decided to test AVAREF, a new pathway for joint review in another study for new visceral leishmaniasis treatments. Similarly, the process involves EC and NMRA from Kenya, Uganda, Ethiopia, and Sudan. A web-based forum, as well as a joint meeting with all parties involved, resulted in a high-quality review of the protocol.

33 Folb P & Olliaro P. Pharmaceutical Policies and Regulatory Control. WHO Drug Information Vol. 14, No. 2, 2000. Available at: <http://apps.who.int/medicinedocs/en/d/Jh1463e/3.html>

34 O'Donnell P. Can FDA Put Some Heat Back Under European Adaptive Pathways? *Applied Clinical Trials*. 2018;27:9. Available at: <http://www.appliedclinicaltrials.com/can-fda-put-some-heat-back-under-european-adaptive-pathways>



## Advocating for an effective, equitable, and needs-driven R&D system

Since its inception in 2003, DNDi has advocated for public responsibility and public policies to address market failures and enable a more effective, equitable, and needs-driven global biomedical R&D system. DNDi advocates for a sustainable global framework for R&D that ensures innovation and affordable access to new health technologies for all.

In the past decade, the issues of medical innovation and access to medicines and other health technologies have been on the political agenda like never before. The 2014 Ebola crisis highlighted the dire lack of treatments and vaccines for epidemic-prone diseases; increased concerns among new constituencies and coalitions of countries (not only in LMICs but also in the US and Europe) about the high prices of drugs have thrown into greater relief the need for transparency in drug pricing and R&D costs, and the right to use TRIPS flexibilities to overcome barriers to access<sup>35</sup> while strengthening calls for a 'public return' on public investments in R&D; and the global crisis of antimicrobial resistance (AMR) and the lack of new antibiotics has pointed to major deficiencies in the existing business model for pharmaceutical R&D. During this period, the policy debate has expanded at the multilateral level, from discussions at WHO on public health, innovation, and IP to high-level meetings at the UN General Assembly, and is also accelerating at regional and national levels.

DNDi has joined MSF and other NGOs, civil society organizations, key governments, and opinion leaders to bring increased attention to the failures of the current system and has offered lessons learnt from its own experience to inform global debates. Writing in *PLoS Medicine* in May 2015, DNDi and a group of renowned global health experts called for the creation of a global health R&D fund and mechanism to address deadly gaps in innovation for emerging infectious diseases such as Ebola, AMR, and a host of other diseases that have been neglected by the pharmaceutical market.<sup>36</sup> DNDi continues to highlight concerns about the fragmented approach to biomedical R&D and has advocated that policymakers 'join the dots' and implement policies in five major domains:

- a global body to identify R&D needs;
- globally-agreed public health-driven R&D priority-setting;
- coordination of R&D efforts to reduce duplication;
- sustainable financing for public health-driven R&D; and
- globally-agreed norms that guide R&D initiatives in a way that encourages collaboration over competition and ensures affordability of end products.

### Important progress has been made

At the intergovernmental level, the creation of the WHO Global Observatory on Global Health R&D is a first important step in collecting evidence on R&D to guide policymaking. In addition, the Health Product Profile Directory, created and developed by TDR on behalf of WHO is a global public good to

DNDi advocates for a sustainable global framework for R&D that ensures innovation and affordable access to new technologies for all.

35 This includes, for example, the use of compulsory licensing by Malaysia, strong positioning on the need for more affordable medicines by the Netherlands and Colombia, and other indications of a growing commitment in this area in Argentina, Austria, Germany, India, Japan, Portugal, Japan, South Africa, and the US.

36 Balasegaram M, Bréchet C, Farrar J, Heymann D, Ganguly N, Khor M, Lévy Y, Matsoso P, Minghui R, Pécoul B, Peilong L, Tanner M, Røttingen JA. A global biomedical R&D fund and mechanism for innovations of public health importance. *PLoS Medicine*. 2015;12(5):e1001831. Available at: <https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001831>

improve the efficiency of efforts to develop new products for neglected diseases and populations as well as threats to global health.<sup>37</sup>

The 2012 report of the WHO Consultative Expert Working Group on R&D Financing and Coordination (CEWG)<sup>38</sup> has led to the definition of what have come to be known as the 'CEWG principles' – affordability, effectiveness, efficiency, and equity, all based on the principle of 'delinkage'<sup>39</sup> – which have become a benchmark of norms to be applied to R&D financed in the public interest.

Several expert groups and multilateral policy fora, including the UN High-Level Panel on Access to Medicines, which released its final report in 2016,<sup>40</sup> and a series of health-related UN high-level meetings in New York, including those on AMR,<sup>41</sup> non-communicable diseases,<sup>42</sup> TB,<sup>43</sup> and Universal Health Coverage (UHC),<sup>44</sup> have all concluded with political declarations that include important commitments made by governments related to investing in R&D for new health technologies, and ensuring equitable and affordable access to these technologies.

DNDi has also engaged in policy advocacy and convened meetings with funders of biomedical R&D that seek to maximize the impact of their investments in R&D through policies to promote open science, transparency, and access. An increasing number of R&D funders, both public and philanthropic, are giving consideration to ensuring equitable and affordable access to products and revising grant agreements accordingly – integrating, for example, access clauses. In Europe, biomedical R&D funding initiatives have adopted a 'Three Os' approach (Open Innovation, Open Science, and Open to the World) that favour the reorientation of R&D towards collaboration.<sup>45</sup>

### **Innovation and access in the context of UHC and the SDGs**

The Sustainable Development Goals (SDGs), adopted by all UN Member States in September 2015, includes a 'health goal', SDG 3.<sup>46</sup> In addition to several disease-



specific targets, this goal includes targets on innovation in and access to essential diagnostics, medicines, and vaccines. In addition, the goal of UHC by 2030 has become the centrepiece of WHO Director-General Dr Tedros' priorities for the organization<sup>47</sup> and was the focus of a UN high-level meeting in September 2019.

DNDi contributed in several policy fora to highlight that UHC cannot be achieved unless new health tools and technologies are discovered, developed, and delivered. There is indeed growing consensus that neither UHC nor the broader goals of SDG 3 will be achieved without a massive effort to overcome the technology gaps that currently exist – particularly for tools developed specifically for the people and places that need them most and that can be implemented at the primary care level.

Progress for the poorest and most vulnerable populations, including those with NTDs, children, and key populations, will be a 'litmus test' of equitable advances in UHC, particularly in relation to innovation in and access to health technologies. A global action plan has been developed unifying 12 agencies to increase coordination and accelerate the implementation of SDG 3, encompassing innovation and access, including through the development of access principles.

37 TDR-WHO. Health Product Profile Directory. Available at: <https://www.who.int/tdr/diseases-topics/product-directory/en/>

38 WHO. Consultative Expert Working Group on Research and Development: Financing and Coordination. 20 April 2012. 65th World Health Assembly, Document A65/24. Available at: [http://apps.who.int/gb/CEWG/pdf\\_files/A65\\_24-en.pdf](http://apps.who.int/gb/CEWG/pdf_files/A65_24-en.pdf)

39 Delinkage describes the idea of removing the link whereby monopoly-based high drug prices are used to recoup R&D investments, by creating alternative incentives based upon cash rewards, and a combination of grants, contracts, tax credits, and other subsidies. Delinkage would transform the business model of the pharmaceutical industry in order to expand access, improve outcomes, and reduce costs.

40 UN. United National Secretary-General's High-Level Panel on Access to Medicines Report, Promoting Innovation and Access to Health Technologies. 14 Sept. 2016. Available at: <http://www.unsgaccessmeds.org/final-report>

41 UN. Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance. 22 Sept. 2016. Available at: [https://www.un.org/ga/search/view\\_doc.asp?symbol=A/71/L.2&referer=/english/&Lang=E](https://www.un.org/ga/search/view_doc.asp?symbol=A/71/L.2&referer=/english/&Lang=E)

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## Fexinidazole – a brand new medicine for the most neglected



The development of fexinidazole – the first all-oral treatment for human African trypanosomiasis (HAT, more commonly known as sleeping sickness), and the first new chemical entity to emerge from DNDi's portfolio – is the best illustration of the organization's alternative, not-for-profit R&D model.

Sleeping sickness occurs primarily in the poorest, most remote rural areas in Africa, affecting people who are arguably among the most neglected and most excluded from medical innovation. The disease is almost systematically fatal if left untreated, and for decades, the only treatment available was melarsoprol, an arsenic-based drug so toxic that it kills one in 20 patients and is so painful to receive that patients describe it as "fire in the veins."

Developing a new treatment for sleeping sickness was part of DNDi's mission from the outset. A target product profile was defined with experts, including members of the HAT Platform, especially from DRC, home to more than 80% of the world's sleeping sickness cases.

DNDi's short-term strategy was to develop a combination of two existing drugs, nifurtimox and eflornithine. Together with Epicentre, MSF, and with support from WHO, Bayer and Sanofi, the nifurtimox-eflornithine combination therapy (NECT) was launched in 2009 and was the first new treatment option for sleeping sickness

in 25 years. Nearly 100% of diagnosed patients with sleeping sickness have received NECT instead of melarsoprol, bringing significant therapeutic benefit to patients. But NECT is by no means perfect: it still requires hospitalization and sophisticated health staff, multiple painful infusions of eflornithine, a lumbar puncture to determine disease stage (it is only effective against the second, deadly stage), and it is burdensome to ship, store, and administer.

DNDi's long-term strategy was guided by the TPP and sought to deliver an all-oral treatment that works for both stages of the disease, meaning patients could potentially avoid systematic hospitalization and painful lumbar puncture.

### **Partnering for success, throughout the drug development pipeline**

Through an extensive compound mining exercise, more than 700 compounds from 15 different sources in academia and industry were screened, in collaboration with the Swiss Tropical & Public Health Institute. These

efforts led to the identification of fexinidazole, which had been in pre-clinical development as a broad-spectrum antiprotozoal drug by Hoechst AG (now Sanofi) since the 1970s (so no IP protection hampered the development of fexinidazole). In 2009, DNDi and Sanofi partnered, with DNDi responsible for pre-clinical, clinical, and pharmaceutical development, and Sanofi responsible for industrial development, registration, and production. After several years of pre-clinical and Phase I trials, DNDi began a Phase II/III pivotal clinical study in DRC and Central African Republic in 2012.



Phase I and preclinical data were published,<sup>47</sup> as were the final results of the Phase II/III study,<sup>48</sup> which showed high efficacy and safety of fexinidazole. Then, in November 2018, the treatment landscape for sleeping sickness fundamentally changed when the EMA provided a 'positive scientific opinion' of the world's first all-oral cure for both stages of the disease (see below for further details). Just over a month later, fexinidazole was approved for use in DRC.

### Supporting the development of new research ecosystems

For many of the clinics involved, it was their first experience conducting a clinical trial. Close collaboration with national sleeping sickness control programmes and the HAT Platform helped overcome the significant

challenges to conducting, in such remote areas, clinical research compliant with international ethical and scientific quality standards.

Clinical research and health system capacity was strengthened through infrastructure improvements – with nine rural district hospitals renovated with solar panels and generators, internet and satellite connections, waste management, and specific medical equipment – creating lasting improvements to the health system that have benefitted clinicians and patients alike. Training was provided to more than 200 researchers, monitors, and practitioners in Good Clinical Practice, universal standard precautions, laboratory diagnosis, patient examination techniques, laboratory procedures, treatment algorithms, pharmacovigilance, and waste management.

### Ensuring rapid access through an innovative regulatory strategy

The regulatory strategy adopted by DNDi and Sanofi was chosen in order to facilitate access, by ensuring participation of WHO endemic countries' NMRAs. Based on the EMA Article 58 procedure, this strategy is detailed on page 32.

### The road to sustainable elimination

DNDi now plans to work hand-in-hand with the national sleeping sickness control programme and key partners in DRC and other endemic countries to introduce and scale up access to fexinidazole, including at the primary health care level, integrating screening, diagnosis, care and treatment into routine health services – and also complete clinical trials for an additional single-dose cure currently in development. Together with fexinidazole, this new medicine, acoziborole, will be the treatment cornerstone of efforts to ensure the sustainable elimination of sleeping sickness.

**DNDi wishes to thank its main R&D partners in the fexinidazole project:** Sanofi, Swiss Tropical and Public Health Institute, HAT Platform, Médecins Sans Frontières, National Control Programmes of DRC, CAR and Guinea, World Health Organization NTD department, Institute of Tropical Medicine Antwerp, Institut National de Recherche Biomédicale de RDC, Institut de Recherche pour le Développement France, Aptuit, SGS, Bertin Pharma (now AmatsiAquitaine), BIOTRIAL, Cardiabase, CBCO DRC, Accelera, Phinc, BaseCon A/S, Bruno Scherrer.

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# CONCLUSIONS



Over the past two decades, several innovative R&D models, including not-for-profit R&D organizations like DNDi, have emerged in order to address a dual failure: the failure of the market to respond to, prioritize, and ensure R&D investments in the needs of patients who do not necessarily represent a 'lucrative market', and the compounding failure of public policy to rectify this unacceptable situation, which has meant millions of people cannot benefit from scientific progress and medical advances.

As has been described throughout this paper, DNDi, as just one small part of this landscape, has – thanks to its founders, partners, and donors – demonstrated that such an alternative model is feasible and can deliver for neglected populations. Eight new treatments have been discovered, developed, and delivered – reducing illness, suffering and death for millions of people – and the pipeline for some of the world's most neglected diseases has started to be replenished, thanks to long-term investments in drug discovery.

The critical ingredients for success have been: ensuring that patients' needs and therapeutic impact are the driving force of R&D efforts; safeguarding scientific and financial

independence in all priority-setting and decision-making; fostering innovation by relying on robust cross-sectoral partnerships and piloting cooperative approaches to R&D that promote collaboration over competition and encourage the greatest possible sharing of research knowledge, data, and costs; facilitating scientific exchange and supporting public leadership for the creation or nourishment of new innovation ecosystems, particularly in LMICs; ensuring access is prioritized at all stages of the R&D process in order to make sure treatments are affordable, available, and adapted to the communities who need them most; and piloting new, potentially transformative approaches to R&D that could help support the emergence of a more effective and equitable global biomedical R&D system.

**The challenges are many and the gains of the past two decades are fragile.**

After a period of tremendous growth in global health financing from 2000-2010 – a 'golden era', during which billions of dollars were mobilized to support programmes in LMICs primarily for HIV/AIDS, tuberculosis, malaria, and maternal and child health,

leading to tens of millions of people receiving treatment or vaccines, and unprecedented declines in under-five mortality, for example – the growth trend appears to be waning. Although there was a successful Global Fund replenishment conference in Lyon, France, in October 2019, according to the Institute for Health Metrics and Evaluation (IHME), from 2010-2017, total growth in development assistance for health was 1% annually, compared with an annual growth of 11.2% during the period 2000-2010 – a 90% reduction.<sup>49</sup>

At the same time, the rapidly changing and volatile political environment, particularly the rise in nationalism across the globe, threatens multilateral initiatives and other investments in global health, including bilateral overseas development assistance, and further marginalizes or directly targets vulnerable populations, such as migrants, those living in extreme poverty, and women and girls – leading to persistent or new unmet medical needs.

### Key questions remain for DNDi and other global health R&D actors concerned about the sustainability of a more needs-driven innovation system that guarantees equitable and affordable access to new health technologies.

Meanwhile, emerging infectious diseases and epidemic-prone diseases, non-communicable diseases, and antimicrobial resistance all loom large as massive global public health challenges. Science denialism is leading to a resurgence of diseases eliminated long ago. And the unprecedented scale and magnitude of the climate crisis will exacerbate these challenges and lead to an increase in vector-borne, water-borne, and other climate-sensitive diseases. Responding to these challenges will require a redoubling of efforts to discover, develop, and deliver new health tools. But while the need to address technology gaps that hamper effective diagnosis, treatment, and prevention of diseases is gaining prominence in discussions about UHC and the SDGs, the risk of fragmentation in the absence of an overarching and sustainable framework to govern and drive public interest R&D hampers progress.

New constituencies and coalitions of countries are emerging on innovation and access issues, driven in large part by concerns about high drug prices, regardless

of disease area or country income level, as well as lack of transparency in drug pricing and R&D costs. Exorbitantly priced cancer and hepatitis C treatments, for example, are destabilizing publicly financed health systems, even in Europe<sup>50</sup> and North America, and pushing privatized systems to a breaking point, leading to public outcry for a greater ‘public return on public investments in R&D’ and increased pressure on companies, payers, and governments to take action on drug prices.

Key questions remain for DNDi and other global health R&D actors concerned about the sustainability of a more needs-driven innovation system that guarantees equitable and affordable access to new health technologies: What national, regional, and international mechanisms need to be put in place to steer biomedical innovation so that it responds to priority needs? What will be the new sources of funding that will sustain needs-driven innovation, access, and delivery? What ‘safeguards’ need to be in place to encourage collaboration, openness, and transparency, and ensure innovations of public health importance are affordable and accessible to all? What new economic models for financing R&D, including incentive mechanisms, will emerge, and will such incentives be directed at the right players at the right stage of the R&D process to ensure innovation and sustainable access? What new areas of collaboration can be explored to mutualize resources and address persistent ‘access bottlenecks’, such as manufacturing, registration, and supply, and how can existing procurement and distribution systems be better leveraged? Are new technologies that have the potential to radically transform human health and human lives being designed or implemented with equity in mind? What new opportunities exist to further develop south-south and triangular partnerships, which foster the creation of approaches to R&D and ‘knowledge hubs’ led by LMICs?

Looking ahead to the next decade, global health R&D stakeholders will need to confront these challenges head-on. For its part, DNDi pledges to do so with a renewed commitment to addressing the needs of neglected populations, a willingness to continue to test novel approaches to R&D that can accelerate innovation in the public interest, and a steadfast commitment to sharing its experience in order to support the emergence of a more effective and equitable biomedical innovation system – one that delivers affordable and accessible treatments and other health tools designed specifically for the people and places that need them most.

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