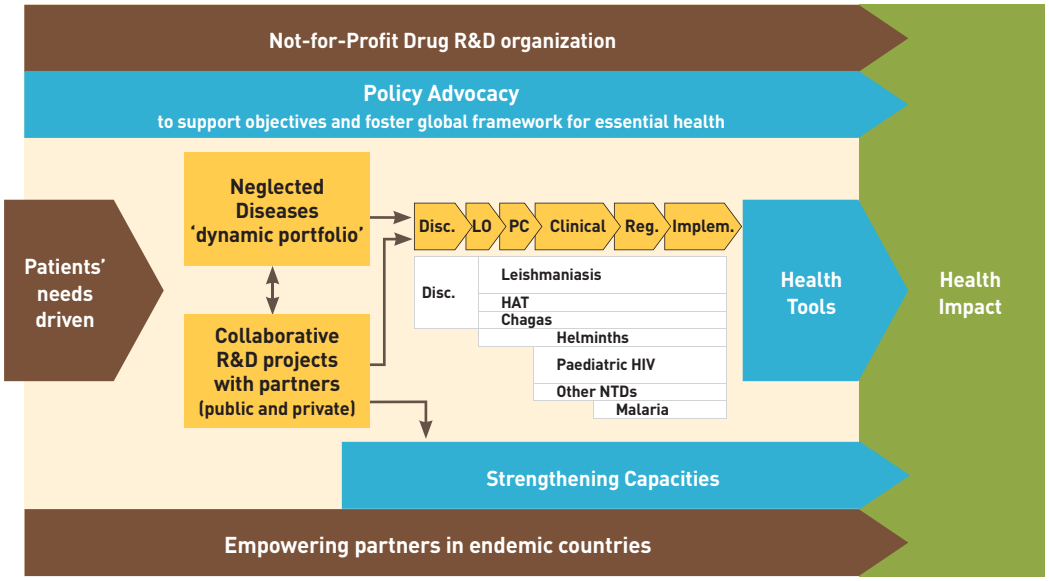
04. DND*i*'S ALTERNATIVE BUSINESS MODEL

A not-for-profit R&D organization, DND*i* builds its disease portfolio through its R&D projects. The business model can be characterized by certain distinguishing traits.

FIGURE 4. **DND*i*'S ALTERNATIVE BUSINESS MODEL**



VISION

SUPPORTING THE VISION

- Guided by and responding to the needs of neglected patients on a not-for-profit basis
- Long-term vision of empowering partners in endemic countries for sustainable change

MISSION

CARRYING OUT THE MISSION

- Advocating for policy changes to respond to patients needs
- Regional platforms to strengthen research capacities in disease-endemic countries and technology transfer where appropriate
- Delivering health tools as public goods

R&D ACTIVITIES

MANAGING R&D PROJECTS IN A DYNAMIC DISEASE PORTFOLIO

- R&D projects sourced at any stage of the pipeline
- R&D networks utilizing the best science worldwide

4.1 | A NOT-FOR-PROFIT R&D ORGANIZATION DEVELOPING HEALTH TOOLS AS PUBLIC GOODS

4.1.1 Public Goods for Health

DND*i* aims to develop treatments that meet neglected patient needs, without seeking to generate profit from its R&D efforts. As such, the products, compounds, or technologies resulting from its partnerships are conceived as public goods[1], adhering to the principles of global access to healthcare (see also Section 4.6). The resources obtained from partners and co-funders are generated through various financing mechanisms, including in-kind contributions (see Section 9 for fundraising information).

Whereas DND*i* does not seek to finance any portion of its activities through revenue linked to the commercialization of its products by third parties, it will consider – on a case-by-case basis – acquiring resources through royalty mechanisms from commercial revenues from its partners (such as ASAQ royalties from Sanofi) in a way that will not impact its vision and independence, or patients' access to the product in question. Such resources are re-injected into research projects.

4.1.2 Intellectual Property Policy

DND*i*'s intellectual property (IP) policy guides its R&D activities and associated contractual agreements with the following guiding principles:

- Treatments should be affordable to patients who need them and **access to these treatments should be equitable**
- **Drugs should be developed as public goods** whenever possible.

Although DND*i* will not necessarily be able to control all IP related to each project, the appropriate licensing rights ensuring equitable access for any treatment it develops are secured in its agreements.

In practice, freedom to operate for DND*i* is obtained through non-exclusive and sub-licensable licensing rights allowing for the execution of all R&D activities necessary to deliver products to patients, including royalty-free distribution in the public sector of disease-endemic countries. DND*i* promotes open source models at all stages of R&D.

4.1.3 New Funding Sources and Mechanisms

Despite the growing attention from public and private donors described in the previous section, funding gaps still remain. DND*i* advocates for additional funding and new mechanisms to address neglected disease R&D challenges, including:

- Funding from emerging economies;
- New funding mechanisms similar to that of the UNITAID model;
- Access to in-kind resources from pharmaceutical and drug development partners to reduce overall development and access costs;
- Creation of Milestone Prizes;
- Seeking synergy with other partners, such as PDPs, to lower overhead, share experiences and resources, and further improve cost effectiveness.

(1) In other words, no individual can be excluded from their use, and use by one person or group does not reduce their availability for another.

4.2 | BUILDING AND MANAGING A DYNAMIC DISEASE PORTFOLIO

DND*i*'s disease portfolio has primarily focused on **kinetoplastid** diseases (HAT, leishmaniasis, and Chagas disease) and malaria. Two new disease areas have been added in response to calls by international organizations and partners.

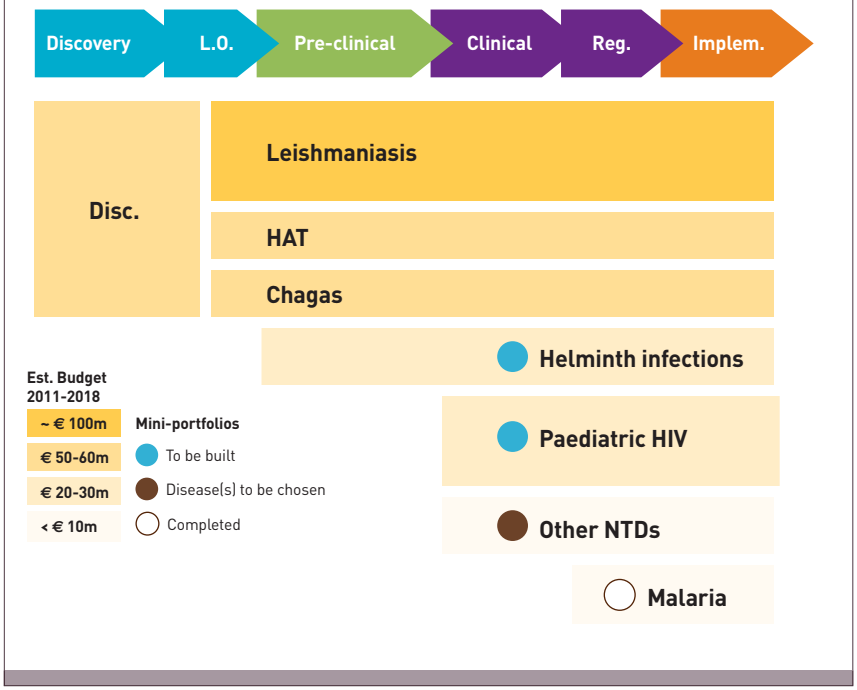
By 2018, the portfolio-related objectives are to:

- Further develop the kinetoplastid disease portfolio, including ongoing discovery activities to feed long-term objectives
- Complete the **malaria** activities and hand these over to partners by 2014
- Develop **mini-portfolios** for **paediatric HIV** and helminth infections
- Consider specific activities or mini-portfolios for other neglected diseases, should a clear need, demand, or opportunity arise, and based on DND*i*'s comparative advantage.

Unlike traditional portfolios fed with projects that span from discovery to late development stages with respect to disease-wide objectives and attrition, **mini-portfolios** are more targeted in their objectives and focus on later stage opportunities with a high potential for success.

For each disease area, DND*i* has a specific strategy, which is updated annually (for key elements of the R&D strategy, see Section 5).

FIGURE 5. **DND*i*'S DISEASE PORTFOLIO FUTURE STATE AND BUDGET IMPLICATIONS**



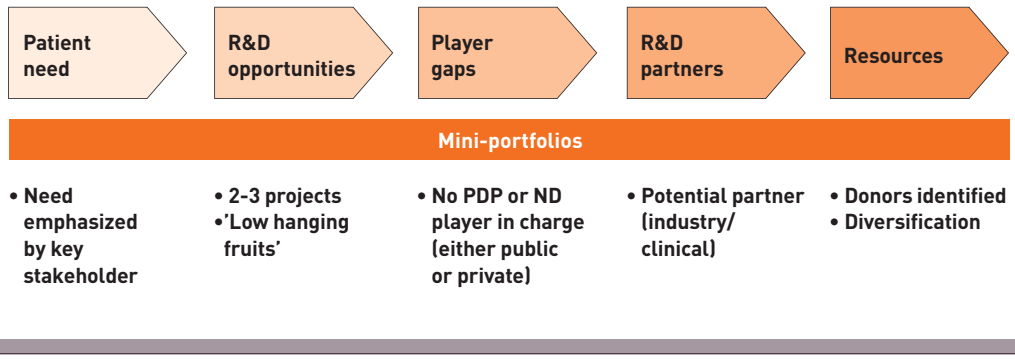
An increasingly systematized approach to decision-making, measuring outcomes, and responsiveness to patient needs will include two main areas of focus:

- Building on experience from its malaria portfolio, DND*i* will elaborate on **metrics for success** and **conditions for concluding activities** in a given disease area.
- **Systematic intelligence work** will be integrated with identification and/or monitoring of:
  - Unmet medical needs
  - Deficiencies in appropriate health tools to address these needs
  - Relevant scientific innovation and technological developments.

By doing so, DND*i* will be able to initiate new R&D projects appropriate for the needs and opportunities.

To manage its dynamic portfolio, DND*i* has developed guiding principles to select new diseases (Figure 6). New disease areas are considered on an opportunistic basis: key stakeholders and internal analyses may emphasize a specific patient need to be considered by the Executive Team. Should R&D opportunities be identified, DND*i* verifies that no other organization can take leadership before considering its own investment. The selection of potential R&D partners and funders complete the case study, which is then submitted to the Board of Directors. Risk analyses are undertaken to support the decision-making process.

FIGURE 6. **DND*i*'S DISEASE SELECTION PROCESS FOR MINI-PORTFOLIOS**



4.3 | MANAGING COLLABORATIVE R&D PROJECTS SOURCED AT ANY STAGE OF DEVELOPMENT

4.3.1 A Collaborative Model

DND*i* does not operate its own research facilities to develop new treatments. It functions based on a collaborative research model, also adopted by other PDPs and certain biotechnology companies, whereby research is outsourced but actively managed and directed by DND*i* personnel, highly experienced in pharmaceutical R&D. DND*i* proactively and continuously identifies research opportunities that have the highest potential to translate into improved treatment options. DND*i* management encompasses integration of research projects into its portfolio, building a full development plan, identification and contracting of appropriate partners, and management of the efficient progression of projects throughout the pipeline.

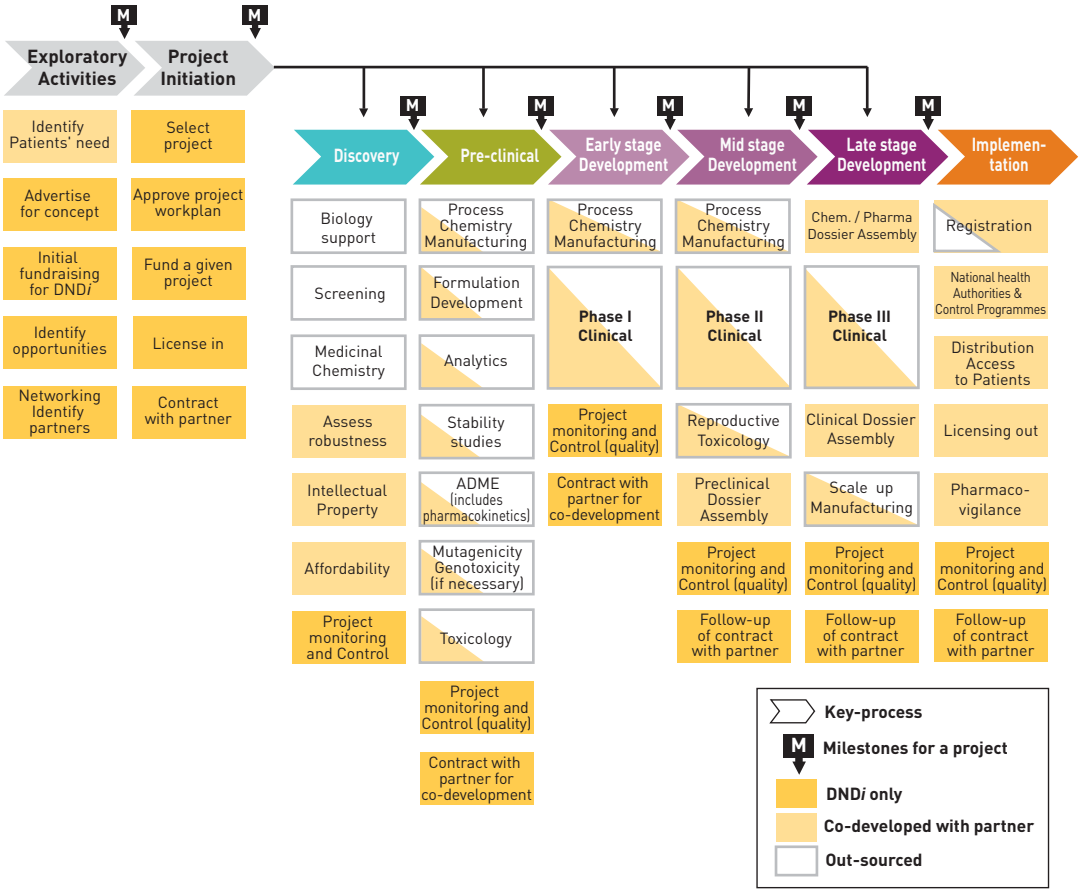
In doing so, DND*i* collaborates with a wide range of partners and contractors in both endemic and non-endemic countries, including:

- Public and academic research institutions and associated institutions;
- Governments and National Control Programmes of disease-endemic countries;
- Pharmaceutical and biotechnology companies, including contract research organizations (CROs) and contract manufacturing organizations (CMOs);
- NGOs, foundations, and other institutions involved in R&D and/or advocacy for neglected diseases;
- Individual experts on any given aspect of pharmaceutical development, neglected diseases, and business practices, in addition to patient representatives.

A team is set up for each project, under the leadership of a DND*i* Head of Programme, to coordinate all relevant partners and expertise. Such collaboration is governed by various types of contractual agreements, ranging from research funding collaborations, to technical service agreements, to long-term co-development partnerships with industrial partners.

DND*i* and its partners share responsibilities at different stages of the drug development process (Figure 7), whereas selection, funding, monitoring, and control of projects are DND*i*'s direct responsibility throughout the development process.

FIGURE 7. **BREAKDOWN OF RESPONSIBILITIES BETWEEN DND*i* AND ITS PARTNERS AT DIFFERENT STAGES OF THE DRUG DEVELOPMENT PROCESS**



4.3.2 Needs-Driven Projects Sourced at All Stages of Development

DND*i*'s portfolio comprises projects in-sourced at any stage of the development process, from early discovery to clinical development. As described in Section 5, five project categories can be distinguished by the nature of the compound/treatment under consideration and by the stage of development or expected time to reach patients.

The DND*i* R&D team conducts a number of exploratory activities which can be built up to full drug development projects or maintained as backup pipeline projects. Through this approach, DND*i* will continue to feed the pipeline of each target disease.

For the selection of new chemical entities, DND*i* focuses on compound libraries from pharmaceutical and biotech companies and will continue to engage partners in the industry. It will also maintain an opportunistic approach with respect to other sources (e.g. PDPs, academia) and build strategies for the future, including greater involvement from emerging economies.

4.3.3 Technology Transfer

In addition to in-sourcing, DND*i* will continue to transfer technologies in fulfilment of its objectives. Transfers can apply to compounds, technologies, or knowledge at all stages of development and implementation.

When possible, contracts with partners (public or private) will include options for technology transfer (e.g. IPK on High Throughput Screening). Examples of such transfer may include drug screening tools through to manufacture of drugs for distribution. Transfer may be implemented within South-South or North-South frameworks (e.g. for ASMQ, Fiocruz/Farmanguinhos – Brazil and Cipla – India; and for ASAQ, a recently signed contract to transfer technology to Zenufa, a manufacturing partner in Tanzania).

In the future, DND*i* will also consider out-sourcing compounds or technologies for others to further conduct research and development, with the possibility of in-licensing at later stages.

4.4 | R&D NETWORKS: UTILIZING AND STRENGTHENING RESEARCH CAPACITIES IN DISEASE-ENDEMIC COUNTRIES

4.4.1 Building upon DND*i*'s Vision and Founding Partners

Starting with its unique governance model, which includes Founding Partners from endemic countries (see Section 7), empowerment of partners in disease-endemic countries is a critical component of DND*i*'s vision and a recognized differentiating factor from other neglected disease R&D ventures. The Founding Partners will continue to reinforce their role by consolidating the networks of regionally contracted collaborators that will be managed by DND*i*.

As an integral part of its mission, DND*i* works with all its R&D partners to build on South-South and North-South collaborations. While capitalizing upon and supporting existing capacity in countries where the diseases are endemic, DND*i* helps to build additional capacity in a sustainable manner through technology transfer, clinical research, pharmacovigilance training, and strengthening of infrastructure.

4.4.2 A Facilitating Role in the Development of Platforms and Other Capacities

DND*i* will continue working with partners in disease-endemic countries, ensuring their close involvement in the entire R&D process, starting from needs identification, via a global network of collaborations and technology transfer. This includes access to chemical diversity, discovery platforms, pharmaceutical and clinical development, and collaboration with National Control Programmes. Such collaboration is exemplified by the HAT Platform and the Leishmaniasis East Africa Platform (LEAP) in Africa, the more recent Chagas Clinical Research Platform in Latin America, and other existing networks in disease-endemic countries.

DND*i* balances the objective of stimulating R&D activity in disease-endemic countries with the urgent need to develop new medicines and carefully assess each potential partner's ability to deliver in a sustainable manner (e.g. effective delivery of study results; active contribution to the registration process). Selection of partners is done case-by-case, taking into account the probability of success given adequate investment. The latter may imply, for example, modestly delaying the start of a trial to ensure sustainable patient access as well as a new research and treatment facility.

Capacity building may include the building or renovation of hospital wards, clinics, and health posts; renovation and re-equipment of clinical laboratories; and training of health service personnel with particular emphasis on providing expertise in clinical trial methodology, Good Clinical Practices and Ethics, patient treatment and evaluation, accurate diagnosis, and follow-up, to name a few.

> DND*i*'s role is that of facilitator, with the objective of **empowering local partners** with contributions such as needs assessments, seed or core funding, knowledge transfer, administrative support, and business development support.

4.4.3 Role of Regional Offices

Implementing DND*i*'s vision of empowering regional partners from disease-endemic countries will be made possible, in particular, through a more reinforced role of Regional Offices. These DND*i* resource centres play a key role in supporting projects, in advocating for access and awareness, and in generating and/or sustaining local and regional initiatives (e.g. Chagas Clinical Research Platform in Latin America). They will increasingly manage R&D programmes from endemic countries under the supervision of R&D management. Delegation of responsibilities from DND*i* Headquarters to the Regional Offices will depend on whether the critical size is present or on partners' capacity. The nature, structure, roles, and responsibilities of each Regional Office are tailored to the local/regional situation and will develop accordingly.

A 'one organization, one strategy' principle will guide DND*i* in this process and, while allowing for maximum flexibility and a pragmatic approach to empowering Regional Offices and partners, it guarantees institutional integrity. DND*i* will not implement a regionalization model whereby each Regional Office would develop its own agenda and manage all operations for DND*i* in a given geographical area. Rather, each Regional Office will develop mid- to long-term strategic plans fully in line and harmonized with the overall organizational objectives, Business Plan, processes, and organization, upon different empowering schemes, which can include activities that are either:

- Initiated and led locally;
- A contribution to DND*i*'s global programmes;
- Run from the Regional Offices on behalf of the whole organization;
- Under direct supervision of Headquarters, especially when partners or local means do not meet the critical needs.

See Section 7 for more information on these and other organizational issues.

4.5 | DEMONSTRATING FEASIBILITY AND IMPACT THROUGH A PORTFOLIO OF BUSINESS MODELS

The magnitude of R&D needs for neglected diseases and the diversity of potential partners are such that DND*i* cannot operate according to a single model. Considering its mission, DND*i* needs to have the institutional agility and flexibility to provide appropriate responses to neglected patients' needs, making no compromises on ethics and the quality of the science required to do so. This is what is meant by the motto 'best science for the most neglected'. As a developing and learning institution, DND*i* is willing to engage in original approaches to the target diseases, portfolio size, product categories, health tools, or access models.

A key element of DND*i*'s current and future work is the economic **appraisal of its model and impact** in terms of:

- Cost tracking and evaluation for **comparative assessments**
- Cost effectiveness and **cost benefit analyses** which will help to further validate and improve the R&D model pursued.

For each activity, DND*i* can utilize different partner categories, collaboration schemes, funding mechanisms, or advocacy activities, and adjust the intensity of its contribution – from light support to leadership.

As part of its ongoing programme management, DND*i* will continue to explore different partnership and business models to assess their feasibility and impact. Its will and capacity to explore innovative approaches – the risks of which are always carefully assessed – makes DND*i* an incubator of R&D solutions for neglected diseases.

FIGURE 8. **DND*i*'S DIVERSITY OF PARTNERSHIPS & MODELS**

4.6 | NEEDS-DRIVEN REGULATORY AND ACCESS STRATEGIES

4.6.1 International Regulatory Standards to Control and Assure Quality

Operating in a highly regulated environment, DND*i* fully adheres to international quality, ethical, and regulatory standards of drug R&D. From the earliest phases of the drug development process, registration requirements are taken into account and all R&D is performed in accordance with international standards.

The research, development, and delivery of a novel drug therapy invariably involve a certain level of risk. Quality is a central component associated with all of the risks: quality of the R&D activities performed and quality of the final product.

To support quality control and quality assurance (QC/QA), DND*i* has built internal and appropriate standardized operating procedures (SOPs) based on the International Conference Harmonization (ICH) and OECD recommendations.

While continuing to 'play by the rules', DND*i* will also continue to advocate for adapted regulatory and registration strategies for neglected diseases (e.g. pushing for regional harmonization).

4.6.2 Registration

DND*i* does not intend to hold market authorization. Building on its experience, it will look for industrial partners to register treatments (e.g. Sanofi for ASAQ) and, on a case-by-case basis, will consider playing a more active role if a given partner is not in a position to lead the registration/recommendation process (e.g. NECT).

With its industrial partners, DND*i* will seek the best-adapted regulatory route to facilitate rapid, field appropriate, and quality-based assessment of each regulatory dossier. Currently, outside of the EU, registration is country-based and not all countries possess the full resources to assess registration files. For diseases that affect entire regions, this time-consuming country-by-country process may delay patient access to treatments in areas where a number of agencies are concerned.

Several options already exist, such as a twinned review between a 'stringent' regulatory agency and a less resourced one (e.g. EMA article 58). Coupled with WHO pre-qualification, these approaches could impact the speed of patient access to new treatments in each country, whilst maintaining the essential standards of quality and contributing to the capacity strengthening of some regulatory agencies, thus promoting South-South exchanges.

Registration, however, is not sufficient. In most cases, adoption of international (e.g. WHO, PAHO) and national treatment guidelines (such as for HAT, VL, and Chagas disease) is also required for the treatments to be recommended, and therefore purchased and used, in the public sector. The case will be made that the new treatment options are indeed safe and effective, but also affordable, field-adapted, and coherent with public health strategies. The latter parameters are not examined by regulatory agencies but are essential for sustainable use. Inclusion of treatments in the WHO Essential Medicines List will also be targeted as an appropriate mechanism to facilitate multi-country uptake of treatments in national programmes.

DND*i*, as part of its mandate to facilitate patient access to treatments, will explore and support, with its regional partners, the most suitable means to facilitate adoption of new treatments delivered.

4.6.3 Enabling Access

DND*i*'s involvement will not end with drug registration or WHO recommendation, even more so now that its portfolio is maturing and the number of products in the implementation phase is growing. DND*i* will take on the responsibility of ensuring that the new tools it develops become useful, accepted, and accessible. Consistent with its collaborative model and the objective to develop public responsibility for neglected diseases, DND*i* will primarily engage in partnerships to ensure appropriate access to treatments, thus not taking or claiming sole ownership for access programmes.

Distribution and overall access scenarios will vary depending on the disease, drugs, relevant countries, and degree of innovation. See Section 6 for more detailed information on DND*i*'s access model.

4.7 | INTERNATIONAL ADVOCACY TO SUPPORT DND*i*'S OBJECTIVES

Working to build awareness about the most neglected diseases in both non-endemic and endemic countries, DND*i* aims to increase and sustain its advocacy efforts for greater public responsibility to address neglected diseases. Political leadership is essential for continued financial support, definition of priorities, the creation of a more favourable environment to stimulate health R&D, and guaranteeing equitable access to new health tools.

DND*i* will continue to ask for greater political leadership from governments of both donor and disease-endemic countries, in addition to international bodies such as the WHO and its Intergovernmental Working Group. Fostering relationships between concerned scientists, research institutes, PDPs, and NGOs is also critical to accelerating the momentum that has been building up since 2000.

DND*i* will do the following to advocate for a more effective neglected disease R&D environment:

- Continue to **engage independent experts** to examine intellectual property, regulatory processes, access to knowledge, and conduct economic appraisals to stimulate the environment;
- Continue to **document experience** gained since its inception via case studies or comparative and transparent appraisals of the business model with regards to R&D effectiveness and costs;
- Encourage the comparative **analyses of non-traditional R&D models** (e.g. PDPs).