DNDi’s primary R&D objective is to deliver a total of 11 to 13 new treatments to patients by 2018 (five to seven more than the six in implementation phase in 2011) and to maintain a robust pipeline to support long-term objectives.

DNDi will fill its pipeline at all stages of development through a mix of short-, medium-, and long-term projects, managed via its collaborative R&D model.

DNDi is proactively developing its portfolio through the identification of:

- Significant unmet medical needs;
- R&D opportunities such as candidate compounds and improved formulations;
- Potential partner organizations for R&D;
- Adequate funding sources.

Concerted efforts to harness discovery activities targeting the three core kinetoplastid diseases are focused on sourcing the most promising anti-parasitic drug candidates. On a disease basis, the portfolio is managed by taking into account the gaps identified within the product portfolio, pipeline projections, and strategic priorities.

DNDi will complete its malaria strategy and launch two mini-portfolios in the areas of paediatric HIV and specific helminth infections.

**FIGURE 9. DNDi’S OBJECTIVES**

<table>
<thead>
<tr>
<th>2003-2011 implementation</th>
<th>Diseases</th>
<th>2012-2018</th>
<th>Beyond</th>
</tr>
</thead>
<tbody>
<tr>
<td>NECT</td>
<td>HAT</td>
<td>Kinetoplastids: 1 or 2 NCEs</td>
<td>Combo with 2 NCEs</td>
</tr>
<tr>
<td>Paed.Benznidazole</td>
<td>Chagas</td>
<td>+ Strong clinical pipeline (Phase II &amp; III)</td>
<td>Combo incl. NCE</td>
</tr>
<tr>
<td>2 VL Combos</td>
<td>Leishmaniasis</td>
<td>VL – 1 treatment [Geographical extension]</td>
<td>Combo with 2 NCEs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CL – 1 treatment</td>
<td>TBD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PKDL – 1 treatment</td>
<td>TBD</td>
</tr>
<tr>
<td>Helminths</td>
<td>1 new treatment for filariasis</td>
<td>TBD</td>
<td></td>
</tr>
<tr>
<td>Paediatric HIV</td>
<td>1 new treatment</td>
<td>TBD</td>
<td></td>
</tr>
<tr>
<td>ASAQ + AQM</td>
<td>Malaria</td>
<td>Completion by 2014</td>
<td></td>
</tr>
<tr>
<td>New NTD</td>
<td></td>
<td>Treatments</td>
<td></td>
</tr>
<tr>
<td><strong>6 new treatments</strong></td>
<td>5 to 7 new treatments including at least one NCE (+ geo. extensions)</td>
<td>+ Strong pipeline (Ph II and III) to deliver additional treatments with NCEs</td>
<td>+ Diseases exit strategies</td>
</tr>
</tbody>
</table>

**5.1 | SYNTHESIS OF OBJECTIVES PER DISEASE AREA**

In addition to the six treatments in implementation phase in 2011, DNDi is committed to:

- Providing five to seven new treatments, including at least one new chemical entity (NCE) and potential geographical extensions;
- Developing a strong pipeline of projects in Phase II and Phase III that could deliver additional treatments with NCEs beyond 2018;
5.2 | PORTFOLIO BUILDING APPROACHES

The three key processes – intelligence and project sourcing, R&D, and project & portfolio management – will be further implemented by DNDi to fill the pipeline by seeking leads and drug candidates at all stages of development (Figure 10). At the post-registration stage, existing and new mechanisms will be leveraged to ensure patient access to treatments through partnerships with industrial partners, international organizations, and national programmes.

Projects will be divided into five categories:

- New treatments (involving NCEs) developed from novel compounds identified through screening, lead optimization, or licensing. These drugs must meet target product profiles (TPPs) and may be used in monotherapy or as part of combination therapies when appropriate;
- New treatments developed from compounds with known antimicrobial/antiparasitic activities (could start at lead optimization or pre-clinical development);
- New indications for existing treatments (therapeutic switching);
- Combinations or new formulations of existing drugs that are better adapted to field conditions and patient needs (paediatric dosage forms, long-acting, new route of administration, fixed-dose combinations, co-packaging, or co-administration);
- Geographical extension of existing treatments, including completion of regulatory dossiers in new countries.

![Figure 10. DNDi's Portfolio Building Mechanism](image)

5.2.1 Sourcing

Building on its experience of sourcing projects since 2003, DNDi has refined its sourcing approach, aiming to:

- Proactively manage access to pharmaceutical companies’ annotated series to accelerate identification of drug candidates;
- Source projects from partners in the public sector;
- Explore new business models for DNDi to co-develop compounds with partners;
- Continuously advocate for investment [public and private] in neglected disease research to secure sources of innovation;
- Stimulate innovation in targeted disease areas via advocacy for public research in emerging economies.
5.2.2 Discovery

Radical improvement of therapies for leishmaniasis, human African trypanosomiasis, and Chagas disease requires the identification, evaluation, and development of novel compounds that are better than current therapies. The screening of (libraries of) compounds in vitro against both molecular targets (crucial enzymes, receptors) and whole organisms to identify novel compounds is a well-established approach in industry and academia. From 2007 to 2010, DNDi built and refined a virtual model of drug discovery capable of producing drug candidates. However, the lack of high quality hits and leads, and the high attrition rate at the hit-to-lead stage necessitates continued adjustment of drug discovery approaches to ensure continued success.

As some chemical classes have a broad spectrum of activities against parasites causing the target diseases, DNDi will further seek access to compound series with proven drug-like characteristics from pharmaceutical and biotechnology partners. Access to partners’ chemical diversity as well as drug-like and annotated compound series is critical to the success of this approach. Several agreements have been entered into with major companies such as Sanofi to screen their compound libraries. DNDi also seeks access to knowledge and know-how associated with such classes to ensure efficient drug development.

DNDi continues to encourage open exchange of information related to drug R&D in the field of neglected diseases. By collaborating with other laboratories/institutions to promote rapid development of new treatments for patients in need, unnecessary duplication of effort is avoided and synergies between research groups created.

For example, DNDi has developed a partnership with the Institut Pasteur Korea (IPK) for High Throughput Screening (HTS) on specific target parasites to help select and progress hits and leads according to its target product profiles and decision matrices. The outcome of this work with IPK (funded by DNDi) is made public for others willing to pursue R&D for neglected diseases.

The virtual drug discovery research framework is operational and has yielded promising candidate compounds. DNDi will continue to streamline its model for more rapid advancement of drug candidates.

Lead compounds identified within this framework will progress into focused lead optimization programmes, which in turn will be implemented by experienced medicinal chemistry groups. Optimized leads will then enter the drug development process of preclinical and clinical development.

5.2.3 Lead Optimization

Building upon its Lead Optimization Consortium framework developed in 2008, DNDi will further leverage key competencies of its partners, and continue to strive for cost effective delivery.

Within its lead optimization activities, DNDi will emphasize the strengthening of its internal competencies in medicinal chemistry and CMC [chemical manufacturing control] to better manage its work with partners and CROs [contract research organizations]. Outsourcing technical operations to cost-effective providers will be augmented with supervision of and advice from consortium partners.

In addition, value-added partnerships in endemic countries will be pursued with the objective of strengthening capacities where and when appropriate.

DNDi counts an increasing number of projects at the late lead optimization stage. Therefore, in order to ensure smooth transition to early development, DNDi’s translational research strategies will be refined and strengthened.
5.2.4 Pre-Clinical and Clinical Development

DNDi will continue to explore the repurposing of existing drugs [such as the antifungal drug E1224 for Chagas]. Therapeutic switching – re-orienting drugs that exist or are in clinical development for other indications – has already proven successful in generating promising new drugs for leishmaniasis and trypanosomiasis. Anti-fungal, anti-bacterial, and anti-malarial drugs are particularly promising drug sources for therapeutic switching. DNDi is closely monitoring developments in these areas, with the aim of co-developing such drugs with partners (including with other PDPs) or in-licensing them to be developed for the specific target disease indications.

For helminth infections [see below], partnerships will be sought with animal health companies.

A ‘pre-competitive approach’ to collaboration will also be pursued, by which DNDi and its partners share approaches and knowledge before launching their own initiatives or projects. DNDi will explore appropriate models accordingly.

DNDi will continue to develop combinations of existing drugs to address immediate patient needs. In the absence of new, highly effective, easier-to-use drugs, combination treatments offer the potential to improve efficacy, reduce treatment duration, and reduce costs, in addition to lowering the risk of drug resistance. Similarly, developing improved formulations that are better adapted to field conditions comprises another approach to address immediate patient needs. This involves short pre-clinical studies followed by clinical studies, and the development or extension of a regulatory dossier. Examples of successful improvement of formulations include the two fixed-dose combinations for malaria (ASAQ and ASMQ), and the paediatric dosage form of benznidazole.

In some cases, existing drugs for target diseases are available in certain countries of endemic regions, but fail to reach patients or are underutilized because they are not registered in other endemic countries. Thus geographical extension of existing drugs represents another approach to delivering near-term benefits to patients in need.

In support of its approach to clinical development, DNDi will:

■ Maintain the capacity to conduct 10 to 12 ongoing trials;
■ Further explore critical pathways for developing improved therapies, including NCEs;
■ Grow its operations in resource-limited locations and sustain capacity strengthening objectives to serve its clinical development and implementation needs;
■ Manage studies according to geographical differences of diseases (e.g. VL);
■ Aim for partners to take full implementation responsibility, yet assess needs for pharmacovigilance and develop/support capabilities accordingly (including implementation of risk management plans and Phase IV studies);
■ Continue to implement QA/QC procedures and comply with ethical and regulatory frameworks;
■ Bridge development and implementation objectives by further empowerment of DNDi Regional Offices;
■ Advocate for increased regulatory capabilities in endemic regions to prepare decision-makers (Ministries of Health, National Control Programmes) and healthcare providers to adopt DNDi treatments.

One of the main challenges for DNDi’s R&D is the ability to advance the increasing number of new drugs through the clinical development, registration, and implementation processes.

5.2.5 Disease Strategies

To guide all components of DNDi approaches [R&D, policy, access, partnerships] leading to the delivery of new treatments, disease strategies are developed for each of the target diseases, and are reviewed and updated on a regular basis. Beyond the critical role of the Scientific Advisory Committee, ad hoc disease committees will be set up to challenge internal approaches, gather input from various stakeholders, and provide insight and guidance [see Section 7].

Full disease strategies are available on the DNDi website.
5.3 | DNDi’S PORTFOLIO

5.3.1 Current Portfolio, October 2011
DNDi’s portfolio has grown to 24 projects (with six treatments in implementation phase – four available and two in registration/recommendation phase) from its initial four projects in 2003. DNDi continues to substantially increase the number of clinical research projects and has developed an integrated strategy for drug discovery, which includes risk management strategies to deal with attrition rate associated with drug discovery and development.

5.3.2 Portfolio Development
The main R&D focus is on successfully managing and progressing on-going R&D projects to sustainably deliver new treatments to neglected patients in the shortest possible time. To ensure that the full discovery and development process flows without interruption, DNDi will use a decision matrix – a core model that is adaptable for each disease and class of compounds – along with review by internal and external experts specialized in the given development stage and therapeutic area.

In addition, the DNDi R&D team continues to build the portfolio of projects for HAT, VL, and Chagas disease through exploratory activities which focus on the pharmaceutical and biotechnology sectors, as well as established academic and public sector groups with expertise in the field. These exploratory activities are essential to fully exploit new opportunities and replace projects in the portfolio when appropriate, allowing the DNDi team to selectively focus on the strongest and most promising activity.

The probability that a given project will lead to eventual drug registration, and the speed of the development processes vary according to the disease, the nature of the compound, the project category, and the stage of discovery or development at which DNDi becomes involved. The risk of compound ‘failure’ or ‘drop-out’ is intrinsic to drug R&D and is based on estimated attrition rates.

For each target disease, DNDi has built a baseline pipeline projection upon:
- Objectives by disease;
- Number and status of ongoing projects (see Figure 1);
- Theoretical attrition rates appropriate for not-for-profit drug development[1];
- Potential for addition of new projects at different stages.

Per disease, the portfolio is managed by taking into account the gaps identified within the existing product portfolio and the pipeline projections and objectives [see Section 5.1]. For each disease, a hypothetical targeted portfolio has been built – based upon DNDi’s experience and adjusted assumptions from its previous Business Plan – and the corresponding financial and human resources estimated [see Section 8].

5.3.3 Discovery Projects
DNDi’s objective is to maintain four series of compounds to feed the pipeline for the three kinetoplastid diseases: Human African Trypanosomiasis, Leishmaniasis, and Chagas Disease.

Compounds in discovery projects are initially tested against all kinetoplastids. Based on the data at this stage, a decision is taken to focus the project on a specific disease. Discovery includes (a) screening of compounds against pathogens that cause the target disease, (b) hit expansion, where chemical series similar to the hits are explored for selectivity, and (c) lead identification, where further in vitro, in vivo, and ADME (absorption, distribution, metabolism, and excretion) studies identify a small series of compounds for lead optimization.

Should DNDi sufficiently feed its kinetoplastid pipeline by 2015, it may envisage a decrease in the number of compound series to be maintained in 2016. However, additional discovery efforts may be pursued should there be a need to support the potential addition of new disease areas.

5.3.4 Human African Trypanosomiasis (HAT)
DNDi has two target product profiles (TPP) for HAT (T. b. gambiense and T. b. rhodesiense). Priority is given to the development of an oral, safe, effective stage 2 HAT treatment to improve current case management, but ideally to be used with the same regimen for stage 1 HAT – this would avoid spinal taps that are currently needed to determine the disease stage in patients. Treatment strategies would then be adapted accordingly.

Ultimately, when coupled with new field-adapted diagnostic tools, such a treatment would efficiently contribute to the control and elimination strategies for HAT, even in the most remote areas.

Alternatively, should an NCE developed up to Phase II or Phase III not show sufficient levels of efficacy in stage 2, its development for the stage 1 indication may be considered to offer a short-term alternative to the current parenteral treatment options.

5.3.5 Leishmaniasis
DNDi has one TPP for an NCE for visceral leishmaniasis. The priority is to develop an oral, safe, effective, low-cost, and short-course (≤10-day) treatment that could replace current treatments, improving and simplifying current case management. Ideally, this treatment would be effective against all forms of disease and adapted for use in peripheral health centres.

Unless the NCE demonstrates very short treatment duration (≤3 days), low potential risk for resistance development, and high ease of use, the objective will be to develop a co-administration of two drugs that are field adapted, therefore easy to deploy by the national programmes, and useful in preventing the development of resistance to each of its components.

Although the ideal TPP is to develop one NCE that would show similar efficacy in all VL-endemic regions, data tend to show that geographical differences of the pathogens exist. It may thus be necessary to adjust the treatment strategies accordingly, a factor that will be assessed throughout the course of development.

For PKDL (post-kala-azar dermal leishmaniasis), DNDi’s objective is to develop a treatment that is shorter course and better tolerated than the currently used long-course antimonial, using existing medications but potentially combining them with an immune stimulant.

For HIV-VL co-infected patients, the minimum objective will be to find treatment options that would limit VL recurrences.

TPPs for PKDL and HIV-VL co-infection will be developed in 2011 and the respective strategies refined.

DNDi’s development approach for cutaneous leishmaniasis (CL) will be pragmatic and opportunistic, and no discovery stage project will be initiated. As CL is a complex disease, with a number of clinical forms of varying severity, the focus will be on those causing the highest public health burden. Once successful treatments have been developed for the latter, their potential for treatment of other forms of the disease will be assessed.

DNDi’s objective will be to develop a treatment for patients with CL caused by L. tropica and L. braziliensis, looking essentially at ‘low hanging fruit’ approaches based on existing treatments or drugs in development. The treatment should be of shorter duration (<21 days for oral), safe, and effective, with no need for close medical supervision.

The CL strategy will be further refined in 2011.

5.3.6 Chagas Disease
For Chagas disease, DNDi has one TPP for an effective and safer oral treatment for the chronic form of Chagas disease, ideally effective also against the acute form of the disease.

Depending on the efficacy and safety results, a combination treatment may be considered to optimize the use of each component, reducing the treatment duration and possibly improving the tolerability of each.

DNDi will also support the development of biomarkers to gain understanding of the disease pathology, ease the development of diagnostic tools, and support drug development (see Figure 8).
5.3.7 Malaria
Two fixed-dose combinations were developed by DNDi with its partners. The first – ASAQ, artesunate + amodiaquine – has now been successfully developed, prequalified by WHO, registered in 30 African countries and India (with over 80 million treatments distributed by the end of 2010). Technology transfer to Zenufa is underway for ASAQ.

The second – ASMQ, artesunate + mefloquine – was registered in Brazil in 2008 and is now in the process of being registered in other Latin America countries as well as Southeast Asia and India. DNDi’s objective will be to complete the current clinical activities on ASMQ in Africa and support the ongoing access issues until adoption and implementation is in place.

DNDi will not be involved in further development of anti-malarial agents and plans to transfer its portfolio to partners by 2014. DNDi will apply lessons learned from its malaria mini-portfolio to the management of other disease portfolios.

5.3.8 Other Neglected Disease Projects
DNDi will continue to advocate for neglected disease R&D and play a pivotal role among stakeholders. Fulfilling its role as an ‘incubator’ for neglected disease R&D solutions (see Section 4.5), DNDi will maintain an opportunistic approach for other neglected diseases, developing specific strategies when appropriate. However, considering the significant investments in the new helminth and paediatric HIV mini-portfolios, DNDi will finalize the pilot phases of these before launching new R&D initiatives.

5.4 PAEDIATRIC HIV

To meet the specific needs of paediatric HIV patients (see Section 3.2.3), DNDi’s objective is to develop an improved first-line treatment for infants and young children under three years of age that is low cost, easier to use, and better adapted for this age group.

5.4.1 Opportunities for Consideration
The scope of the paediatric HIV mini-portfolio is dedicated to the needs of children with HIV under three years of age in need of first-line therapy, regardless of prior ARV exposure. DNDi convened, in April 2011, a panel of paediatric HIV experts to define the TPP and identify the gaps and opportunities.

The current TPP includes: appropriate dosage forms usable across WHO weight bands, high genetic barrier to resistance, no cold chain needed, well tolerated, no lab monitoring required, and affordable. Ideally, the treatment will also be compatible with TB medicines. Exploratory activities have been initiated. The TPP is available on DNDi’s website, and a detailed strategy will be developed in 2011.

5.4.2 Project Implementation
DNDi will partner with organizations with demonstrated experience in HIV R&D. Potential development partners will likely include generic and pharmaceutical companies, academic groups in African countries, NIH, MRC, ANRS, as well as implementation partners such as the UNITAID Medicines Patent Pool, the Clinton Health Access Initiative (CHAI), MSF, and National Control Programmes.

DNDi’s approach consists of the following phases:
- **Pilot phase**: full assessment of opportunities, feasibility (including laboratory work), and adjustment of the strategy, with an estimated budget of approximately EUR 2 million (by end of 2012);
- **Development phase**: two to three projects to be developed by DNDi, with an estimated budget of EUR 10 to 15 million (2013-2015);
- **Adjustment phase**: adjustment of approaches taken, according to needs and impact, and potentially stop, grow, or spin off the activity (after 2015).
5.5 | HELMINTH INFECTIONS

To meet the specific need introduced in Section 3.2, DNDi’s objective is to develop a new treatment that can be used by Mass Drug Administration (MDA) programmes devoted to the control and elimination of onchocerciasis and lymphatic filariasis (LF) in Loa loa co-endemic regions. A drug with macrofilaricidal activities has the potential for broader treatment with greatly reduced treatment cycles (still within MDA programmes) for onchocerciasis and LF in other regions, thereby reducing drastically the length and number of MDA campaigns. The TPP will be defined in 2011.

5.5.1 Opportunities for Consideration

Flubendazole has been identified as the immediate opportunity. Additional opportunities will be assessed through a landscape analysis, with the intention of selecting one or two candidates emanating from the animal health industry or leads in development in biotechnology and academic labs.

5.5.2 Project Implementation

Potential partners have been identified, including Michigan State University and McGill University. Additional potential partners will be sought in 2011, and will include pharmaceutical and biotechnology industry and academic collaborators.

DNDi will adopt a phased approach (2011-2012: approximately EUR 4.5 million; 2013-2015: approximately EUR 10 to 15 million) to managing a well-focused mini-portfolio.