INVESTING IN THE DEVELOPMENT OF NEW ANTIBIOTICS AND THEIR CONSERVATION

A PROPOSAL FOR A GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT FACILITY TO PROMOTE RESEARCH, RESPONSIBLE USE, AND ACCESS TO NEW ANTIBIOTICS

UPDATED CONCEPT NOTE[1]
18 DECEMBER 2015

EXECUTIVE SUMMARY

The WHO Global Action Plan on Antimicrobial Resistance (GAP-AMR) calls for the creation of new partnerships to foster the development of new antibiotics. To implement this part of the GAP-AMR, WHO and DND*i* propose the creation of a **'Global Antibiotic Research and Development Facility', an independent product development partnership,** to develop new antibiotic treatments addressing antimicrobial resistance and to promote their responsible use for optimal conservation, while ensuring equitable access for all in need.

The Facility will work closely with all stakeholders in the field of antibiotic research and development (R&D) – including pharmaceutical and biotechnology companies, startups, other product development partnerships, academia, civil society, and health authorities – from countries of all income levels to develop new antibiotic treatments. It will:

- address global public health and specific needs of low- and middle-income countries;
- target products that industry will not develop due to foreseen lack of profitability;
- pilot the use of alternative incentive models that support conservation of and access to new antibiotics based on DND*i*'s experience in implementing alternative R&D models for neglected diseases; and
- ensure that new antibiotics are affordable to all in need.

In the short term, the Facility will start by identifying priorities for the development of new antibiotics and antibiotic regimes not addressed by other actors. Based on this analysis, it will launch short-term R&D projects to develop needed new therapeutic solutions, such as missing paediatric formulations, combinations, new formulations, or improved regimens of existing antibiotics. In the long term, the Facility will develop a broader portfolio of new antibiotic treatments and see them through to registration. Carefully aligned with existing initiatives that invest in new antibiotics, the Facility's uniqueness lies in addressing global public health needs and placing emphasis on products or projects that industry does not invest in.

On 1 December 2015, the DND*i* Board of Directors agreed to facilitate the set up and host the Facility for the start-up phase (initial two years) and to provide the scientific environment and infrastructure to ensure an effective incubation period.

[1] The Concept Note was revised to reflect the discussions during the technical consultations held at WHO on 13 November 2015.

World Health Organization

DNDi Drugs for Neglected Diseases *initiative*

OUTLINE OF THE GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT FACILITY

There is general agreement that no single measure will solve the lack of R&D for new antibiotics. A partnership model for product development based on the experience with neglected diseases is an important element of the overall strategy. Such a partnership can test alternative incentives that also contribute to conservation of and access to new antibiotics such as milestone prizes, buy-outs, and staggered end-stage prizes/payments. By doing so, a product development partnership will provide an important alternative to the traditional profit-oriented pharmaceutical approach.

VISION

In cooperation with the public and private sectors, develop new antibiotic treatments addressing antimicrobial resistance and promote their responsible use for optimal conservation while ensuring equitable access for all by setting up an international public-private partnership that will focus on global health needs.

A THREE-PRONGED APPROACH

The Facility will pursue three parallel objectives:

1. **Research and product development:**
   - develop improved formulations or combinations that may prolong the life of existing antibiotics through short-term product development projects;
   - work with partners on rapid and (near) point-of-care diagnostics; and
   - support innovative and paradigm-shifting approaches to the development of new antibiotics.
2. **Conservation:**
   - directly build in conservation strategies in the R&D process; and
   - propose conservation strategies for antibiotic treatments, taking into account issues related to animal husbandry.
3. **Access:**
   - implement and test new incentive models enabling the de-linkage of the cost of R&D from the price of the product; and
   - promote access for all in need, while minimizing unnecessary and non-rational use.

GUIDING PRINCIPLES

The work of the Facility will be based on the following principles:

- New antibiotics have to be affordable and should be subject to a global conservation agenda.
- There is a need for a global mechanism to finance and conserve new antibiotics. Public investment into development of new antibiotics should come with appropriate obligations to governments, regulators, producers, and distributors with respect to the marketing and responsible use of these new products to avoid the rapid build-up of drug resistance.
- Sustainable investment should be coordinated at country and international level to avoid dispersion of resources.
- R&D should focus on the most significant drug-resistant bacterial infections to answer global priority public health needs.
- Science shall be the sole driver and determine the fate of supported projects to promote highly innovative approaches.
- The governance model shall ensure appropriate representation of all relevant stakeholders and preserve the necessary independence of the Facility.

THE ROLE OF DND*i*

DND*i* will host, for the incubation period, the Facility's personnel and provide necessary infrastructure to set up activities rapidly. An initial start-up team will be constituted at DND*i* and will report to the countries and institutions accepting to finance the start-up phase. Ultimately, the team will include professionals with backgrounds in public health, biomedical research, infectious diseases, health economics, antimicrobial research and development, product formulations, business development, financing, drug markets, and drug regulation.

THE ROLE OF WHO

WHO will facilitate the incubation of the new Facility in line with the mandate provided by the GAP AMR. WHO will have no active role in the daily work of the Facility nor will the Facility be hosted by WHO. However, WHO will provide technical input where needed, including on the identification of global needs, financing strategies, target product profiles, and conservation strategies. In WHO, one person will act as the liaison for the Facility. Under the GAP-AMR, WHO will also develop options for a global framework for development and stewardship of new antibiotic treatments. As part of the implementation of the GAP-AMR, WHO will report on the R&D pipeline and current R&D initiatives in the area of antibiotics. The data will feed into the WHO Global Observatory on Health R&D.

WORK STREAMS AND DELIVERABLES OF THE FACILITY

During the start-up phase of two years, the initial team hosted by DND*i* is going to focus on the priority work streams listed below.

WS 1. SCIENTIFIC

- Identify short-, medium-, and long-term projects (see examples below) to develop antibiotic treatments that industry or others will not undertake due to high risks of failure or lack of commercial incentive, taking into account the need for appropriate diagnostic approaches.
- Identify global priority needs and develop priority target product profiles (TPPs), taking into account work already done. TPPs will prioritize infections threatening large populations worldwide, assure suitability in resource-limited settings and attempt to anticipate AMR evolution.
- Constitute a working group of experts in basic and applied microbiology, clinical microbiology, antibiotic development, patient care, diagnostics, and public health to provide advice.

WS 2. BUSINESS DEVELOPMENT

- Secure initial partnerships with start-ups, universities, research agencies, biotechnology and pharmaceutical companies, and contract research organizations to initiate collaboration on specific projects.
- Connect and coordinate activities with existing scientific and business networks and advocacy groups to ensure complementarity and identify synergies.
- Explore alternative incentive models that support conservation of and access to new antibiotics.
- Identify the appropriate legal form of the Facility.
- Develop strategies to build conservation into the R&D of new products.
- Develop an access-driven intellectual property policy.
- Establish a full business plan for the Facility.

WS 3. ADVOCACY AND FINANCING

- Engage in advocacy to support conservation, responsible use, new R&D models, and incentives.
- Engage with all possible donors and investors, and develop and test innovative financing mechanisms to secure financial support.
- Define the financial needs to support the initial product portfolio and related activities and the longer term financial needs (business plan).

WS 4. GOVERNANCE STRUCTURE

- Develop a governance model that prioritizes a global health approach, represents patients' needs, obtains the support of governments, and ensures independence.
- Identify potential individuals for the Board of Directors and Scientific Advisory Board.

SCIENTIFIC STRATEGY

SCIENTIFIC GOAL AND AIM

The overall goal of the Facility is to reduce mortality and morbidity due to important bacterial infections, especially those where drug resistance is an increasing problem. Central to this is the concept that patient care can be improved through the development of new tools or by optimization of existing tools. For example, in the case of malaria, significant improvement in care and delay of emerging resistance has been achieved through drug combination use, new fixed-dose combinations including paediatric formulations, and rapid diagnostic tests. The scale-up of these new products was facilitated by The Global Fund to Fight AIDS, Tuberculosis and Malaria. Unfortunately, no such scenario exists for antibiotics. Thus, the management of many bacterial infections, often presenting as main syndrome fever, remains empirical. Restricting use alone is not the answer in low- and middle-income countries where still more children die from lack of access to treatment than from drug resistant bacteria. Determining whether a sick infant needs an antibiotic is complicated by a lack of simple diagnostic tests and appropriately adapted quality assured formulations.

Currently, there is a growing risk of drug resistance in important pathogens causing (gram-negative) sepsis and diseases such as typhoid and gonorrhea. In low- and middle-income countries, neonates and children are particularly vulnerable sub-groups. Insufficient work is done to address these needs. The Facility will focus on these global health needs, address specific barriers to improving patient care, and promote responsible use of antibiotics.

PORTFOLIO APPROACH

The Facility will develop a portfolio approach to:

- improve and prolong the use of current antibiotics;
- exploit 'low-hanging fruits' to improve the management of neglected bacterial infections; and
- explore innovative approaches to tackling AMR.

These three objectives can be broken down to short-, medium-, and long-term projects that will be further elaborated below.

INTERVENTIONS

The objectives can be translated into possible interventions. The Facility will endeavor to:

- develop better paediatric formulations (form, dosage, shelf-life);
- develop new formulations of existing drugs (appropriate dosage, administration route);
- review and possible re-engineer 'forgotten' antibiotics;
- develop combinations of existing drugs to address AMR;
- facilitate clinical trials in low and middle-income countries of relevant antibiotics that are in the R&D pipeline;
- explore innovative but risky projects, including adjuvants', anti-virulence, dormancy breakers, biomodulators, or phages that venture capital and industry are not financing;
- promote with partner organizations (such as the Foundation for Innovative New Diagnostics - FIND) the development of diagnostics that can optimize the use of new and current antibiotics; and
- jointly with WHO, develop and test new approaches to conservation.

The Facility will ensure its work does not duplicate that of other initiatives and organizations. It will also ensure that relevant research ongoing in existing spheres can be appropriately transferred to meet low- and middle-income country needs and contexts. Active partnerships will play a key role in translating proposed interventions into concrete outcomes.

PROJECTS

Below is a summary of ideas for projects. These ideas are 'placeholders' to demonstrate the potential scope of the Facility, but have not yet undergone a thorough scientific review. More work needs to be done to develop a complete rationale for these and additional projects to be examined in the coming months. Projects will be developed according to disease priorities, but also according to gaps and opportunities, especially for already-existing antibiotics.

MEDICINES

- Paediatric/reformulations: improved paediatric formulation of Amoxicillin/clavulanic acid, rectal antibiotic for community-based neonatal sepsis (ceftriaxone)
- Improve paediatric formulation of fusidic acid, streptomycin, or colistin for resource-limited settings

DISEASES

- Typhoid fever: combination treatments, repurposed drugs
- Melioidosis: accelerate the development of an existing new chemical entity (NCE) outside of bio-threat use for affected developing countries
- Gonorrhea: accelerate development of an existing NCE for developing country use (formulation), including in HIV-positive patients
- Gram-negative infections: from repurposing to potential innovative approaches

APPROACHES

- Develop (open access) combination screening platforms
- Develop (open access) in vivo platforms
- Develop (open access) platform for improved formulations
- Support disruptive scientific approaches (e.g. anti-virulence) that are too risky for venture capital and industry
- Promote, with partner organizations, the development of diagnostics that can optimize the use of new and current antibiotics

While the main focus of the Facility will be on drug development, it will also collaborate with institutions such as FIND to accelerate the development of important diagnostic tests for resource-limited settings. Such examples could include a rapid diagnostic test that can differentiate bacterial and viral infections, a multiplex (fever) test to accurately diagnose important bacterial infections, and tests that can accurately identify resistance to specific antibiotics. Such potential tests already have analogies such as a rapid diagnostic test for malaria or the assay for the simultaneous detection of tuberculosis and rifampicin resistance directly from sputum. WHO, both through one of its demonstration projects[2] and with FIND, is building target product profiles to accelerate development of such AMR-relevant diagnostics. Potential diagnostic tests may also be important for identifying future epidemiological trends and hence needs, and accelerating the clinical testing of new antibiotics.

In summary, the Facility, from a scientific perspective will add value by:

- covering neglected areas, e.g. combination and reformulation work that is unlikely to be undertaken by either industry or current research programmes;
- facilitating clinical trials in low- and middle-income countries of relevant antibiotics that are in the R&D pipeline (e.g. gonorrhea);
- providing open access to platform tools for the research community; and
- supporting projects that are lacking sufficient financial incentives, or are too risky for investors.

CONSERVATION

Developing new antibiotic treatments will only have a lasting impact if we change the way we use them. The fact that traditional market incentives will not guide the development strategies of the Facility will allow for a public health needs focus. It will also allow for taking conservation into account in the design of the R&D pipeline, so that conservation and access are built together into the product development. When bringing products to the market, the Facility, with its industry partners, will develop innovative approaches in packaging and labelling that support responsible use.

The Facility will develop an access-driven IP policy for newly developed tools, and support controlled distribution and appropriate use of new antibiotics.

[2] http://www.who.int/phi/implementation/ANDI_ChinaNDI_documents.pdf

DELIVERABLES, TIMELINES, AND APPROXIMATE INITIAL BUDGET

Years 1-2: Activities and deliverables will include

- Identification of short-term, medium-, and long-term research projects ready to be initiated during this period
- Identification of the appropriate legal form and governance of the Facility and establishment of an independent legal entity
- Development and publication of priority TPPs
- Set up of a working group and steering committee, comprised of public and private partners engaged with the Facility
- Development of a sustainable funding model
- A full business plan and budget of the Facility for a minimum 5-year period
- Human Resources plan and expansion to further strengthen the team
- Develop a monitoring and evaluation (M&E) framework

WHO will develop options for a global development and stewardship framework; develop an overview and analysis of the R&D pipeline that will feed into the WHO Global Health R&D Observatory; and provide an overview of current R&D initiatives in the area of antibiotics.

Years 3-5: Activities and deliverable will include

- Initiate implementation of short-term projects and implement new projects identified through the preparatory work
- Implement the business plan, including innovative R&D proposals
- Secure additional funding to support implementation of business plan
- Establish a Board of Directors and a Scientific Advisory Committee

WHO will pursue the implementation of the Global Action Plan, including conservation strategies.

BUDGET

Seed funding of 3 million EUR is required for the start-up phase (two years) based on the assumption that four to six full-time members are needed to build the core team. This budget covers salaries of the start-up team that will be hired within the DND*i* infrastructure, some overheads (mainly IT/Telecommunication, travel, consultancies, meetings), and the initial activities for selected short-term projects. It will also cover the resources required to raise further funding for new projects and the subsequent phases of the Facility.

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ANNEX

CONTEXT

Antimicrobial resistance (AMR) is a major public health challenge. It compromises global human development, threatens the achievements of modern medicine, and undermines economic development and stability of social systems. AMR affects all countries regardless of their economic classification. The combined result of increased bacterial resistance against current antibiotics and the lack of research to identify new classes of antibiotics threatens human health at a global level. Industry mostly abandoned the field of antibiotic R&D because of its limited financial attractiveness, the scientific challenges inherent to antibiotic drug discovery, and the complex regulatory framework. This has partly contributed to the emergence of untreatable, multi-resistant strains of pathogens that are killing an increasing number of people worldwide. The need for new measures and incentives to overcome bottlenecks in the development of new antibiotics is widely recognized.

WHY A NEW INITIATIVE?

A number of initiatives have been launched in the past years that aim to reinvigorate the antibiotic R&D pipeline. While this development is positive, even taken together, the initiatives still fall short of providing all the necessary tools to cope with the magnitude of the public health challenges faced today. In June 2015, the G7 therefore identified a need to:

> *'engage in stimulating basic research, research on epidemiology, infection prevention and control, and the development of new antibiotics, alternative therapies, vaccines and rapid point-of-care diagnostics'.*[3]

In October 2015, the G7 Ministers of Health declared that they will:

> *'explore the feasibility and need of setting up a global antibiotic product development partnership for new and urgently needed antibiotics, vaccine development, alternative therapies and rapid point of care diagnostics and seek collaboration with […] WHO and Drugs for Neglected Disease initiative (DNDi)'.*

The Facility is also a response to many other calls to action that recognize that no single initiative will be enough to address the AMR problem:

- The European Joint Programming Initiative on Antimicrobial Resistance recommends the creation of 'incentives for the development of new antibiotics, and alternatives for antibiotics such as vaccines';
- Action on Antibiotic Resistance (ReAct), an independent global network, advocates for increased investment in R&D of new antibiotics;
- The ongoing UK Independent Review on Antimicrobial Resistance, chaired by Jim O'Neill, calls for a global fund to finance research for new antibiotics;
- A 2014 Report to the US President on Combating Antibiotic Resistance recommended the creation of new incentives for the commercial development of new antibiotics through partnerships with industry;
- In 2014, the Lancet Infectious Diseases Commission called for a 'new sustainable global model for the discovery, development, and distribution of new antibiotics';
- In the same year, the World Alliance Against Antibiotic Resistance called for 'new economic business models to support the cost of innovation, while safeguarding public health interests'.

[3] http://www.bmg.bund.de/fileadmin/dateien/Downloads/G/G7-Ges.Minister_2015/G7_Health_Ministers_Declaration_AMR_and_EBOLA.pdf

HOW DOES THE FACILITY RELATE TO THE WHO GAP-AMR?

In May 2015, the Sixty-eighth World Health Assembly adopted the Global Action Plan on Antimicrobial Resistance (GAP-AMR). The GAP-AMR points out that:

> *'no major new class of antibiotics has been discovered since 1987 and too few antibacterial agents are in development to meet the challenge of multidrug resistance'.*

It calls for new concepts for providing incentives to innovation and promoting cooperation between policy-makers, academia, and the pharmaceutical industry. The Facility follows precisely such a cooperative approach. More specifically, under Objective 5 the GAP-AMR requests the WHO Secretariat to explore with Member States, intergovernmental organizations, industry associations, and other stakeholders, options for the establishment of a new partnership or partnerships to:

- coordinate the work of many unlinked initiatives aiming to renew investment in research and development of antibiotics;
- identify priorities for new treatments, diagnostics, and vaccines on the basis of emergence and prevalence of serious or life-threatening infections caused by resistant pathogens;
- act as the vehicle(s) for securing and managing investment in new medicines, diagnostics, vaccines, and other interventions;
- facilitate affordable and equitable access to existing and new medicines and other products while ensuring their proper and optimal use;
- establish open collaborative models of research and development in a manner that will support access to the knowledge and products from such research and provide incentives for investment.

The Facility addresses a number of these tasks, notably based on the outcome of two expert meetings held in 2014 with a number of representatives from Member States, intergovernmental organizations, NGOs, industry associations, and other stakeholders. This coincided with DND*i*'s new Business Plan 2015-2023, which laid the foundations for exploring new disease areas within its own portfolio and/or the possibility of incubating independent initiatives to address unmet, urgent/emerging needs. At the first meeting, hosted by WHO, experts discussed a number of options to further the development of new antibiotics and their conservation. The second meeting was held in conjunction with DND*i* to explore more specifically the possibility of using a product development partnership type of model, one of which has proven successful in the area of neglected diseases.[4] The proposed model comprises open, collaborative R&D that enables access to proprietary and non-proprietary knowledge and products in a scheme that ensures affordable access to newly developed medicines, as mentioned under Objective 5 of the WHO GAP-AMR.

The initial phase is aimed at defining, with the help of Member States, industry, academia, civil society, and other experts and stakeholders:

- the scope of the Facility;
- its governance model;
- the needs at a global level and specific gaps in developing countries;
- a set of short-term projects to be initiated, and the long-term priorities.

[4] http://www.dndi.org/images/stories/pdf_aboutDNDi/DNDiModel/DNDi_Modelpaper_2013.pdf

This work will be carried out by taking into account the emergence and prevalence of serious or life-threatening infections caused by resistant pathogens in line with the GAP-AMR Objective 5 as well as the specific needs of developing countries. The latter ensures that any new product has the necessary characteristics to respond to unmet needs worldwide and is not restricted to the health systems of some developed countries.

HOW DOES THE FACILITY RELATE TO OTHER EXISTING OR ONGOING INITIATIVES?

In recent years, several important programmes have been set up to support antibiotic research in various countries.[5]

Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients. IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. One of its priorities is antimicrobial resistance. IMI's programme, New Drugs 4 Bad Bugs (ND4BB), focuses on the scientific, regulatory, and business challenges that are hampering the development of new antibiotics. ND4BB includes, among others, the creation of a pan-European network of excellence of clinical investigation sites, basic research to tackle in particular gram-negative bacteria, the development of a specific drug discovery platform for antibiotics, and the exploration of new economic models for antibiotic development (DRIVE-AB).[6] It should be noted that these activities fall entirely under the responsibility of the pharmaceutical partners of the consortium.
Facility complementarity: The Facility will focus on the short and medium term to address certain urgent needs (see 'The Global Scientific Strategy' section below) and on the specific needs of developing countries. The work of the Facility will be coordinated in such a way as to complement the work of IMI. EFPIA, IMI's industry partner, participated in the expert meeting in December 2014, and DRIVE-AB leaders actively contributed to developing the concept for the Facility.

EU Joint Programme Initiative on Antimicrobial Resistance has been set up to pool national research efforts to spend public R&D resources more efficiently. Joint Programming is used in different areas to overcome the fragmentation of national research programmes in particular where challenges are global in nature. The development of new preventative and therapeutic approaches is only one of many areas that form part of the Joint Programming Initiative on AMR. Research priorities are set out in the Strategic Research Agenda.[7] The latter is implemented through launching joint calls for proposals to facilitate cross-border research projects.
Facility complementarity: The Facility could be one of the implementers under these EU joint calls for proposals, in particular in two priority areas of the Strategic Research Agenda that are in line with the envisaged scope: improvement of pharmacokinetics and pharmacodynamics of neglected antibiotics, and development of treatment protocols based on combination therapy using existing and new antibiotics.

US Biomedical Advanced Research and Development Authority (BARDA) directly supports companies that develop new antibiotics through its Broad Spectrum Antimicrobials Program. BARDA, for example, launched a Portfolio Facility with GlaxoSmithKline to support the development of a number of new antibiotics. BARDA actively participated in the meetings held in 2014.

[5] This is not an exhaustive list. An additional evaluation of AMR initiatives in developing countries and emerging economies will be undertaken and brought into this perspective.
[6] http://www.imi.europa.eu/content/nd4bb
[7] http://www.jpiamr.eu/activities/strategicresearchagenda/

Facility complementarity: similar to the above, the Facility will explore opportunities for cooperation with BARDA, and with its developing country focus, not only avoid any duplication of scientific efforts but potentially extend the target geographic areas of the work of BARDA.

The UK Independent Review on Antimicrobial Resistance, chaired by Jim O'Neill, was commissioned by the UK Prime Minister to analyse and propose concrete actions to tackle the global problems of antimicrobial resistance. Its final report is due in summer 2016. The Review will assess the extent to which market failure is responsible for the lack of investment in R&D of new antimicrobials and short-, medium-, and long-term interventions, which could be undertaken by governments and other funders to stimulate investment in new antimicrobials for human use.[8] In 2015, the Review published initial proposals to kick-start antibiotic drug discovery efforts at a global level. The proposals include channeling new funds into early-stage research as well as creating a fund for product development to buy out new major breakthroughs. The latter would ensure a predictable and viable market for new antibiotics and, by doing so, provide an incentive for companies to invest.[9]
Facility complementarity: The Facility fits very well into this new landscape and could become one of the implementers for R&D under the proposed R&D fund.

WHY IS DND*i* THE RIGHT ACTOR TO INCUBATE THE FACILITY?

Created as a not-for-profit R&D organization headquartered in Switzerland, DND*i* was set up by seven founding partners: the Indian Council on Medical Research; the Oswaldo Cruz Foundation, Fiocruz, Brazil; Institut Pasteur, France; the Kenya Medical Research Institute; the Malaysian Ministry of Health; Médecins Sans Frontières; and the Special Programme for Research and Training in Tropical Diseases, WHO-TDR (as permanent observer). What was initially an informal MSF group that began to bring together the then-missing evidence of the lack of appropriate treatments for underprivileged population groups, the 'Drugs for Neglected Diseases Working Group', with the Nobel Prize money from MSF, incubated DND*i* in 2003.

DND*i* has successfully developed a robust pipeline of drugs and treatments for the most neglected diseases, including 15 New Chemical Entities (NCEs) spanning early research phases up to clinical development, and has delivered six treatments. Among the latter are two artemisinin-based combination therapies (ACTs) in fixed-dose formulations for adults and children, both of which aimed at providing much needed fixed-dose combinations that were adapted to the specific needs of the patients, helped to improve patient case management, and delayed the development of resistance. Other treatments delivered include a set of treatments for visceral leishmaniasis in Asia, a combination therapy for visceral leishmaniasis in Africa, a paediatric dosage form of an existing drug for the treatment of Chagas disease, and a combination therapy for the treatment of human African trypanosomiasis. DND*i* uses a virtual R&D model, meaning that it does not own laboratories but works with partners who carry out the research on its behalf. DND*i*'s cost of development ranges from EUR 6-20 million for an improved treatment, and EUR 30-40 million for a new chemical entity (NCE). With attrition factored in, these estimates are EUR 10-40 million for an improved treatment, and EUR 100-150 million for an NCE to be developed (this does not include the in-kind contribution of pharmaceutical partners). This model has proven effective[10] and in its overall Business Plan 2003-

[8] http://amr-review.org/node/5
[9] http://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf
[10] See policy brief: 'An Innovative Approach to R&D for Neglected Patients: Ten Years of Experience and Lessons Learned by DND*i*' http://www.dndi.org/images/stories/pdf_aboutDNDi/DNDiModel/DNDi_Modelpaper_2013.pdf

2023, DND*i* estimates a budget of EUR 650 million to develop 16-18 treatments and ensure a robust pipeline for its targeted disease areas. [11]

DND*i* has given specific focus to patient needs in low and middle-income settings through a combination of long-term strategies (building a portfolio with NCEs) and short-term strategies (reformulations, new combinations, and repurposing of existing drugs). The R&D conducted has been made possible by the partnerships developed with 130 entities worldwide, including over 20 pharmaceutical companies and 9 biotechnology companies, and through the set up of three clinical research platforms, which build capacity while conducting clinical research in resource-limited settings.

As part of its business model, DND*i* adopted an access-driven IP policy,[12] has supported innovative regulatory harmonization and regulatory capacity strengthening efforts notably in Africa,[13] and promotes delinkage[14] in its agreements with pharmaceutical and academic partners by agreeing that the products resulting from the research and development projects be made available at cost of manufacture plus a small margin to ensure the sustainable production of the products, also known as 'at cost plus'.

[11] See Business Plan 2015-2023: A dynamic portfolio approach to address neglected patients' needs: http://www.dndi.org/images/stories/pdf_publications/DNDi_Business_Plan_2015-2023.pdf
[12] DND*i*'s Intellectual Property Policy: http://www.dndi.org/images/stories/pdf_aboutDNDi/ip%20policy.pdf
[13] See two reports: 'The Road to Regulatory Harmonization for Africa: Accelerating Access to Essential Medicines and Vaccines', and 'Registering New Drugs: The African context' http://www.dndi.org/advocacy/regulatory.html
[14] See policy brief: 'Transforming Individual Successes into Sustainable Change to Ensure Health Innovation for Neglected Patients: Why an Essential Health R&D Convention is Needed' http://www.dndi.org/images/stories/advocacy/DNDi_Policy_brief_CEWG_lowres.pdf