Evaluation of the Product Development Partnerships (PDP) funding activities

- The UK Department for International Development (DFID)

- The German Ministry for Education and Research (BMBF)

Report

This report summarizes and evaluates the operations, performance and achievements of the Drugs for Neglected Diseases initiative (DNDi), the Foundation for Innovative New Diagnostics (FIND) and the European Vaccine Initiative (EVI) for the period of 2009 to 2013.

Ian Boulton
ian.boulton@tropmedpharma.com
Stefanie Meredith
stefanie@globalhealthconsulting.net
Thomas Mertenskoetter
thomas@tomlifescience.com
Finnja Glaue
finnja@tomlifescience.com

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Abbreviations

Abbreviation	Explanation
AA	American Appraisal
ADG	Associate Director General
AECID	Spanish Agency for International Development
AMA	Apical Membrane Antigen
AMFm	Affordable Medicines Facility - malaria
ASAQ	Artesunate/Amodiaquine
ASMQ	Artesunate/Mefloquine
AusAID	Australian Agency for International Development
BBVA	Banco Bilbao Vizcaya Argentaria
BCG	Boston Consulting Group
BD	Becton Dickinson
BMBF	German Ministry of Education and Research
BMGF	Bill and Melinda Gates Foundation
BoS	Board of Stakeholders
BSC	Board Science Committee
Canton GE	Canton of Geneva
CATT	Card Agglutination Test for Trypanosomiasis
CCRP	Chagas Clinical Research Platform
CDC	Centers for Disease Control and Prevention
CE	Conformité Européenne
CEO	Chief Executive Officer
CFO	Chief Financial Officer
CFR	Case Fatality Rate
CH Gov	Government of Switzerland
CMO	Chief Medical Officer
CSF	Cerebrospinal Fluid
CSO	Chief Scientific Officer
DAC	Development Assistance Committee
DALY	Disability-Adjusted Life-Year
DFAT	Department of Foreign Affairs and Trade (Australia)
DFID	Department for International Development (UK)
DGIS	Directorate-General for International Cooperation (The Netherlands)
DiCo	Diversity Covering
DNA	Deoxyribonucleic acid
DNDi	Drugs for Neglected Diseases initiative
DNTD	German Network to Fight NTDs
DoP	Diseases of Poverty
DST	Drug Susceptibility Test
e.g.	for example (*exempli gratia*)
EC	European Commission

EDCTP	European & Developing Countries Clinical Trials Partnership
EEIG	European Economic Interest Grouping
ELISA	Enzyme-Linked Immunosorbent Assay
EML	Essential Medicines List
EMVI	European Malaria Vaccine Initiative
EPTB	Extra-Pulmonary TB
EU	European Union
EUR	Euro
Euvac	European surveillance network for selected vaccine-preventable diseases
EVI	European Vaccine Initiative
EXPAND-TB	Expanding Access to New Diagnostics for TB
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FIND	Foundation for Innovative New Diagnostics
FM	Fluorescence Microscope
FTE	Full Time Equivalent
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
GFATM	Global Fund to Fight AIDS, TB and Malaria
GHIT	Global Health Innovative Technology Fund
GIZ	German Association for International Cooperation
GMP	Good Manufacturing Practices
GRADE	Grading of Recommendations Assessment
GSK Bio	GlaxoSmithKline Biologicals
HAT	Human African Trypanosomiasis
HIV	Human Immunodeficiency Virus
HIV-VL	HIV-Viral Load
ICMR	Indian Council for Medical Research
IGRAs	Interferon-Gamma Release Assays
IMI	Innovative Medicines Initiative
IP	Intellectual Property
IVD	In Vitro Diagnostics
JSI	John Stone Inc.
KEMRI	Kenyan Medical Research Institute
KfW	Kreditanstalt für Wiederaufbau
LAMP	Loop Mediated Isothermal Amplification
LEAP	Leishmaniasis East African Platform
LED	Light Emitting Diode
LLC	Limited Liability Company
LMIC	Low- and Middle Income Countries
LPA	Line Probe Assay
LPV	Lopinavir
MAEE/AFD	French Ministry of Foreign and European Affairs/ French Agency for Development

MDR	Multi Drug-Resistant
MGIT	Mycobacteria Growth Indicator Tube
mill	Million
MMV	Medicines for Malaria Venture
MoH	Ministry of Health
MoU	Memorandum of Understanding
MRC	Medical Research Council (UK)
MSF	Medicins sans Frontières
MTB/RIF	Mycobacterium Tuberculosis/ Rifampicin Resistance
MVDP	Malaria Vaccine Development Program
MVI	Malaria Vaccine Initiative
NCE	New Chemical Entity
NECT	Nifurtimox-Eflornithine Combination Therapy
NICE	National Institute for Health and Care Excellence (UK)
NIH	National Institutes of Health
NIHAID	National Institute of Allergy and Infectious Diseases (USA)
NTDs	Neglected Tropical Diseases
PCR	Polymerase Chain Reaction
PDP	Product Development Partnership
PEPFAR	The United States President's Emergency Plan for AIDS Relief
PoC	Point-of-Care
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RDT	Rapid Diagnostic Test
RTS,S	Lead candidate malaria vaccine
RTV	Ritonavir
SAC	Scientific Advisory Committee
SD	Standard Diagnostics
SDC	Swiss Agency for Development and Cooperation
SSG&PM	Combined use of Sodium StiboGluconate and ParomoMycin
STAG	Strategic and Technology Advisory Group
TB	Tuberculosis
TBVI	TB Vaccine Initiative
TDR	Special Programme for Research and Training in Tropical Diseases
ToR	Terms of References
TPP	Target Product Profile
UBS	Union de Banques Suisses
UK	United Kingdom
UN	United Nations
US	United States
USA	United States of America
USAID	United States Agency for International Development

USD	United States Dollar
VAT	Value-Added Tax
VfM	Value for Money
VL	Visceral leishmaniasis
VSPAC	Vaccine Science Portfolio Advisory Council
WHO	World Health Organization
WHO-TDR	WHO Special Programme for Research and Training in Tropical Diseases
XDR	Extensively Drug-Resistant
yr	Year

1. Executive Summary

Product Development Partnerships (PDPs) have played an important role in improving the funding and accelerating development of novel and much needed interventions to address issues of global health, especially for poor and disadvantaged populations. Through their ability to bring together partners from academia, industry, the public sector and multilateral agencies to develop effective, affordable, appropriate and accessible products, PDPs have also stimulated increased collaboration of the pharmaceutical industry to work on the diseases of poverty (DoP).

The aim of this report is to provide information to The UK Department for International Development (DFID) and the German Ministry for Education and Research (BMBF) about the value of their current investments and help making informed decisions on future PDP investments through an evaluation of the operations and performance of FIND and DNDi over the period 2009-2013. In addition, the performance and operation of EVI over the period 2009-13 was assessed building on the results of an existing external review of EVI which was carried out in 2012-2013.

This evaluation included a thorough review and analysis of relevant documentation and interviews with stakeholders of DNDi & FIND, members of the PDPs' boards, steering committees, and advisory boards, the PDP Funders Group, key informants at WHO, Global Health Partnerships, EDCTP, and other multilaterals, private sector partners of the PDPs and country–level stakeholders.

DNDi: Since 2007, the Drugs for Neglected Diseases initiative (DNDi) has delivered 1 new treatment per year and has met its 2007 target of 6 novel treatments for Malaria, Human African Trypanosomiasis (HAT, Sleeping Sickness), Visceral Leishmaniasis and Chagas disease by 2014. These are all "low-hanging fruit" that could be developed rapidly and with a high probability of success as they are either re-purposing existing drugs or developing combinations. DNDi recognises that these have been relatively easy development programs and further success will be more difficult to achieve.

DNDi is a well-governed organisation, with oversight of management being supplied by a competent and engaged Board. Scientific oversight is provided by a strong Scientific Advisory Committee (SAC). DNDi has a robust strategic planning process which is actively reviewed by both management and the Board. They have developed two strategic plans in the period under review: 2007-2014 and an update covering 2011-2018.

There is a well-developed budgeting process in place, with resources allocated across several dimensions – by project, by function, by geography, and by stage of development. DNDi has been successful in raising the necessary finances from a variety of donors to sustain its project portfolio and other aspects of its strategy and it is clear that the organisation is financially sustainable under present circumstances.

Most clinical trials are conducted through the three regional disease-specific platforms (LEAP - Leishmaniasis East African Platform, HAT Platform, CCRP - Chagas Clinical Research Platform) and are compliant with global Good Clinical Practice (GCP) standards. DNDi will face a major challenge to grow its clinical trial capacity as it projects 15,000 subjects over the next 10 years. Also, the nature of the studies is changing from simple implementation studies to full developmental clinical trials including developing new chemical entities (NCE).

DNDi has built up close collaborations with several pharmaceutical companies and has earned respect as a professional collaborator. Their expertise and access to development and clinical capacity in disease endemic countries is highly valued.

DNDi has integrated access-related activities into all development steps, learning from experience that it needs to remain involved as a facilitator to ensure partners can work effectively together to deliver interventions to patients. The implementation of new medicines developed by DNDi has had considerable impact on morbidity and mortality in the affected populations.

FIND: Since 2003 the Foundation for Innovative New Diagnostics (FIND) has acquired and integrated technical and field expertise in development, clinical evaluation, and implementation of diagnostics in the

fields of tuberculosis (TB), malaria, HAT and other kinetoplastids. These new diagnostics address very different needs: from individual case management and public health approaches to disease elimination or eradication.

From 2009 – 2013 FIND significantly contributed to the registration or WHO endorsement of 5 new diagnostics in previously neglected areas. FIND has considerably advanced the field of diagnostics for the respective diseases, especially in the field of TB diagnostics. Again, some low hanging fruit may have made initial work easier to accomplish, and future innovations might be more difficult to achieve and more resource intensive.

FIND has built up strong collaborations with several industry partners. Partners express respect for FIND as a reliable and professional collaborator. Importantly, FIND also provides diagnostics developers with access to their large TB, Malaria and HAT specimen banks. This supports biomarker discovery work, assay development and validation and can be used to quickly and effectively test the feasibility of new prototypes or concepts at low cost.

In 2011 – 2013 FIND went through a financial and organisational crisis. However, it has demonstrated its ability to orchestrate a self-critical review, organisational change and strategic adaptation. FIND has addressed the issues and shortcomings on multiple levels and is now a viable PDP with revised direction, strengthened governance and renewed energy.

FIND has also strongly diversified its funders' base. Current weighted projections of committed, expected, and projected income are sufficient to fund FIND's work from 2014 through to 2016/2017, beyond then additional funding is projected to be required to meet the resource needs of its strategy and goals.

EVI: Over the last fifteen years, the European Vaccine Initiative (EVI) has demonstrated its ability to create an enabling environment for malaria vaccine development and, more recently, for other diseases of poverty. To date it has funded 24 malaria antigen combinations in 32 vaccine formulations and taken 16 candidates to phase I clinical trials. Three candidates were transferred to other partners for phase IIb trials and one of these is currently in further development. The current EVI portfolio is comprised of 20 projects with 16 vaccine candidates under development.

EVI has developed, and is implementing, a new strategy for proof of concept which combines phase Ia and phase Ib clinical trials in a unique protocol which aims to accelerate the pace and reduce the cost of the clinical development of vaccine candidates**.**

EVI enables and facilitates early stage discovery research, preclinical and early clinical development of vaccine candidates and differs in its business model from other PDPs, which support product development along the entire product development chain including clinical phase III and market introduction (like DNDi), or focuses more on deployment and implementation (as FIND does).

EVI has also undergone some organisational changes during the period 2009-2013. It has worked to reorganise the secretariat functions towards a project management oriented structure. Strengthening of the governance has continued.

EVI works to mobilise resources for projects and provides both funding and expertise required to take experimental vaccine candidates efficiently from discovery and preclinical R&D into clinical trials. This gap in vaccine development is both technically and legally complex and has been traditionally under-financed and EVI does fill an important niche.

Based on the American Appraisal's review of EVI's financial performance and an update from EVI, EVI does have short-term sustainability and has been successful in raising the funds needed to sustain its portfolio and possibly even expand its scope. However, the longer-term sustainability is heavily dependent on unrestricted funding – currently only available from the Irish Aid and GHIT funds.

Summary: It is clear from this and other recent assessments that PDPs have played a major and important role in the development and deployment of much-needed interventions for the control and elimination of neglected infectious diseases. This work needs to be continued and PDPs supported over the long-term. Of

most value to the PDPs is unrestricted funding[1], as it ensures they have the maximum flexibility to achieve their strategic objectives, and that they are not dominated by a single donor's strategy. It is difficult to properly measure the impact and value for money of PDPs without clear guidance from funders about a single and consistent set of measures.

Detailed recommendations for each of the PDPs evaluated can be found in Section 10 of the main report. The overall recommendations are:

- Public funders should continue to support PDPs with long-term financing in order to ensure there is a steady stream of needed interventions for neglected infectious diseases. This funding should be mostly unrestricted or semi-restricted.
- All PDPs should seek to diversify their funding base (as DNDi is doing) in order to ensure that they have the flexibility to set and follow their own strategy and not be driven by the requirements of one dominant funder.
- Funders should agree amongst themselves on the measures of impact and value for money, and to give clear guidance to PDPs (amongst others) to ensure comparisons can be made in a consistent manner.

[1] See definitions of terms in footnotes 2 & 3

2. Introduction

DFID and BMBF are both funders of PDPs and have commissioned this evaluation of FIND, DNDi and EVI. FIND and DNDi received funding from both DFID and the BMBF and in addition, the BMBF funds EVI.

The purpose of this joint report is to evaluate the operations of FIND and DNDi and their performance in meeting their specific objectives and overall mission over the period 2009-2013. In addition, the performance and operation of EVI over the period 2009-2013 was assessed building on the results of a recent external review of EVI that was carried out in 2012-2013. The aim of this report is to provide information to the funders about the value of their current investments and help making informed decisions on future PDP investments.

This evaluation addresses five key objectives using the Development Assistance Committee's (DAC) criteria of relevance, effectiveness, efficiency, impact, and sustainability. The specific objectives of this report were to evaluate (1) the achievements and relevance of the PDPs in relation to their missions, (2) the impact of government funding for the PDPs in question, (3) the capabilities of the PDPs in relation to their missions, (4) the PDPs contribution to the goal of accelerated access and (5) the value for money of each PDP.

The methodology essentially follows the strategy as outlined in the Request for Proposals. This included a thorough review and analysis of relevant documents and interviews with stakeholders of DNDi and FIND, as well as members of the PDPs' boards, steering committees, and advisory boards, the PDP Funders Group, key informants at WHO, Global Health Partnerships, European & Developing Countries Clinical Trials Partnership (EDCTP), and other multilaterals, private sector partners of the PDPs and country–level stakeholders (Annex: 11.1 List of Interviewees & Questionnaire Respondents). All recommendations are consolidated at the end of the report in Section 10.

3. The Value of the PDP Model

PDPs were originally developed to address the gap between the unmet need for new treatments and other interventions for diseases of poverty in the developing world, and the resources available to develop them. There is little if any commercial market to incentivise private sector organisations to invest in the discovery, development, and deployment of new interventions for these diseases and still be able to make a commercial return on their investments.

In many cases of the more neglected diseases (such as the kinetoplastid diseases focused on by DNDi and FIND), the expertise and knowledge about the diseases is widely spread and research groups are not always accessible or even known to the innovators and developers. PDPs have served a useful purpose in building networks of academics, clinical research centres, sample libraries, screening facilities, etc. into which the organisations undertaking development can tap into. PDPs are able to build and manage consortia of interested groups for the development of particular interventions where one organisation is not in a position to undertake the entire project. PDPs can also overcome barriers to communication between industrial organisations caused by intellectual property or anti-trust concerns. This is especially valuable in the development of combination products using drugs from two competing companies. Representatives from the pharmaceutical industry have highlighted that PDPs play an instrumental role in breaking down the institutional barriers between partners who otherwise would not work together and allowing for R&D initiatives that would not previously have been possible.

For the innovators, PDPs offer a mechanism to de-risk the product development process for neglected diseases. If all or part of the development of the needed interventions can be funded by an external organisation, the private sector[2] can justify putting some of its resources into actually carrying out the work.

The major private foundations active in this field – the Bill & Melinda Gates Foundation (BMGF) and the Wellcome Trust – are large enough and have the capacity and expertise to technically review individual project proposals from both funding and scientific perspectives, and make informed decisions about whether-or-not to support particular projects or require changes. A few of the public sector funders follow these procedures but others do not have the capacity or the detailed scientific and technical expertise to be able to review individual product development projects. Their focus is on reviewing funding applications at a disease or patient group/population level, or on the overall strategy of the applicant organisation.

In supporting PDPs, funders are able to tap into the scientific and technical expertise and mechanisms that each PDP has built up. They are also able to share the portfolio risk of each PDP with the other funders that support the specific PDP. The portfolio approach diversifies risk, increases the likelihood of overcoming the barriers to developing combination therapies, and decreases overall likelihood of failure. This approach can reduce costs through the use of platform approaches, the screening of compound libraries for applicability against multiple diseases, selection of only the most promising candidates for later stage development, and the leveraging of not only finance but technical expertise and infrastructure from a range of different partners.

Drug, vaccine and diagnostic development is lengthy and uncertain, leading to a need for stable long-term financing. The main identified risk associated with funding PDPs relates to funding sustainability as most funding to PDPs from public sector and private foundations is relatively short (between two and five years, while drug and vaccine development can take up more than 10 years).

PDPs have been very successful in revitalising the discovery and development landscape for neglected infectious diseases. Some initial results are now starting to be seen as new interventions are deployed:

- GeneXpert© from FIND, a test which can detect TB and resistance to rifampicin, a key drug in the current TB treatment regimen
- Various new drugs from DNDi and MMV
- Vector control interventions from the Innovative Vector Control Consortium (insecticide quantification kit, Actellic® CS)
- A meningitis vaccine, MenAfriVac from the Meningitis Vaccine Project – among others

They offer the public sector a way to invest in the development of new interventions by sharing of risk and tapping into global networks that otherwise would not be available to them if they only funded projects on a bilateral basis.

[2] In this report, the following definitions apply:

Public Sector – governmental organisations, predominantly at national or state level
Private Sector – for-profit organisations, e.g. pharmaceutical companies
Private Foundations – philanthropic organisations, e.g. Bill & Melinda Gates Foundation, Wellcome Trust, Medicins sans Frontières

4. Impact of Government Funding

Generally speaking, government funding is given as unrestricted grants[3] that the PDPs can use as they choose, or as semi-restricted to parts of the PDPs' portfolio, but still with freedom for the PDPs to allocate resources between projects in this part of their portfolio. The diversification of funding sources allows the PDPs to develop and own their strategy, which donors can then buy into. Unrestricted funding also gives PDPs the flexibility to move resources between individual projects quickly and efficiently depending on progress against the project milestones and target profiles. It also allows them to support the capacity-building and advocacy work that is essential to the overall delivery of their strategies, but which may not be easily allocated to a particular project.

Some stakeholders expressed that to be able to achieve ambitious goals a sufficient budget is needed. A strong framework of financial confidence is needed to develop the full potential of the PDPs.

As Government funding priorities generally follow international consensus opinions on global health needs and requirements, it is usually aligned with other public funding sources. Private Foundation (e.g. BMGF) funding is much more shaped by internal perspectives (e.g. of the principals).

Private sources of funding (e.g. Wellcome Trust or BMGF) are much more likely to give restricted grants and this reduces the flexibility and speed of response of the PDP to developments both in its portfolio and in the external environment. PDPs need to refer back to the funder for permission to make the appropriate responses. It may also introduce duplication of project review, as both the PDP and the funder will have mechanisms to check progress against their Go/No Go criteria. The need to align these reviews introduces another level of complexity to individual project management.

Interviewees stressed that restricted funding significantly reduces the PDPs' independence, especially if there is over-reliance on one-or-two such funders without a balancing stream of diversified unrestricted funding. A proper balance between unrestricted and more restricted funding needs to be struck by the PDPs and their supporters to ensure the most efficient way to deliver on projects.

In order for the risk-sharing (outlined in Section 3: The Value of the PDP Model) to be most effective, there is a strong argument for funders to provide funds to PDPs either as unrestricted funds or semi-restricted only by disease or target patient populations. This then allows the PDPs maximum flexibility and efficiency in applying their resources to the most promising projects and to shift resources quickly when a particular project fails to meet its desired Go/No Go decisions.

Constraints on Funding From a donor's view, funding to PDPs can be restricted in different ways:

- Limited to a specific disease, product area or stage of development
- Limited to a group of projects (portfolio funding)
- Limited to a specific project to the exclusion of all others
- Limited to the exact submitted budget – any changes or variations needing prior approval
- Limited to a certain timeframe (usually after the signing of a funding agreement and within a specific year).

[3] In this report the following definitions apply:
Restricted funding – The funds can only be used for a specific and named purpose and any changes to or reallocation of these funds has to have the prior approval of the funder.
Semi-restricted funding – the funders restrict the use of their funds to specified diseases or patient/population groups, but the funded organisation can reallocate the funds between individual projects in order to target the resources at the most productive ones.
Unrestricted funding – The funded organisation has complete flexibility to allocate resources between projects and portfolios to ensure that resources are targeted at the most productive ones.
However, while these definitions are generally agreed, their detailed interpretation may vary between PDPs and reported data may reflect these detailed differences in interpretation.

5. Measuring Value for Money and Impact

For donors, assessing or demonstrating the value for money (VfM) of the organisation or project they are funding has grown in prominence as the donors want, and need, to see that they are spending their money wisely and to demonstrate their accountability to their stakeholders. Essentially, VfM involves looking at "the optimal use of resources to achieve the intended outcomes"- and in the case of PDPs this is ultimately the potential for impact on poverty and health in developing countries.

Currently, public sector assessment of VfM of PDPs involves looking at the "three Es"[4]:

- Economy: getting the best value
- Efficiency: maximising the outputs for a given level of inputs
- Effectiveness: ensuring that the outputs deliver the desired outcome

It is possible to evaluate the organizational inputs through assessing efficiency and effectiveness of the PDP operations, which are short- and medium-term issues. However, assessing the long-term outcome and impact is much more challenging.

The PDPs are essentially R&D organisations working on products that can take anything from 5-10 years, or more, to reach the market, so donor investment in PDPs must be viewed as a long-term (and risky) venture.

It is difficult to know how to measure the potential impact of a product that is still years away from deployment. Positive clinical trial data is one way – but this may not be able to show that a new intervention is unambiguously better than other ones and there is still the inherent risk of failure at the next stage.

Health impact assessment measures reduction of mortality/ morbidity/ transmission of disease, but even once a product is available, in the diseases of poverty space this is difficult (given the poor quality of the data available globally). Mortality and morbidity data by disease is limited both by poor diagnosis and by poor record keeping. Similarly the impact of a single intervention is limited by poor data. Moreover, the new intervention is most likely only contributing to improved health outcomes rather than totally responsible.

Often the only reliable measure of impact is the number of interventions delivered, but this is not corrected for actual and appropriate usage. Measuring the impact of diagnostics is further limited by inevitable inefficiencies in the potential pathway that patients have to navigate from initial contact with the healthcare system to final diagnosis, as well as the ability of the endemic country health systems to properly integrate the use of the diagnostic tool with an appropriate treatment regimen[5].

VfM of a new product may be through its impact on market dynamics, e.g. increasing the number of products on the market, lowering prices though competition, ease of use etc. The health impact is the ultimate priority of the donors and may be the fundamental mission of the PDPs, but their ability and responsibility to measure it is open to question.

[4] As defined by the UK National Audit Office, see: http://www.idrc.ca/EN/Documents/Value-for-Money-Partnership-Practices-3.pdf The OECD has identified a fourth E: Equity to ensure that the VfM analysis accounts for the importance of reaching different groups. However this has not been evaluated in this report.

[5] For a detailed discussion of this issue in respect of tuberculosis, see Hsien-Ho Lin, David Dowdy, Christopher Dye, Megan Murray & Ted Cohene: Bull World Health Organ 2012;90:739–747A | doi:10.2471/BLT.11.101436

6. Drugs for Neglected Diseases initiative (DNDi)

6.1. Business Model & Strategy

DNDi was established in 2003 as a collaborative, patients' needs driven, not-for-profit drug R&D organisation. Its founding partners are Médecins sans Frontières (MSF), Oswaldo Cruz Foundation, Indian Council for Medical Research (ICMR), Kenyan Medical Research Institute (KEMRI), Ministry of Health of Malaysia, and Institut Pasteur, with WHO-TDR (a Special Programme for Research and Training in Tropical Diseases of the World Health Organization) as a special observer. Its mission is:

"To **develop new drugs**, or new formulations of existing drugs, for patients suffering from the most neglected communicable diseases. Acting in the public interest, DNDi will **bridge existing R&D gaps** in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners."

DNDi believes that a major part of its success to-date is due to its unique business model (see Annex 11.2.1 DNDi Business Model).

6.2. Achievement & Relevance

The 2007-2014 Business Plan set the objective of delivering 6-8 new treatments for visceral leishmaniasis (VL), human African trypanosomiasis (HAT), Chagas disease, and malaria by 2014 and to establish a strong R&D portfolio that addresses patients' needs. It also aimed to build and use sustainable development capacity in disease endemic countries, to advocate for the need to continue to develop new drugs for neglected diseases, and for increased public responsibility in this field. The Business Plan was updated in 2011 to cover the period 2011-2018. It increased the number of new products to be delivered to 11-13 by 2018, while exiting from malaria and starting work on "mini portfolios" in paediatric HIV and specific helminth infections (notably filarial disease).

The major target diseases – VL, Chagas, & HAT (kinetoplastid diseases) – have traditionally been ignored for the development of new treatments and patient care has suffered as a result. The development of new products has become a priority and DNDi is now filling this important gap. It has established a full drug discovery and development system to take new chemical entities (NCEs) from identification through compound screening through to regulatory approval. In the process it has developed a network of partners with whom it can expedite this process. It is the only organisation working on drug development for these neglected diseases.

Since 2007, DNDi has delivered 1 new treatment per year and has met its 2007 target of 6 novel treatments by 2014:

2007: ASAQ: Artesunate/Amodiaquine Fixed-Dose Combination (FDC) (malaria)

2008: ASMQ: Artesunate/Mefloquine Fixed-Dose Combination (malaria)

2009: NECT: Nifurtimox/Eflornithine Combination Therapy (HAT)

2010: SSG&PM: Sodium Stibogluconate/Paromomycin Combination Therapy (VL)

2011: Benznidazole paediatric dosage form (Chagas disease)

2011: Novel treatments for VL in Asia (single-dose AmBisome®: combinations based on AmBisome®, miltefosine, and paromomycin)

These are all "low-hanging fruit" that could be developed rapidly and with a high probability of success as they are either re-purposing existing drugs or developing combinations (especially FDCs). DNDi recognises that these have been relatively easy "quick wins" and that further success will be more difficult to achieve.

Malaria

DNDi's work on the development of ASAQ in collaboration with Sanofi was essential in enabling a less expensive antimalarial FDC to be made available more quickly than would otherwise have been the case. This allowed malaria control programmes in Africa to access an alternative FDC to Novartis' artemether/lumefantrine.

The work on ASMQ with Fiocruz has had less impact. This drug was targeted more at the Asian antimalarial market, but delays in getting the drug available in that part of the world has meant that its impact is not what was originally hoped for. DNDi has recognised that this was due to a weakness in the selection of the original implementation partner and is taking steps to add other partners who can ensure access in Asia.

Human African Trypanosomiasis

The development of NECT has had a major impact on the treatment of HAT in the field. As with the antimalarials, the concept of this combination was already established, but it took the intervention of DNDi to drive the development through to completion in a short space of time. NECT has now replaced the toxic melarsoprol as the treatment of choice for Stage 2 HAT.

Visceral Leishmaniasis

DNDi has widened the availability of key drugs for the treatment of VL – paromomycin, liposomal amphotericin, miltefosine – through new regulatory approvals in disease endemic countries and supported the development of novel combinations of these drugs and shortened treatment courses. These projects have widened the choice of and reduced costs of treatment for affected populations.

Chagas Disease

DNDi's development of a paediatric formulation of benznidazole has filled an important gap in the drugs available to treat this disease, allowing better treatment for children in a disease where early treatment is important for final outcomes.

It has also established three disease-related capacity building platforms to support the three main target diseases – LEAP, HAT Platform, and the CCRP. In addition, it has established a network of Regional Offices to support its advocacy work as well as to conduct clinical trials in endemic areas and work with ministries of health and regulatory authorities in major target disease-endemic countries. Two Country Support Offices have been established in Japan and the USA as fund-raising and advocacy operations. Some of the offices are independent legal entities and some are legally branches of DNDi in Geneva.

More details of DNDi's achievements can be found in Annex 11.2.5 DNDi Achievements.

6.3. Impact of Government Funding

From its inception, DNDi has had a policy to avoid being overly dependent on one donor. Its target is to be funded 50:50 by the public and the private sectors, with no one donor giving more than 25 % of total income in one year. This diversification of funding sources has always been intended to allow DNDi to develop and own its strategy, which donors can buy into. DNDi does accept funding restricted to individual projects, but ultimate decision-making on the progression of individual projects remains with DNDi. Management are clear that funders must buy into the DNDi strategy before accepting funding from them. For further details, see Annex 11.2.2 DNDi Funders.

During the period in question, DNDi has been able to achieve its funding diversification target:

Table 1: DNDi - Funding by Source 2009-2013

(EUR mill)	2009	2010	2011	2012	2013
Public	11.768 (55.9 %)	11.889 (47.5 %)	13.457 (52.1 %)	16.280 (54.6 %)	17.813 (57.0 %)
Private[6]	5.856 (27.6 %)	9.413 (37.6 %)	8.320 (32.2 %)	8.756 (29.3 %)	8.249 (26.4 %)
Founders[7]	3.492 (16.6 %)	3.631(14.5 %)	3.956 (15.3 %)	4.750 (15.9 %)	4.949 (15.8 %)
Other income	0 (0.0 %)	0.084 (0.3 %)	0.096 (0.4 %)	0.061 (0.2 %)	0.231 (0.7 %)
TOTAL	21.267	25.018	25.831	29.846	31.242

In the same period the proportion of restricted and unrestricted funding has been:

Table 2: DNDi - Split between Restricted and Unrestricted Funding 2009-2013

(EUR mill)	2009	2010	2011	2012	2013
Unrestricted	11.257 (52.8 %)	11.111 (50.3 %)	12.046 (46.6 %)	9.306 (31.2 %)	10.909 (34.9 %)
Restricted	10.010 (47.2 %)	13.907 (49.7 %)	13.786 (53.4 %)	20.540 (68.8 %)	20.333 (65.1 %)
TOTAL	21.267	25.018	25.831	29.846	31.242

Private sector funding is almost exclusively restricted (97.4 %), so the importance of funding from the public sector and from the Founders in maintaining the flexibility of unrestricted funding has been essential in allowing DNDi to pursue its strategy (see Section 4 Impact of Government Funding).

6.4. Capabilities

Governance

DNDi is a well-governed organisation, with oversight of management being supplied by a Board of between seven and 13 members. Each of the six founding partners can nominate one Board member with WHO-TDR as a permanent observer. Board members serve for a maximum of three terms of four years. Two seats are reserved for "patient representatives" to ensure the voice of the ultimate beneficiaries of the work of the organisation is heard. In addition, with the exception of MSF, donors are excluded from Board membership. The Chair is elected from the Board members and serves for a maximum of six two-year terms. The current Chair is Prof Marcel Tanner (Director of the Swiss Tropical and Public Health Institute) and there are ten Board members in place (as of 01 November 2014). The Board usually meets every six months.

Scientific oversight is supplied by a Scientific Advisory Committee (SAC), which has a minimum of five members. Members serve for a maximum of three four-year terms. The SAC is currently chaired by Prof Pierre-Etienne Bost (Institut Pasteur) and has 17 members, drawn approximately 50:50 from institutions in the "North" and the "South", as well as a mix of public and private sector representatives. Few other institutions such as The Gates Foundation, National Institutes of Health (NIH) and Medicines for Malaria Venture (MMV) attend the SAC meetings as observer, but are not members.

There is a properly documented process for selection and appointment of Board and SAC members. This governance structure has evolved over the lifetime of the organisation and is currently stable.

The SAC reviews all projects on a six-monthly basis in depth and reports on progress against clear Go/No Go criteria to the Board, who have the final decision on the allocation of resources against individual projects. All projects have well-defined target product profiles which have been developed to meet the needs and

[6] Private in this context includes private foundations and private sector.
[7] Principally MSF.

constraints of the environments the products will be used in and are published on DNDi's website. The SAC also advises the Board on the relevant aspects of DNDi's strategy.

Financial oversight is also supplied by the Audit Committee of the Board.

Based on the minutes of the Board and SAC meetings, there is robust and detailed interrogation of all management proposals. It is clear that management work closely and well with the Board and SAC, but are not given automatic approval for their proposals. This is best illustrated by the discussion over the decision to commence work on the mini-portfolios for paediatric HIV drugs and filariasis. Both the Board and SAC are maintaining a close watch over these decisions to ensure that DNDi does not suffer "mission creep" away from its core strategic focus on kinetoplastid diseases and spreads its resources too thin.

DNDi also holds an annual event to bring together key global stakeholders. This gives opportunities for groups not directly represented in the formal governance structures of DNDi to have input into the thinking of the organisation. There are also regional meetings organised through the Disease Platforms and the Regional Offices that allow for more stakeholder feedback to the organisation.

Strategic Planning

DNDi has a robust strategic planning process which is actively reviewed by both management and the Board. They have developed two strategic (or "Business") plans in the period under review – one covers 2007-2014, and an update to cover 2011-2018. The current plan covers not only the R&D strategy, but also the business model, access strategy, organisation & governance, financing, and human resourcing. In line with best practice, the strategy has been developed in an iterative manner driven by management but with proper consultation and input from the Board. The SAC has been involved in reviewing the scientific aspects of the strategy. The Board and Management continue an active discussion to ensure that the Strategy remains relevant and appropriate. This again is reflected in the ongoing debate about the diseases that should be included in the portfolio.

Risk Management

DNDi has a well-documented risk management strategy, including a comprehensive risk register. The register is updated annually by management and reviewed by the Board annually as part of the Annual Plan discussions. The Register covers discovery & preclinical, clinical & access, targeted diseases, mini-portfolios, business development, operations, regional offices, advocacy, fundraising, & financial. Identified risks are matched with mitigation strategies. There is no specific section of the register covering reputational risk – given the need to maintain a high reputation in order to attract resources to the organisation and maintain its influential status, it would be advisable to consider including reputational risk specifically in the register going forward.

In addition to the Risk Register DNDi's risk management tools include:

- Internal control and audit processes and manuals
- Internal policies (e.g. conflict of interest, anti-corruption)
- R&D guidelines, compliant with international standards and local regulations
- Internal Quality Assurance (QA) function
- Insurance (including liability insurance for clinical trials)

Ad hoc risk reviews may take place if a particular risk emerges, with a clear pathway through management to the Board (if necessary).

DNDi, in its Risk Management Policy, recognises that it may need to take on some level of operational risk in the interest of the patient (which it has placed central to its Mission and Strategy) to ensure new products are available as quickly as possible. DNDi characterises such risk as:

- In the absence of an ideal treatment candidate for a specific disease, DNDi will invest further in an alternative compound with an acceptable risk/benefit profile
- Create innovative clinical trial designs to fast track drug development

- Carry-out clinical trials in challenging areas of disease endemic countries
- Put in place or encourage innovative regulatory strategies
- Transfer technology to guarantee a second production source and secure the supply chain

Financially, DNDi operates on a conservative basis. In the 2013 Accounts, 90 % of its assets were held in cash or cash equivalents and its current ratio (current assets/current liabilities) was 1.74, showing that it was well able to cover its financial liabilities and minimise financial risk.

Budgeting

There is a well-developed budgeting process in place, with resources allocated across several dimensions – by project, by function, by geography, and by stage of development.

Capacity for Change

DNDi has shown a strong capacity to alter their strategies and plans depending on the changing environment. This has been achieved through their robust strategic planning process, the strong involvement of both Board and management, close connections through their local networks with the situation on-the-ground, and recognition of the need to foresee issues before they become problems and respond to them early.

Clinical Trial Management & Capacity

Most clinical trials in DNDi's main target diseases are conducted through the three regional disease-specific platforms (LEAP, HAT, CCRP). These platforms:

- Bring together key regional actors in the health field, including ministries of health, national control programmes, regulatory authorities, academia, civil society groups, and pharmaceutical companies, as well as clinicians and health professionals.
- Utilise, capitalize upon, and reinforce clinical capacities in endemic regions, and address infrastructural requirements where necessary.
- Provide on-site training in clinical research in sometimes very remote settings.
- Support registration and implementation of products.

The regional platforms are seen as a key element in DNDi's overall strategy to achieve its mission. The platforms have allowed for adequate clinical trial capacity to be built up, and the forward planning of the project portfolio can identify further capacity needs and how to address them.

DNDi conducts clinical trials to global Good Clinical Practice (GCP) standards and this ensures minimal problems with regulatory review of the studies. The platforms allow for the development of a cadre of trained trial monitors to be built up across a region. In the case of LEAP, trial sites in one country are being monitored by monitors from another country in the platform to maintain objectivity and quality. Phase 1 studies are conducted in European centres but using subjects of sub-Saharan African ethnicity. Synopses of clinical trial protocols are reviewed by three members of the SAC to ensure quality. DNDi will face a major challenge to grow its clinical trial capacity as it projects 15,000 subjects over the next ten years. Also the nature of the studies is changing from simple implementation studies to full developmental clinical trials including developing NCEs.

Communications with Stakeholders

DNDi has a well-developed communication and advocacy strategy and approach. Annual plans with well-defined objectives are produced as part of the annual planning process. The communication targets are extensive (including the scientific community, policy makers, donors, global health experts, and civil society). DNDi sees correctly that it is important to include communications at the regional level, and the Regional Offices are a key component for this. The communications plan is aligned with and supports the overall mission, especially to raise awareness of the neglected diseases it is targeting. A wide range of

communication tools are used, and two-way communication is encouraged, especially through meetings and events, especially the annual Partners' Forum or similar events.

Some interviewees did express the view that DNDi could do more communications in collaboration with other PDPs, either to explain the benefits of the PDP model or to promote wider awareness of the neglected diseases that it works on alongside other PDPs.

Financial Sustainability

DNDi has been successful in raising the necessary finances to sustain its project portfolio and other aspects of its strategy. Table 3 shows the forecasted income needed to meet the 2011-2018 Business Plan and the actual amounts raised:

Table 3: DNDi - Forecast & Actual Income Requirements

(EUR mill)	2011	2012	2013	2014	2015	2016	2017	2018
Forecast	29.9	34.3	35.5	40.2	40.8	39.8	40.8	40.1
Actual	25.8	29.8	31.2					

While the actual income (as reported in the Annual Financial Report) has been lower than the Business Plan forecast, it does not appear to have significantly impeded DNDi's work to meet its mission. Given that the forecast need is relatively flat at around EUR 40 mill/year, and DNDi's track record of attracting funding from a variety of donors, it is clear that the organisation is financially sustainable under present circumstances. Fuller details of the income and expenditure over the period under evaluation are found in Annex 11.2.3 DNDi Income and Expenditure Statement 2009-2013.

Each year a fundraising plan is generated, showing the funding gap for the next three years and the potential ways to be used to fill the gap. This plan is approved by the Board. In order to ensure financial sustainability, DNDi is actively seeking to diversify its funding base. The 50:50 public to private ratio and <25 % from any one donor rules are the starting points, and new donors are being constantly identified and pursued (see Annex 11.2.2 DNDi Funders).

DNDi aims to be able to take a potential new treatment through the entire discovery and development process. This is in addition to achieving better treatments for the target diseases through short- and medium-term objectives by repurposing or reformulating work that achieves quick wins for patients. Full development is a long and expensive process, based upon pharmaceutical industry numbers. DNDi's business model enables it to reduce the cost of discovery and development, e.g. through conducting clinical trials in disease-endemic countries and collaborating with other institutions (rather than building and retaining in-house expertise). However, it will need to keep this under careful review to ensure the forecast financing needs are adequate as more projects and programmes move from compound screening and candidate selection to full clinical development.

Collaboration with Industry & the Private Sector

DNDi has built up close collaborations with several pharmaceutical companies and has earned respect as a professional collaborator. Its expertise and access to development and clinical capacity in disease endemic countries is valued. However, DNDi remains dependent on its existing relations with Sanofi and Cipla. DNDi has expressed concerns about the limited number of private sector partners who are prepared to collaborate on drug development at the clinical stages, but this is a reflection on the level and prioritisation of companies' resources available rather than a comment on DNDi's capabilities. It does raise the challenge of more work having to be managed directly by DNDi itself and the potential impact on future resource needs as discovery projects move into full clinical development. This is an area that DNDi will need to keep under constant review. DNDi does have a policy of not being a marketing authorisation holder, which is advisable, but again underlines the need to get industrial partners in place for the implementation phase as early as possible, even if these partners will not be able to be a major part of the product development.

6.5. Contribution to Accelerated Access

DNDi has developed a strategy for access as part of the overall Business Plan 2011-2018. It recognises that:

- The TPPs for new products must properly reflect the needs of affected populations and the environment in which care has to be delivered;
- An industrial implementation partner needs to be identified and terms agreed as early as possible. DNDi's access policy are written so that long-term supply agreements with manufacturers are at lowest cost-of-goods-sold, with a price to enable widespread access and IP that also ensures global access;
- Local operation in disease-endemic countries is essential to ensure access;
- There is no one-size-fits-all approach that is suitable in the diseases and geographies that DNDi is operating in.

DNDi has learnt from experience that it is not enough to rely on implementation partners to ensure access, but that it needs to remain involved as a facilitator to see that partners can work effectively together to deliver the interventions to patients. Access is not a separate department within DNDi, as the organisational philosophy is to build it into all aspects of its work.

The impact of DNDi's work is summarised in the table below:-

Table 4: DNDi - Impact of Developments[8]

Impact	Comment
Disease Burden	**HAT:** estimated cases = 20,000/yr. (fatal disease) **VL:** estimated cases = 200 – 500,000/yr. (fatal disease) – only surpassed by malaria and lymphatic filariasis among Neglected Tropical Diseases (NTDs). **Chagas disease:** infected patients = 8 million: 12,000 deaths/yr.
Cost of Treatment	**Malaria:** ASAQ was launched in 2007 priced at USD 1/adult & USD 0.5/paediatric course of treatment, in line with the target established for affordable malaria treatment by the global community. **HAT:** NECT treatment is 50 % less than existing monotherapy, reducing treatment from 14 to 10 days and removing need for overnight infusions. **VL:** SSG&PM combination treatment developed reduce treatment time from 30 to 17 days. Drug costs reduced from USD 56 to 44.

[8] The table was provided by DNDi on request from the reviewers. DNDi noted some concerns on the limitations of the methodology as the accuracy of these figures for lives saved or cases adverted has been developed on rough calculations based on different case fatality rates for the various diseases.

Impact	Comment
Guidelines	**WHO Essential Drugs List additions:** • Benznidazole Paediatric (Chagas) • NECT (HAT) • SSG&PM combination (VL) • ASAQ & ASMQ (malaria) **Stage 2 HAT:** • NECT adopted in all 8 HAT Platform countries. 99 % of Stage 2 patients now treated in line with these guidelines in 12 countries. **Visceral Leishmaniasis:** • Brazilian guidelines revised on basis of DNDi data (2014). • WHO Expert Committee recommended SSG&PM for first-line treatment in East Africa (2010)
Regulatory Approvals	**Benznidazole Paediatric Formulation:** • Approved in Brazil, Argentina, Bolivia, and Paraguay. **Malaria:** • ASAQ registered in 35 countries (incl. 31 African). • ASMQ registered in 6 countries.

Impact Estimation

As detailed in section 5 (Measuring Value for Money and Impact), measurement of the health impact of interventions in the diseases of poverty space is difficult, given the poor quality of the data available, both at a global level and from DNDi's sources.

The impact (as reported by DNDi) in terms of treatments delivered shown in the table below:

Table 5: DNDi - Impact of Developed Treatments[9]

Disease	Treatments distributed	No. of reported cases/yr.	Deaths/yr.	Case Fatality Rate (CFR)	Lives saved
Malaria	ASAQ: 320 mill (2007-2014)	207 mill (2012)	0.6 mill (2012)	0.3 %	963,600
Malaria	ASMQ: 1.2 mill (2008-2013)				
HAT	NECT: 13,000 (2009-2013)	6,871 (2013)	9,110 (2010)	100 %	13,000
Visceral Leishmaniasis	SSG&PM *Combination for Africa* 25.000 patients (2009-2013)	200,000 – 400,000	20,000 – 40,000	10 %	2,500
Visceral Leishmaniasis	*Combinations for Asia* 1,600 patients treated in Pharmacovigilance (PV) study since 2011				160

[9] The table was provided by DNDi on request from the evaluation team. DNDi noted some concerns on the limitations of the methodology as the accuracy of these figures for lives saved or cases adverted has been developed on rough calculations based on different case fatality rates for the various diseases.

6.6. Value for Money

DNDi's business model delivers Value for Money (VfM) for donors in the following ways:

Economy

DNDi makes every effort to keep costs to the minimum without jeopardising its ability to fulfil its mission. The disease platforms and other collaborators in disease-endemic countries help to keep development costs to a minimum. Its main role as a facilitator and co-ordinator of projects means that it can out-source work to the most appropriate collaborators in its network and not have to retain a large and expensive expertise in-house. DNDi projects that its model will allow it to develop a new drug (NCE) completely for EUR 100-150 million including the usual attrition rate in the field of infectious diseases (without in-kind contributions), which is an order of magnitude less than industry standards. It remains to be seen if this is realistic. However, it has a well-developed budgeting system and good Board oversight to ensure that budgets remain both realistic and achievable.

DNDi's 2011-2018 Business Plan states that *"In order to deliver upon its mission, DNDi will not always consider the lowest costs. Serving its capacity strengthening and advocacy objectives may sometime require strategic rather than solely cost-effective choices. With clearly set guidelines, DNDi will need to ensure its resources are delivering the most value to its social mission."* The Plan sets an objective of non-Social Mission Costs of 11 % income. In the five years under evaluation, these costs have risen from 10 % in 2009 to 13.4 % in 2013 related to additional costs arising from DNDi's efforts to diversify its funding base (see Annex 11.2.3 DNDi Income and Expenditure Statement 2009-2013).

Interviewees have suggested that DNDi could consider more pooled procurement of certain key services to further reduce costs (e.g. collaborating with MMV and TB Alliance over contracting with laboratories or Phase 1 clinical centres, where the needs are similar).

Efficiency

Through the Regional Offices, DNDi is able to more efficiently liaise and communicate with ministries of health and regulators. This ensures a more efficient path for the new treatments that they have developed to be taken up by the health systems in the affected countries. It has a well-established discovery and development process in place (involving both internal project teams and external review processes) that ensure projects move through the process in an efficient way. In addition, by having a high proportion of its income in unrestricted funds, it allows for quicker and more efficient re-allocation of funds between projects, depending on progress of each project against the pre-set Go/No Go criteria.

Effectiveness

To-date, DNDi has been very effective in delivering on its mission and on its target of 6 novel treatments by 2014. It has a broad portfolio with a range of projects across all stages of discovery and development for all the target diseases (see Annex 11.2.4 DNDi Project Portfolio). This is supported by a talented staff with the range of experience needed to deliver on the portfolio. It has effectively built capacity through the disease platforms and has also formed an effective network of Regional Offices. It remains active in advocating for its core target of the kinetoplastid diseases.

Internal Measurement of Value for Money

DNDi does not currently measure value in purely monetary terms, preferring to look at the value to the patients and the impact of its work in terms of treatments delivered (see Table 5: DNDi - Impact of Developed Treatments). This reflects two things. Firstly, there is the lack of a viable commercial market for many of its drugs. Secondly, the disconnection of the cost of development from the cost to the patient, so as to increase the affordability of treatments by removing the need to recoup development costs in the price of the treatment. However, measurement of VfM remains an issue that they are keeping under constant review, given the interest of many donors on this.

6.7. Conclusions

It has been impressive from the interviews with stakeholders on the near universal praise both for the work of DNDi and the manner in which it carries this out. Interviewees have been at a loss to find fault with the business model, governance, operations, or financing of the organisation. The main concern expressed has been over the potential for "mission creep" away from the core focus on kinetoplastid diseases. There has been recently discussion about a further move into hepatitis C, in addition to the agreed moves into paediatric HIV and filarial disease. These moves represent a real risk of diluting efforts on the core parts of the portfolio. It is important that DNDi remains focused on delivering needed NCEs and not simply being seen to be active in a range of disease spaces, at the risk of jeopardising its ability to bring genuine NCEs for kinetoplastids diseases all the way through the discovery and development process. However, it is reassuring that the SAC and the Board have these issues under close and continuous review.

DNDi has clearly contributed to improving access for key drug interventions in malaria, HAT, Chagas disease, and VL. In addition, through the disease platforms, it has been successfully building capacity in disease-endemic country level, with plans to make this sustainable *post*-DNDi. It has a clear strategy to build on this early success, but remains dependent on ensuring a stable and sustainable source of funds, something for which it is acutely aware and devotes considerable resources to achieving.

7. Foundation for Innovative New Diagnostics (FIND)

7.1. Business Model & Strategy

FIND was established in 2003 to help to ensure that new diagnostic tools are developed for infectious diseases that disproportionately affect the poor and disadvantaged. Effective, reliable, inexpensive, and appropriate diagnostic tests are fundamental to support evidence-based decisions at all levels of the health system. They are needed to better manage patients, reduce disease transmission, lower drug- resistance and increase optimal allocation of resources. Use of reliable diagnostic tools underpins drug and vaccine research, and they are essential for disease surveillance and to prevent incorrect treatments which lead to the development of drug resistance.

FIND is a non-profit foundation with its headquarters located in Geneva and with offices in New Delhi (India), Kampala (Uganda) and Cape Town (South Africa). Although initially focussed on TB, FIND's portfolio now includes HIV, malaria, HAT, leishmaniasis, Chagas disease, Buruli ulcer, and hepatitis C.

FIND's mission and vision (as updated in the new 2015 Strategy[10]) are:

- ***Vision:*** *A world where diagnosis guides the way to health for all people*
- ***Mission:*** *Turning complex diagnostic challenges into simple solutions to overcome diseases of poverty and transform lives*

To support the vision and mission, FIND works around four strategic goals (see also Annex: 11.3.1.1 Outline of FIND's New Five-Year Strategy 2015 - 2020):

1. **Catalyse development:** By identifying needed diagnostic solutions and removing barriers to their development,
2. **Guide use & policy:** By leading products through the clinical trials pathway to global policy on use and market entry,
3. **Accelerate access:** By supporting uptake and appropriate use of diagnostics to achieve health impact, and
4. **Shape agenda**: By improving understanding of the value of diagnostics and strengthen the commitment to their funding and use.

In 2011 – 2013 FIND went through a major period of change, caused by having accumulated a significant financial deficit with resulting serious concerns regarding the organisation's governance and senior management. FIND has addressed the issues and shortcomings on multiple levels and is now a viable PDP with revised direction, strengthened governance and renewed energy. In various interviews collaborators and stakeholders have commended FIND for its contributions to advancing the development of game-changing diagnostic technologies, including the final demonstration and implementation.

7.2. Achievements & Relevance

Since 2003 FIND has acquired and integrated into its operations a deep technical and field expertise in the development and implementation of diagnostics in the respective diseases and shares its expertise and know-how with its development partners. These new diagnostics address very different needs: from

[10] Per new 2015-2020 Strategy http://www.finddiagnostics.org/resource-centre/reports_brochures/find-strategy_2014.html ; originally: Our vision is of a world where everyone has equitable and timely access to high quality and affordable diagnosis.
Our mission is to drive the development and early implementation of innovative diagnostic tests that have a high impact on patient care and disease control in low-resource settings.

individual case management and public health approaches to disease elimination or eradication strategies. They also fulfil specific purposes: detecting infections and cases, detecting drug resistance, monitoring individual disease stages or treatment response or monitoring disease epidemiology in large populations.

One of FIND's unique contributions to the field is its ability to demonstrate the utility of new diagnostics and to support their market entry after product development[11]. This includes support for the collection and provision of appropriate data on test performance and use for regulatory approval, endorsement by normative agencies (e.g. WHO) and national health authorities in a rapid and cost-effective manner, as well as building in-country capacity for implementation through comprehensive training programmes for health workers and laboratory and infrastructure strengthening. From 2011 – 2013 FIND scientists have co-authored or supported the research of over 70 journal publications[12].

Major product developed launched: From 2009 – 2013 FIND has significantly contributed to the registration of 7 new diagnostics in previously neglected areas and delivered on some of main strategic goals as laid out in the original FIND business plan from 2003 and annual business objectives 2009 – 2011. See also Annex 11.3.5.1 FIND Achievements.

Table 6 gives an overview of major products developed and launched that received the CE mark[13] for in vitro diagnostics in the European market, were endorsed by WHO or registered elsewhere.

Table 6: FIND - Major Products Developed Launched

Diagnostic	Industry Partner	Purpose	Progress
LED fluorescent microscope	Zeiss (Germany)	For TB bacilli detection with higher sensitivity	WHO endorsement 2009
Xpert MTB/RIF	Cepheid (USA)	An automated rapid test for TB and multidrug-resistant TB strains	CE mark 2009, WHO endorsement 2010, for Extra-pulmonary TB and TB in children 2013
TB LPA 2nd line	Hain Lifescience (Germany)	Test for TB and resistance to 2nd line TB-drugs	WHO endorsement 2013
TB LAMP	Eiken (Japan)	A manual molecular test for TB	CE mark 2011
Malaria LAMP	Eiken (Japan)	A manual molecular diagnosis and detection test of very low parasite density	CE mark 2012, WHO endorsement 2014
HAT LAMP	Eiken (Japan)	Sensitive molecular test for HAT, potentially to test of cure, and for predicting relapses when treatment is not successful	Japanese COFS for export only 2012
HAT RDT	Standard Diagnostics (Korea)	A lateral flow rapid diagnostic test to screen for HAT	Korean FDA 2012

LPA: Line Probe Assay LAMP: Loop-mediated isothermal DNA Amplification RDT: Rapid Diagnosis Test

[11] The development process of diagnostics differs from the R&D of medicines considerably, and can be divided in five stages: Feasibility, Development, Evaluation, Demonstration and Implementation (see Annex 11.3.4.2 FIND Project Portfolio Development and Achievements over Time).

[12] Scientific articles by FIND team and partners: http://www.finddiagnostics.org/resource-centre/scientific-articles/

[13] The CE mark (Conformité Européenne) is a mandatory conformity marking for certain products sold within the European Economic Area (EEA) since 1985 and is also found on products sold outside the EEA that are manufactured in, or designed to be sold in, the EEA. The CE marking is the manufacturer's declaration that the product meets the requirements of the applicable EC directives.

Three achievements should be highlighted (for a more complete overview see Annex 11.3.5.1 FIND Achievements):

- **Xpert® MTB/RIF** (Xpert) is a new cartridge-based assay used in a multi-disease testing platform that simplifies molecular testing by integrating and automating the three processes required for real-time PCR-based molecular testing. The support of the development of the Xpert can be regarded as one of the most significant contributions of FIND and has been identified by several interviewees as a game changer that has revolutionized the management of TB in many countries. Xpert has experienced a broad uptake globally with over 5 million cartridges procured in the public sector of 80 low- and middle-income countries. Country data has confirmed significant increases in case detection and reductions in time to treatment and misdiagnoses for TB and MDRTB. In 2013 the WHO recommended that Xpert also be used for diagnosing TB in paediatric and HIV patients, where diagnosis of TB can be rather difficult.
- **Rapid Diagnosis Test (RDT) for HAT:** This first ever RDT for HAT (using lateral flow format) was launched in December 2012. The test is cheaper ($ 0.50), more cost-effective and more sensitive than the traditionally used card agglutination test for trypanosomiasis (CATT), both in active and passive screening, and is being used in 5 out of 7 projected countries (currently in 166 health facilities) to accelerate elimination of the disease.
- **Specimen Banks:** FIND provides diagnostics developers with access to its specimen banks, which have been highlighted by various interviewees as an invaluable resource for the field. The large TB, malaria and HAT specimen banks have a broad and unique variety of well-characterized samples of clinical strains and panels of different geographic origins, with different genotypes, and drug susceptibility characteristics. They support biomarker discovery work[14], assay development and validation. Banked materials can be used to quickly and effectively test the feasibility of new prototypes or concepts at low cost. Using stored specimens for product validation and for comparative studies of performance across different diagnostic platforms results in much lighter clinical trial needs and provides a cost-effective mechanism for the robust evaluation of diagnostic technologies.

FIND recognized that there is still an urgent need for PoC diagnostics, specifically in TB and that the efforts to develop the much wanted RDT for TB is still limited from the failure to identify biomarkers. Also efforts to develop a test for HAT stage 2 are being re-considered due to falling prevalence and scientific hurdles.

Interviewees pointed out that FIND has contributed immensely to the field of diagnostics for the respective diseases. Specifically in the field of TB diagnostics FIND has been productive within a short time period. This may be because the initial work was rather easy to accomplish (“low hanging fruit”), and future innovations might be more difficult to achieve and more resource intensive. For more detail see Annex 11.3.5.1 FIND Achievements.

[14] The lack of diagnostic markers is currently one of the biggest bottlenecks to the development of the most critically needed diagnostics for a number of diseases.

7.3. Impact of Government Funding

Funding Diversification

Although previously heavily dependent on funding from the BMGF, FIND had been able to achieve significant funding diversification in 2009 – 2013, which can be seen by an increase of total funds as well as a changing proportion between public and private funds received. See Annex 11.3.2.1 FIND Funders and Table 7: FIND - Funding by Source 2009-2013.

Table 7: FIND - Funding by Source 2009-2013

(EUR mill)	2009	2010	2011	2012	2013
Public	7.0 (37 %)	16.3 (48 %)	11.3 (58 %)	11.4 (49 %)	31.8[1] (75 %)
Private[15]	11.8 (63 %)	17.6 (52 %)	8.2 (42 %)	11.7 (51 %)	10.6 (25 %)
TOTAL	18.8	33.9	19.5	23.1	42.4

[1]Increase mostly due to large funding by GFATM

In the same period FIND has been successful in increasing the proportion of unrestricted funding (Table 8).

Table 8: FIND - Split between Restricted and Unrestricted Funding 2009-2013[16]

(EUR mill)	2009	2010	2011	2012	2013
Unrestricted	0 %	11 %	9 %	23 %	22 %
Restricted	100 %	89 %	91 %	77 %	78 %

From its original dependence on a single donor, FIND is now working on a balanced funding portfolio of restricted, semi-restricted, and unrestricted funding to ensure organizational sustainability. See also Section 4 Impact of Government Funding.

7.4. Capabilities

Governance

Organisational Development: Within the observation period FIND has undergone several significant changes and transitions within its leadership, having 3 CEOs within 3 years (2011 – 2013). As a result of two external evaluations by the Boston Consulting Group (March 2011 and June 2013, initiated by the then major funder BMGF) significant recommendations to strengthen the organisation and correct failings in financial and other procedures were made. FIND has been implementing significant changes to the organisation including a revision of governance structures, accounting routines and financial management. It also conducted a critical look back on its strategy, approach, and performance.

Board of Directors: FIND has improved the competence of the board and the geographical spread (Switzerland, France, Germany, USA, India, and Brazil) which will be further increased from 8 to 10 members by March 2015[17]. Additional membership of ex-industry experts is also being considered. Since 2012 Board Committees on Audit and Finance, Remuneration, and Science have been introduced which address concerns raised in previous evaluations regarding the financial management. A committee for policy and advocacy is also being considered.

[15] Private sector in this context includes private foundations, such as the Bill and Melinda Gates Foundation.
[16] Data provided by FIND CFO
[17] There are also discussions ongoing regarding the chair of the SAC being a permanent ex officio member of the FIND board.

Scientific Advisory Committee (SAC): Recent changes have significantly strengthened the external scientific oversight and advice available to FIND. The SAC (nominated by the Board) Chair (currently Marcel Tanner) regularly presents to the Board. It currently has 15 members from 8 countries[18]. FIND encourages donors to participate in the SAC (however not on the Board).

SAC recommends to the Board which project applications it feels are worthy of support, but the final decision is taken by the Board. The SAC also advises the Board on the overall scientific strategy – either directly or through its Science Committee (BSC) – and on the best technology and disease portfolio options for FIND in line with its strategic objectives. It also reviews the overall scientific management process of projects. As requested by the Board or the BSC, the SAC provides expertise on diagnostics development, licensing, as well as any other public health or scientific issues.

The SAC does not make final decisions on specific project progress and detailed shaping of the portfolio – these and individual project Go/No Go decisions are made by the respective FIND programme heads. However, moves into new areas need to go through SAC and Board, as these may come at an opportunity cost to other disease areas. FIND is currently discussing how to appropriately involve the SAC in the portfolio decision-making process. It should be noted that FIND feels it has more projects and many smaller projects compared to other PDPs like MMV and DNDi, so believes that individual project reviews by SAC are impractical. The SAC does advise on the continued relevance of a particular platforms (e.g. LAMP) to ensure FIND is not wedded to something when better or more appropriate technologies are being developed.

Senior management team: The CEO's management span is very wide (see Annex 11.3.1.2 FIND Organogram 2014). The problem has been acknowledged and there is a hiring plan to recruit a Chief Medical Officer (CMO) and Chief Access Officer (CAO) who will head up the regional offices. However, FIND is currently waiting for clarity on funding for 2015 and beyond to make these hires.

Strategic Planning

As a consequence of the financial and leadership issues, FIND carried out an assessment to look at options of merging with another PDP (details of which were not shared with the consultants). However, there was broad consensus among the stakeholders consulted that there is an important role for FIND as an independent organisation. Instead, in 2014, as a result of a diligent review of previous experience and in consultation with key stakeholders, FIND developed a new organizational strategy and product development approach for 2015- 2020, adapting to a now richer and more engaged private sector environment and shifting funding policies of some large donors. For more detail on the importance of diversification of funding sources see Section 4 Impact of Government Funding.

The new strategy 2015 – 2020[19] readjusts the way FIND contributes to the development of diagnostics and interacts with the field and collaborators. Many of the interviewees stated that the new strategy looks promising. However, it remains to be seen how this will be implemented, what effect it will have on the diagnostics landscape, and if it will meet the organisation's Vision and Objectives.

In this new five-year strategy FIND's role as bridge builder between developers and implementers and as a mobilizer is to become more relevant. FIND plans to shift its historical focus from actively developing new tests in collaboration with private sector companies to one that is centred on what FIND calls "packaged solutions". This also reflects upon the fact that funding is now also becoming available directly to the private sector for product development.

FIND wishes to expand its role as a translator between the technical world of product development and the realities of end-users and seeks to make linkage to treatment and care issues by moving from a single

[18] Switzerland, USA, Germany, UK, UAE, DRC, Canada, and Argentina

[19] The FIND Strategy 2015 -2020 can be found here http://www.finddiagnostics.org/resource-centre/reports_brochures/find-strategy_2014.html. An outline of the strategy is presented in Annex 11.3.1.1 Outline of FIND's New Five-Year Strategy 2015 - 2020

disease-specific lens to also consider syndrome-based approaches that better address clinical realities. For more detail see Annex 11.3.1.1 Outline of FIND's New Five-Year Strategy 2015 - 2020.

Cross-cutting themes will play a larger role e.g. the "Support for Success" program, through which the support of industry experts is provided to test developers – particularly to small and medium enterprises to help overcome product design, manufacturing and marketing hurdles faced by many of these developers.

The priority disease areas for 2015 – 2020 are: Tuberculosis and Acute Febrile Respiratory Infections, Malaria and Acute Febrile Syndrome, Hepatitis C, and NTDs. For each of these four main areas FIND has identified development / policy priorities and the corresponding enabling interventions needed. This analysis guides the focus of the 5 year strategy until 2020 and the deliverables FIND has set out to work on. Beyond these four areas FIND will also have mini-portfolios in areas affecting reproductive and child health: HIV, sexually transmitted infections, and infections and nutritional deficiencies in children under five years old, however at this point it is unclear how this will be managed avoiding dilution of impact.

Capacity for Change

As outlined above FIND has demonstrated its ability to orchestrate a self-critical review, organisational change, and strategic adaptation. This is particularly important in light of the change in BMGF's funding strategies to PDPs (BMGF is directing more funding to the private sector). FIND will work with its industry partners to access governmental funding available for technology innovation.

FIND has a strong track record in adapting the technology development when the TPP cannot be met e.g. discontinuing or reprioritising projects (in the case of restricted funded project, with the permission of the relevant donors).

Product Development and Clinical Trial Management & Capacity

FIND has offices in India and Uganda, a laboratory in Kampala for proof-of-principle and feasibility work, and a training centre in Bangalore for building diagnostic laboratory capacity. Over 4,400 laboratory staff in developing countries have been trained in the last four years. FIND has over 60 partners in developing countries that participate in trials and implementation. Several interviewees commended FIND for their capability to execute clinical trials of diagnostics candidates diligently and efficiently. Recently, FIND has started its first R&D partnerships with Argentina and Colombia, where joint research is being carried out on Chagas disease[20].

Risk Management

While FIND does not have a formal risk register in place, there are ongoing considerations to implement one. The Board conducts ad-hoc risk assessments. Routine risk monitoring is integrated into project management processes with quarterly reviews, however with no formal documentation. FIND has identified the need for proper documentation of the risk review process.

Financial Planning and Management

In 2011 the financial accounting system was revised and systems overhauled. Original accounting policies had led to an inappropriate recognition of income and the restatement of income revealed an accumulated deficit of USD 6.03 mill in 2010, which was mostly due to overhead spending without related funding base. See Annex 11.3.3 FIND Income and Expenditure Statement 2009 – 2013 for more detail. This deficit was fully covered by several funders in 2012 and 2013. In 2013 a USD 0.69 mill surplus was carried forward. In the 2012 Accounts, 74 % of FIND's assets were held in cash or cash equivalents.

[20] FIND partners on the project include: Instituto de Investigaciones en Ingeniería Genética y Biología Molecular (INGEBI/CONICET) in Argentina; London School of Hygiene and Tropical Medicine (LSHTM), UK; Pontificia Universidad Javeriana and Universidad de los Andes in Colombia; and Eiken Chemical Co. in Japan. http://www.finddiagnostics.org/programs/hat-ond/chagas/lamp-for-chagas.html

FIND has significantly reduced the overhead spending from 21 % in 2011 to 11 % in 2013. Table 9 shows staff full time equivalents (FTEs) (without consultants) have peaked in 2012 and reduced thereafter:

Table 9: FIND - Full Time Equivalents 2010-2014

	2010	2011	2012	2013	2014
FTEs	34.6	37.2	39.6	33.8	29.8

Currently staff is thinly spread across the board, not just in back office functions, and some interviewees have expressed concern on this. However, according to senior management, the staff remain very committed and are working well within these constraints.

Financial Sustainability

FIND is currently raising the necessary finances to sustain its project portfolio and other aspects of its strategy. For more details on the income and expenditure over the period under evaluation see Annex: 11.3.3 FIND Income and Expenditure Statement 2009 – 2013. Funding projections are now weighted[21]. The following table 10 shows the income forecast needed to meet the 2011-2018 Business Plan and the actual amounts raised:

Table 10: FIND - Forecast & Actual Income Requirements

(EUR mill)	2011	2012	2013	2014	2015	2016	2017	2018
Income Forecast				40.65[1]	53.47[1]	35.24[1]	32.64[1]	23.77[1]
Actual Income	29.5[2]	33.2[2]	32.5[2]					
Income Needs					39.0[3]	39.0[3]	39.0[3]	39.0[3]

[1] Per 2014 FIND funding forecast (Weighted Total Funding Projections: Committed + Expected + Prospect)
[2] See Annex 11.3.3 FIND Income and Expenditure Statement 2009 – 2013
[3] Projected average annual financial needs in new FIND Strategic Plan 2015 – 2020 (See Annex 11.3.1.1 Outline of FIND's New Five-Year Strategy 2015 - 2020), additional specific requests for work by funders beyond strategy not represented

FIND has also diversified its funders' base. See Annex 11.3.2.1 FIND Funders for more details. To maintain this FIND has recognised the need to foster relations with donors on an ongoing basis, rather than just when applying for a particular grant.

Current weighted projections of committed, expected and projected income are sufficient to fund FIND's work through to 2016/2017, beyond then additional funding is projected to be required to meet the resource needs of FIND's strategy and goals. There is insecurity around some funding streams (DGIS, DFAT, etc.). FIND is working to get funders to commit to a defined length of grant to enable better financial planning and more flexibility: 3 years is FIND's preference. Other funding sources are also being evaluated: EU Horizon 2020, EDCTP, and IMI.

As mentioned previously, budgetary limitations have created difficulties for hiring staff; FIND compensates this with strong consultant networks.

[21] The algorithm had been developed by the previous CFO and the data is populated by senior management team; a broad input is used to avoid over-optimistic estimates of success by any one person.

FIND's Resource Mobilisation Action Plan for 2015 lays out goals and activities for building strategic partnerships with funders, further revenue diversification (similar to DNDi's diversification strategy) and steps to increase the visibility of FIND's efforts in addressing diagnostics public health needs.

Communications with Stakeholders and Advocacy

FIND leadership is cognisant of the need to improve its communications with stakeholders and has integrated this goal into their new 2015 – 2020 strategy. They aim to ensure that the organisation is not perceived as detached from the field, and that potential conflict-of-interest issues are carefully managed and transparency is maintained throughout. FIND is also aware that some partners might have been alienated in the past when collaborative achievements were claimed by FIND with no credit to the partner, and is anxious to avoid this in the future.

Advocacy strategy and approach in the new 2015 – 2020 strategy will build on more sophisticated communication plans which will demonstrate the importance and value of diagnostics in global health. For example the value of good diagnostics to avoid unnecessary/ inappropriate treatment, using better diagnostics to measure success or failure in clinical trials, and the resulting savings to health systems and donors.[22]

Collaboration with Industry & the Private Sector

FIND has built up strong collaborations with several industry partners: Cepheid, Alere, Kalon Biologicals, Standard Diagnostics, Eiken and others. Partners express respect for FIND as a reliable and professional collaborator, who shares its expertise, advice, pathogen specimen banks, and access to clinical trial capacity in disease endemic countries.

7.5. Contribution to Accelerated Access

FIND has concluded from experience that it is not enough to rely on implementation partners to ensure access, and that it needs to remain involved as a facilitator to ensure partners work effectively together to deliver interventions to patients. Access related activities are integrated into the specific disease programmes:

- TPPs for new products reflect the needs of affected populations and the environment in which the diagnostic tool has to perform and narrow the possible product development choices to those products which can be affordable and accessible.
- Industrial implementation partners are identified and terms agreed as early as possible. FIND's access policy is written so that long-term supply agreements with manufacturers are at lowest cost-of-goods-sold, with a price to enable widespread access and IP that also ensures global access.
- Local operations in disease-endemic countries are supportive in local implementation and training to ensure access.

For sales of FIND supported products please see Annex 11.3.5.3 Annual Sales of FIND supported Products 2009 – 2013.

Impact Estimation

The impact of availability and use of appropriate diagnostics is dependent on the ensuing treatment or intervention, which makes it very difficult to give any real estimation; only proxy indicators are therefore available. The data in the table below come from WHO data and best-case scenarios.

[22] This article by the Board Chair of FIND develops this argument in more detail: M. Kessel, Diagnostics as the first line of defense in global health security Nature biotechnology 32, 6 June 2014; M. Kessel, Neglected diseases, delinquent diagnostics. Sci. Transl. Med. 6,226ed6 (2014)

Impact estimations in terms of diagnostics delivered are shown in the table below:

Table 11: FIND - Estimation of Impact of Developed Diagnostics[23]

Disease	FIND co-developed Tests distributed	No. of reported cases/yr.	Deaths/yr.	Case Fatality Rate (CFR)	Lives saved
TB	Xpert MTB/RIF: 5.03 million LPA: 1.45 million Liquid Culture: 25.2 million worldwide, not only LMICs Rapid Speciation: 2.48 million	5.7 million notified cases (2013)	1.46 million	25.6 %	37 million (2000-2013)*
Malaria	LAMP malaria***: 35,376	207 million (est. 2012)	0.627 million (2012)	0.3 %	3.3 million (2001-2012)
HAT	Rapid test: 249,700	6,871 (2013)	9,110 (2010)	100 %	No data**

All data on cases reported, deaths and case fatality rates from WHO data. All numbers are approximate.

*Estimates on impact of TB tests introduced through FIND (based on modelling) are: Up to 100k lives saved per year through LPA and liquid culture; 300k lives (20+% decrease in TB mortality) saves a year through Xpert only once fully rolled out; 20+% reductions in average infectious period; 25+% decrease in prevalence.

**Since the introduction of the 3 FIND co-developed HAT tests in combination, the number of HAT cases has decreased by about 30 %.

*** Note that the application for this test is elimination settings, e.g. areas with very low parasitemia – Not possible to estimate impact using these numbers. LAMP can be used to help eliminate malaria in 22/99 malaria countries, which is the potential impact for this test.

7.6. Value for Money

Economy

FIND has made a big effort to lower its running costs without compromising its mission and the proportion of programmatic spend out of total spend is consistently lean with regard to running/administrative costs. It is leveraging co-funding/ in-kind contributions from the private sector and also points to evidence of how it is leveraging other PDPs for drug or vaccine trial platforms by "piggy-backing" on trials. The new strategy is expected to enhance FIND's value for money in that it is streamlining its approach and reducing costs, working more as an enabler and is not funding manufacturers but working with them to find funding through the various industry incentives that exist – although this still has to be seen.

Efficiency

The use of a portfolio approach allows funding to be redistributed if individual projects are stopped when they do not meet their milestones. This means more efficient use of funds combined with the fact that quick Go/No Go decisions can be made by the programme managers.

[23] The table was provided by FIND on request from the evaluation team. FIND noted some concerns on the limitations of the methodology and metrics, as the accuracy of these figures for lives saved or cases adverted has been developed on rough calculations based on different case fatality rates for the various diseases.

FIND's specimen banks[24] are an important resource for the field as they support biomarker discovery work, assay development and validation. The banked materials can be used to quickly and effectively test the feasibility of new prototypes or concepts at low cost. The use of the reference material for product validation comparative studies of performance across different diagnostic platforms results in much lighter clinical trial needs and provides a cost-effective mechanism for the robust evaluation of diagnostic technologies.

FIND will work more on cross-cutting themes, e.g. the "Support for Success" programme [25]. This provides the support of industry experts to developers of new tests – particularly to small and medium ones. It helps them to overcome product design, manufacturing, and marketing hurdles and adds efficiency to the process.

Effectiveness

Despite the problems FIND has encountered in the last few years, it has been very effective in delivering on its mission in the evaluation period with 7 products registered or endorsed by WHO. See also Section 7.2 Achievements & Relevance.

FIND has also established a support programme to establish need and bottlenecks for diagnostic delivery, and to tackle the structural problems of a slow development process such as a high rate of market entry failure. In this capacity FIND is making significant contributions to robust pipeline development for partners, and is recognised as a core partner to WHO in pipeline and laboratory development. FIND is also working to develop strong and well-functioning laboratories that are able to offer quality assured services, increasing the reach of diagnostic testing, and has stepped up post-market surveillance of product performance to monitor product and user performance. The quality assurance data from FIND informs procurement, leading to use of higher quality tests.

Internal Measurements of Value for Money

Given the challenges around quantifying the value created for the money spent, FIND uses intermediate proxies for value: Patients diagnosed with FIND technologies, RDTs tested, people trained, etc. Achieving real values e.g. estimated incremental DALYs, or estimated changes in treatment, requires a greater investment. FIND considers it important that there is a meaningful process and engagement around this - the framework for value for money measurement (and its application) is evolving.

Indicators for Value for Money suggested by FIND are detailed in Annex 11.3.5.4 FIND Value for Money Indicators and Drivers.

Conclusions

After a difficult period, FIND is now a stronger and more mature PDP, which is not only highly competent to support the development of new diagnostics, but has also developed a clearer vision and concept of its own role and realm it can fill within the complex and evolving landscape of diagnostics for NTDs. Despite the potentially disruptive transitions, FIND has remained true to its vision and mission throughout the evaluation period, supporting the development of much-needed diagnostics for neglected/poverty related diseases through robust and simple as possible technologies.

The new strategy should enhance FIND's value for money in that it is streamlining its approach and reducing costs, working more as an enabler and is not funding manufacturers but working with them to find funding through the various industry incentives that exist – although this still has to be seen.

[24] Link to FIND TB specimen bank information: http://www.finddiagnostics.org/programs/tb/find_activities/tb_specimen_bank.html
[25] Link to Support for Success (S4S) information: http://www.finddiagnostics.org/scouting_support/index.html

8. European Vaccines Initiative (EVI)

In line with the ToRs, this assessment was undertaken using the external review carried out by American Appraisal (AA) in 2012 and the additional report on achievements and financing from July 2013. The evaluation team also reviewed the PDP Funders reports from 2012 and 2013, annual reports, information from the website and a conversation with the EVI, but did not directly conduct additional stakeholder interviews or verify source documents.

As noted above, this assessment was based on the AA evaluation. However, the AA evaluation had different objectives and ToRs in that recommendations were made to EVI and its board (not funders) in areas for improvement, strengthening etc. It was not easy to find answers to address this evaluation's ToRs and so some clarification was sought directly from EVI when the information could not be found, or was not clear, in the various documents available. Even so, from an assessor's perspective, EVI was the least transparent organisation to review. Its annual report, the financial information, funding to EVI and funding for the projects were challenging to understand.

8.1. Business Model & Strategy

EVI is very different from the other two PDPs under evaluation (as well as other PDPs in general) both in structure and mission. The European Malaria Vaccine Initiative (EMVI) officially commenced operations in March 1998 and was hosted and integrated first by the Bergen Foundation in Norway and then from 2006 to 2009 by the Statens Serum Institute in Denmark. In 2009, as a result of strong influence from the European Commission (EC), and following the legal model of the European and Developing Countries Clinical Trials Partnership (EDCTP), EVI was registered in Germany as a not-for-profit European Economic Interest Grouping (EEIG)[26] between the founding Universities of Stockholm and Heidelberg. It is now based in Heidelberg. In 2010 the EEIG was expanded to include the Biomedical Primate Research Centre, Rijswijk, the Netherlands Vaccine Institute, Bilthoven and in January 2011, the Jenner Vaccine Foundation in Oxford and the Royal College of Surgeons in Dublin, Ireland. In 2014, the Institut Pasteur, Paris, joined the EVI EEIG.

This EEIG construct gives ownership of the organisation to its members (representing the member states) and aims to create a more active involvement of both the founders and their countries.

However, in practice it appears to be a fairly cumbersome structure and some stakeholders as well as the American Appraisal's evaluation questioned whether the EEIG is the most appropriate construct for EVI. They have also questioned its location in Germany, mainly due to the position of German government towards taxes (VAT)[27] on EEIG's. Also, there are issues in terms of restrictiveness when it comes to the amount of country member seats on the EVI Board and liability of all members, as expressed in the review by American Appraisal.

EVI is a small organization - only 16 staff with 11 FTE, compared with 48 full time staff at FIND and over 100 at DNDi (the Path MVI currently has a staff of around 40 FTEs although it has had over 60 before).

The EVI aims to provide a mechanism through which the development of vaccines for diseases of poverty (DoP) can be accelerated within Europe and in low income countries.

EVI's stated mission is "To create an environment to accelerate the development and clinical assessment of vaccine candidates; promote affordability and accessibility of vaccines for diseases of poverty in low income populations; seek to align all major stakeholders and act as a focal point to ensure the successful development of vaccines for diseases of poverty for low income populations."

[26] The purpose of the grouping is to facilitate or develop the economic activities of its members by a pooling of resources, activities or skills (EU website, 2011).
[27] The Netherlands government have VAT exempted EDCTP which is also an EEIG.

With the 2009 expanded scope from malaria vaccines to vaccines for DoPs, including NTDs, the mandate of EVI is to promote affordability and accessibility of vaccines for diseases of poverty in low income populations. EVI's approach is to support projects selected from public calls for proposals or identified within EVI's partnership network. Proposed projects are scientifically –technically reviewed by EVI's independent Scientific Advisory Committee (SAC), which makes recommendations to the EVI Board. The Board then takes the formal decision regarding project support. EVI then works with the collaborators to raise the money needed to support the project. This funding is therefore by definition restricted to the particular project, and the business model does not require significant unrestricted funding. If sufficient unrestricted funding is available EVI can also directly fund projects from this.

8.2. Achievements & Relevance

With the global health agenda focussed on malaria elimination, a key tool missing from the current arsenal is an effective vaccine that would contribute to the interruption of transmission of malaria and disease. The most advanced vaccine for malaria, RTS,S - developed by the Malaria Vaccine Initiative (MVI) and GlaxoSmithKline (GSK Bio) and funded by the BMGF- shows low protective efficacy (<50 % efficacy). The work on RTS,S has given valuable lessons, and helped develop regulatory pathways for malaria vaccines. However, this encouraging but less than satisfactory result indicates the need for continued efforts to develop the next generation of more efficacious malaria vaccines (with >75 % efficacy). EVI's role in support of development of vaccine candidates for NTDs and other diseases of poverty[28] is also highly relevant to the London Declaration of 2012[29] and the push for elimination of NTDs.

EVI enables and facilitates early stage discovery research, and preclinical and early clinical development of vaccine candidates. Therefore it differs in its business model from other PDPs, which support product development along the entire product development chain including clinical phase III and market introduction (DNDi, MMV, TB Alliance), or focuses more on deployment and implementation (FIND). EVI's scope of operation is in facilitating the transition from academic research to vaccine candidate. The specific objective of EVI is to "bridge the conceptual and operational gaps between the bench product (e.g. candidate molecules) through further validation of bench testing, small-scale cGMP production and clinical testing". EVI is following an "*integrator business model"*[30] and supports translational research on vaccine candidates up to clinical phase II. Successful vaccine candidates are subsequently transferred to partner organisations including private sector companies for them to take the vaccine into further clinical development. In the clinical development of vaccine candidates, EVI works closely with EDCTP, amongst others.

EVI works together with its EEIG members to mobilise resources for projects and provides both funding and expertise required to take experimental vaccine candidates efficiently from discovery and preclinical R&D into clinical trials.[31] This gap in vaccine development is both technically and legally complex and has been traditionally under-financed.

EVI has five main activities (see Annex 11.4.1 EVI Activities). However, this report focusses on the vaccine development activities.

Over the last fifteen years, EVI has demonstrated its ability to create an enabling environment for malaria vaccine development and, more recently, for other DoPs. To date it has funded 24 malaria antigen combinations in 32 vaccine formulations and taken 16[32] candidates to phase I clinical trials. Three candidates were transferred to other partners for phase IIb trials, two of these did not show efficacy in IIb trials and

[28] For definition please see EVI's term as stated on their website
[29] http://unitingtocombatntds.org/resource/london-declaration
[30] http://www.euvaccine.eu/news-events/events/evi-15th-anniversary-symposium
[31] http://www.euvaccine.eu/
[32] EVI reported that since the discussion with them, they now have an additional malaria vaccine candidate so a total of 17

were terminated, and one of these is currently in further development as it showed very good results in clinical trials (over 60 % efficacy). GSK and MVI are interested in the latter and are looking at the potential of combining it with the RTS,S vaccine to increase effectiveness.

The current EVI portfolio is currently comprised of 20 projects with 16 vaccine candidates under development. With co-funding from the BMBF and others, including the EC, French and Danish funders, EVI is currently the only PDP working to advance the development of vaccines against placental malaria. As EVI broadens its scope, currently three of the ongoing projects focus on diseases other than malaria (S. paratyphi, S. aureus and a universal influenza vaccine candidate). EVI is also participating in another project with a disease over-arching focus which studies the interplay between poverty-related diseases and helminth infections. See Annex 11.4.3 EVI Project Portfolio July 2014.

EVI has participated in and coordinated several EU funded projects under the Sixth and Seventh Framework Programme (e.g. TRANSVAC, OPTIMALVAC, EDUFLUVAC, INYVAX, IPROVE). In line with EVI's strategy plan, EVI's role as coordinator of EC projects is on deciding on the selection of the partners and the research and developing strategy, as well as the operational work. When EVI is asked to partner in EC projects coordinated by another institution, the EVI's independent SAC is consulted to ensure that this partnership is in line with the EVI scope.

EVI has developed, and is implementing, a new strategy for proof of concept which combines phase Ia and phase Ib clinical trials in a unique protocol which aims to accelerate the pace and reduce the cost of the clinical development of vaccine candidates. This involves an earlier and stronger collaboration between African and European clinical investigators. See Annex 11.4.4 Classical Clinical Development Path and EVI Fast-Track Clinical Development Path.

EVI's other achievements include:

- Capacity strengthening and support for training endemic country scientists
- Capacity building, for example regarding Good Clinical Laboratory Practice (GCLP)
- Harmonization - supporting good research practices and methodologies to generate comparative and reproducible results;
- Services - providing services and service platforms to accelerate R&D of vaccine candidates.

8.3. Impact of Government Funding

As reported by the AA assessment, EVI's income consists mainly of public funding coming from the EC, national Government funding and EDCTP. Recently, EVI obtained funding from the GHIT Fund, Japan, a public-private partnership between the Government of Japan, Japanese pharmaceutical companies, and the BMGF.

The EC funding to EVI is for both vaccine R&D and project coordination. EVI's core funding is currently primarily from its core donor, Irish Aid. Unlike FIND and DNDi however, some 75 % of its public funding is restricted. This is because, as explained earlier in section 8.1 Business Model & Strategy, EVI selects the projects it wishes to support first and then seeks funding as a second step.

The decision also, to be based in Germany has brought some financial constraints regarding VAT payment, and the BMBF funding cannot be used to pay VAT. EVI does its best to find solutions to these limitations and is working with Deloitte to look at how to change the tax structure.

Since 2012, EVI has been developing and implementing a novel strategy to diversify sources of funding and they now show a more diversified funding structure, with GHIT Fund and Irish Aid providing core funding (Table 12).

Table 12: EVI - Grants made to EVI as of November 2014

Country	Type of Funding	Amount to EVI (EUR mill)	Dependency in %
European Union: European Commission	Restricted	6.2	24 %
Ireland: Irish Aid	Unrestricted	5.0	20 %
EDCTP	Restricted	9.1	35 %
Japan: GHIT	Unrestricted	0.7	3 %
Germany: BMBF	Restricted	4.5	18 %
Total		**25.5**	**100 %**

8.4. Capabilities

Governance

The governance structure of EVI is determined by its EEIG status, thus its Board is made up of one representative member of the EVI EEIG (with a maximum of 3 members/member state), the EVI SAC chair and chair of the EVI board of stakeholders (both of these are non-voting members).

The Board of Stakeholders (BoS) gives a voice to EVI's donors and stakeholders from vaccine development and target populations/ countries. BoS oversees financial management and makes recommendations to the EVI Board on governance and good practice.

The EVI SAC makes recommendations to the EVI Board on scientific direction, technologies, and on selection of applications for funding. The profile for SAC members was drawn up by the Board and members are chosen for their defined expertise as well as adhering to gender and geographical balance.

Although governance structures were in place for EMVI, with the transition to EVI a consultant worked with the organisation to recommend how to strengthen and improve the governance in 2011-2012. This led to the reorganisation of EVI secretariat functions towards a project management oriented structure, with the creation of the steering committee which is responsible for assessing the technical, scientific, and financial risks with a bi-monthly reporting to the Board.

As this was a "light touch" review of EVI, the Evaluation Team did not have the opportunity to review the minutes of the Board or SAC committees in order to make any value judgement on the robustness of the governance process. However, from the annual reports, the AA report and stakeholder comments, it appears that the Board and BoS meetings are still focused on predominantly technical, scientific, and strategical, and less on financial oversight. The American Appraisal's evaluation observed *"it might be advisable that one or some of the board members should be financially literate with at least one director being sophisticated concerning financial reporting and accounting"*.

To address this, a Finance and Risk Management Committee has now been set up with members from the Board. However, in the opinion of the evaluation team, the Board and/or BoS would benefit from members with a broader expertise in finance, communication, and governance.

Portfolio Management

The SAC oversees a rigorous selection of vaccine candidates resulting in a well-managed and diversified portfolio. The six-monthly SAC review process has also shown clear Go/No Go recommendations to the Board with projects that do not meet the defined target product profile terminated. In 2013, EVI had a balanced portfolio in terms of development stage with 7 in preclinical, 8 in phase I/IIa and 1 in phase IIb. However, there seems to be a lack of documented criteria by which the Board may decide to reject or modify a recommendation of the SAC.

Strategic Planning

As a result of the AA review and recommendations, EVI is currently working on a new strategic plan in line with funding structures and areas of market failure which will be launched in December 2014.

Risk-Management

According to the AA evaluation, EVI does have appropriate risk management in place at project and enterprise level since 2012, but did not have a risk committee at Board level. EVI now does have a risk management committee and since 2012 has a risk register which is now considered standard good practice.

Budgeting

The AA team did a thorough review of the financial reporting and analysis and reconciled the two different cost structures - nature and project - that EVI reports on. AA reported no issues but financial reporting will be improved by the preparation of their accounts in *"a more recognizable format and differentiation between restricted, unrestricted, and deferred income"* – a move that EVI has taken on board. In the 2013 accounts, 98 % of its assets were held in cash or cash equivalents. See Annex 11.4.2 EVI Profit and Loss 2010 to 2013.

Clinical Trials Management and Capacity

EVI's role is bridging the pre-clinical and early clinical trial phases, before passing the vaccine candidates over to organisations like EDCTP. Research is taking place in both European and DoP endemic research settings. EVI maintains direct contact with, and participates actively in, working groups on national and international ethics and regulatory frameworks but, as per its statutes, EVI can act as a clinical trial sponsor only by decision of the EVI Board. The clinical trials supported by EVI are sourced out to clinical trial sponsors and investigational centres that have been selected through a rigorous selection process. The trials are conducted to Good Clinical Laboratory Practice (GCLP) and/or Good Clinical Practice (GCP).

Communications with Stakeholders

As noted by the AA review, external communications with stakeholders and potential stakeholders needs to be strengthened and improved. The evaluation team is aware that EVI is working on a communication strategy and improved advocacy material. Although EVI does have a very limited budget for this (compared with other PDPs), better targeted advocacy is not necessarily achieved by increasing the budget.

EVI does have a strong European /African focus but maintains good connections with other developing countries. EVI has also worked with other stakeholders to influence policy (e.g. UNITAID, WHO, EU, Malaria Vaccine Funders Group, PDP EU coalition), and the annual EVI Rendezvous is a forum for sharing information and dialogue with its stakeholders.

In 2002, EVI/EMVI has initiated with MVI, WHO, and USAID the Malaria Vaccine Funders Group. Memorandum of Understandings (MoU) with PATH-MVI, USAID, and a Memorandum of Intent with WHO were signed. Later on MoUs were signed with TBVI, MVDP, Brighton Collaboration, and Sclavo Association. EVI management informed the evaluation team that since 2008, their executive director attends the Vaccine Science Portfolio Advisory Council (VSPAC) of MVI (review of MVI portfolio) and the scientific director attends EVI SAC meetings and the EVI Rendezvous (where the EVI portfolio review takes place). In addition, EVI and MVI had a three year joint project (OPTIMALVAC) coordinated by EVI which aimed to harmonise immune-assays for malaria vaccine development. Together with DNDi and PATH-MVI, EVI is currently co-chair of the PDP EU coalition which has organised recently important and successful advocacy events such as parliamentary hearings and evenings in several EU member states (e.g. Germany, the Netherlands) and participated in such efforts on EU level in Brussels. Finally, EVI is actively involved in the recently established German Network for NTDs (DNTDs) which has the aim to bring together different stakeholders.

Financial Sustainability

The AA review did an in-depth analysis of EVI's financial performance and based on this and an update from EVI, the evaluation team can conclude that EVI does have short-term sustainability. It has been successful in raising the funds needed to sustain its portfolio and even expand its scope.

However, the longer term sustainability is heavily dependent on unrestricted funding currently only available from the Irish Aid and GHIT funds although EVI is working on a strategy to raise funds outside its traditional donors.

Collaborations with the Private Sector

EVI's public-private partnership model includes substantial collaborations with the private sector (Annex 11.4.5 EVI Partnerships) and EVI is also working on setting up clear collaborations with private sector, e.g. with Sanofi and GSK who are interested in the Universal Flu project as well as the ME-TRAP chimpanzee adeno vector malaria vaccine.

8.5. Contribution to Accelerated Access

As EVI works upstream and is only involved in translational research, this is not in its scope – but there is a clause in the funding agreements that access must be thought through to the next stages in development, according to the Council Regulation (EC) *953/2003* on tiered prices. EVI has a strong conviction that developing countries should be involved at all stages, so all projects have an African/disease endemic countries' institution involved from the beginning to make sure candidates are appropriate.

8.6. Value for Money

Efficiency

EVI has a small secretariat (compared with other PDPs) staffed full-time by experts with extensive experience in the fields of basic research, vaccine development, programme management, clinical trials, regulatory affairs, and administrative support. It works on a much smaller budget than the other PDPs but, according to one source, the productivity is similar to MVI in terms of the pipeline, but at a much lower cost.

EVI has good research governance and evidence of being able to prioritize and drop projects that are not likely to deliver best. Co-funding allows EVI to work with all the researchers in Europe.

The analysis in 2013 by the AA review showed that total project costs account for 97 % of EVI's total costs, of which 5 % relates to project development costs and the remaining 3 % is attributed to overhead /administrative costs. EVI's management costs are extremely low, figures from the last three years show a range of 4.02 % in 2011, 2.20 % in 2012, and 3.7 % in 2013.

EVI points to its choice of producing subunit antigens as long synthetic peptides and not the more expensive to-produce recombinant vaccines (such as the RTS,S) as a more cost efficient approach. Additionally, the new strategy for proof of concept combining phase Ia and phase Ib clinical trials aim to both reduce the lead times and the costs. See Annex 11.4.4 Classical Clinical Development Path and EVI Fast-Track Clinical Development Path.

Effectiveness

EVI has continued to progress vaccine candidates through early stage development and has shown it can facilitate vaccine development to phase II clinical testing (examples of MSP3 and GMZ2 blood stage vaccine candidates within 3-6 years).

Under the lead of EVI, the TRANSVAC consortium has developed a European roadmap for sustained vaccine R&D.

Internal measure of value for money

Internal analysis indicated that for every EUR 1 spent on fundraising, EVI was able to raise almost EUR 87 of funds. This was verified by the AA report but it is not entirely clear what contribution the funding partners make in this calculation.

8.7. Conclusions

EVI is recognized for fostering standardization and harmonization within European vaccine development efforts as well as its role in addressing the translational gap between potential malaria vaccine candidates developed through basic science, and limited industrial production, and early stage clinical trials. As reported in the Medical Research Council review of vaccine research 2014 *"Costs for early translational work are high, and so any partnership or networking activities that lead to shared resources could be very beneficial – not only in the UK, but EU-wide*."

The EVI does fill this niche and offers an alternative PDP model to that of the BMGF funded PATH-MVI that can continue to maintain a robust pipeline of vaccine candidates for DoPs. The value of EVI is that they provide a highly specialised, expert-driven filter for early candidate selection. By reducing the number of potential candidates sooner, funding can then be kept for the best candidates. With this "integrator model" it is critical that there are willing (private sector) partners to take candidate vaccines forward into phase III clinical trials and beyond into product rollout.

9. Lessons Learnt

The lessons learnt from this evaluation can be summarised as follows:

1) PDPs remain crucial to the development and deployment of badly needed new interventions for neglected infectious diseases, such as the kinetoplastid diseases or the diagnosis of TB. In the absence of PDPs, it is highly unlikely that these interventions would have become available in any reasonable timeframe.
2) Unrestricted funding is vital for PDPs to be able to operate effectively in delivering on their strategy and not being at the mercy of a single dominant funder. It allows quick reallocation of resources between projects depending on their progress, to ensure their most efficient use.
3) Unrestricted funding allows PDPs to better align with globally developed Public Health Strategies.
4) PDPs need stable and long-term funding. The development of new interventions, especially drugs, is long and complex, and without the assurance of this stable funding, developers are much less likely to wish to work with the PDPs or their funders.
5) Small amounts of unrestricted funds can still make a difference to PDPs, allowing them to explore or pilot higher risk projects.
6) It remains challenging to properly measure impact and value for money because of the lack of a commonly agreed measure or set of metrics. This in turn makes it difficult to comparatively evaluate the work of individual PDPs in a consistent way.
7) Many products have only just been deployed or are still being in development, also making measuring impact challenging.
8) It is essential for PDPs to have very strong financial expertise and oversight both at Board and senior management level.

10. Recommendations

The recommendations from this evaluation are:

10.1. General

- Public funders should continue to support PDPs with long-term financing in order to ensure there is a steady stream of needed interventions for neglected infectious diseases. This funding should be mostly unrestricted or semi-restricted.
- All PDPs should seek to diversify their funding base (as DNDi is doing) in order to ensure that they have the flexibility to set and follow their own strategies and are not be driven by the requirements of one dominant funder.
- Funders should agree amongst themselves on the methodology and measures of impact and value for money, and to give clear guidance to PDPs (amongst others) on this to ensure comparisons can be made in a consistent manner.

10.2. DNDi

- Ensure that the core focus on kinetoplastid diseases is retained, as DNDi's disease coverage has widened. It is important that DNDi deliver much needed interventions rather than just being active in a particular disease arena.
- Broaden the base of companies who have fully committed to work with DNDi in the late stage development and deployment of the products in development, to ensure that each project has a clear industrial partner who will ultimately be responsible for deploying the product. These partners should be brought on-board as early as possible in the development process.
- Collaborate more with other PDPs in the procurement of common services (e.g. laboratory or analytical) to improve economies of scale in their purchase.
- Collaborate more with other PDPs on promoting the value of the PDP model to funders and stakeholders and to also promote wider awareness of the target diseases and the need to support work to combat them.
- Include reputational risk as a topic in the organisational risk register.

10.3. FIND

- Make the Chair of the SAC a permanent ex officio member of the Board.
- Complete the hiring plan for a CMO and CAO to reduce the management span of the CEO, who is currently overstretched. This depends on adequate resources being confirmed by funders.
- Project-level risk monitoring is already implemented, however, a formal risk register with a minimum of annual review by the Board should be put in place.
- Carefully monitor the implementation of the 2015-2020 strategy and quickly course correct where needed.
- Proactively manage potential conflict-of-interest issues and maintain transparency throughout
- Increase the visibility of FIND's efforts in addressing diagnostics public health needs and ensure fair credit to collaborators and partners.

10.4. EVI

- Re-evaluate if the current EEIG structure is the most appropriate for the organisation to adequately achieve its aims.
- Ensure that there is more financial expertise both on the Board and at the Senior Management level.
- Better documentation of the Board decision-making process, especially the criteria by which the Board judge the recommendations of the SAC and by which they may decide to reject a SAC recommendation.
- Strengthening of the communications with funders and stakeholders (actual and potential).

11. Annexes

11.1. List of Interviewees & Questionnaire Respondents

Acknowledgements
The review team would like to extend sincere thanks to all the PDP staff, Donors and other stakeholders interviewed for their time, insights, and for providing background documentation and information for the review. Thank you also to DGIS and their consultants at technopolis group, who gave access to a parallel evaluation of PDP funding, including DNDi and FIND, on behalf of the Dutch government.

General Interviewees

Affiliation	Interviewee
Chatham House	David Heymann
Clinton Health Initiative	David Ripin, Zachary Katz
DGIS	Wieneke Vullings
DNDi: GSK Spain	Jose Maria (Pepe) Fiandor-Roman
DNDi: KEMRI	Monique Wasunna
DNDi: Sanofi	Robert Sebbag
DNDi: Scientific Advisory Committee (SAC)	Simon Croft, Pierre-Etienne Bost
DNDi: University of Khartoum, Sudan	Ahmed Mudawi Musa
EDCTP	Charles Mgone
FIND: Makarere	Enock Matovu
FIND: University of Cape Town	Mark Nicol
FIND: McGill	Mahdu Pai
FIND: Cepheid	Dave Persing
FIND: 42T	Frank Tully
FIND: Big Tec	Chandrasekhar Nair
FIND: Chair, Board of Directors	Mark Kessel
FIND: Chair, Scientific Advisory Board (SAB), DNDi: Board	Marcel Tanner
Global Network on Neglected Tropical Diseases	Neeraj Mistry
International Diagnostics Centre	Rosanna Peeling
PDP Funders' Group	Alex Fullem
Policy Cures	Mary Moran
Swiss Development Corporation	Susanna Hausmann
Technopolis Group	Thyra de Jonge
WHO	Jean Georges Jannin
WHO TDR	John Reeder, Robert Terry

Internal Interviewees

Position	Interviewee/ Contact Person
DNDi	
Chief Executive Director	Bernard Pécoul
Director of Finance and Planning	Laurence Vielfaure
Director of Research & Development	Graeme Bilbe
Director of Fundraising & Advocacy	Jean-François Alesandrini
Medical Director	Nathalie Strub Wourgaft
Director of Operations	Thomas Saugnac
Head of Fundraising	Michele Joanisse
Policy and Development Coordinator	Nina Holzhauer
FIND	
Chief Executive Officer	Catharina Boehme
Senior Advocacy & Resource Mobilization Officer	Jérome St-Denis
Head of Finance	Louisa Chaubert
Head of Operations	Sharon Saacks
Head of Malaria & AFS	Iveth González
Head of NTDs	Joseph Ndung'u
EVI	
Chief Executive Officer	Odile Leroy
Chief Financial Officer	Sten Larsen
Head, Project Management	Regitze Louise Thøgresen
Business Development Consultant	Harry van Schooten
External relations	Natalie Imbault
Business Unit Leader	Stefan Jungbluth
Project Manager	Nicola Viebig

11.2. DNDi Annexes

11.2.1 DNDi Business Model[33]

The key points of the DNDi Business Model are as follows:

Four Pillars of an Alternative R&D Model designed to address unmet patients' needs

1. Patient-centric approach to the R&D process.
2. Open access to knowledge and patient access to treatments.
3. Financial and scientific independence.
4. Building and sustaining solid alliances with public and private partners, including in endemic countries.

Key components for success

1. Put the specific needs of patients in developing countries upfront, at the start of the innovation process.
2. Break the link between the cost of R&D and the price of products.
3. Ensure that the fruits of innovation are accessible and affordable.
4. Integrate global health R&D monitoring, coordination, and financing.
5. Strengthen and harmonize regulatory capacities in endemic regions to facilitate implementation of new health technologies.

Costs

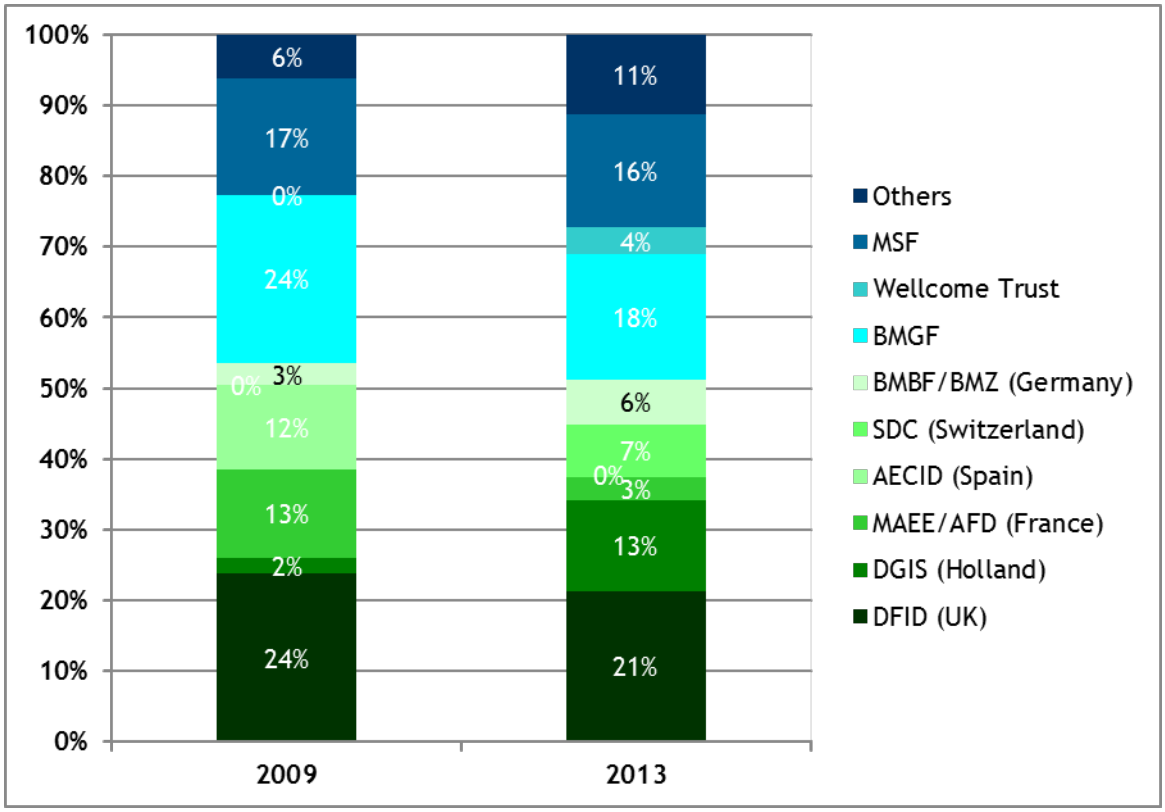
DNDi's estimates its cost of development to range from EUR 6-20 mill for an improved treatment, and EUR 30-40 mill for a new chemical entity. However, the usual attrition in the field of R&D for infectious diseases, and the inherent risk of failure, should be taken into account, bringing the cost range to **EUR 10-40 mill** for an improved treatment, and **EUR 100-150 mill** for an NCE.

[33] Source: DNDi website (http://www.dndi.org/about-us/business-model/dndis-model.html)

11.2.2 DNDi Funders [34]

DNDi's principal funders in 2009 (the first year of the evaluation) and 2013 (the final year) are shown in the figure below:

Figure 1: DNDi - Income by Funder (percentage)



In the period under review, DNDi has increased its funding from EUR 21 mill in 2009 to EUR 31 mill in 2013. It has also diversified its donors from 14 major donors (individually identified in its Annual Report) to 21 donors in 2013. In 2009, the largest donors were DFID (24 %), BMGF (24 %), and MSF (17 %). By 2013 the largest funders remained DFID (21 %), BMGF (18 %), and MSF (16 %).

In 2009 the German Government (through BMZ) donated EUR 0.68 mill (3 % total). In 2011 BMBF committed to a four year programme of EUR 8 mill of which EUR 5.1 mill (6 % total) was recognised in DNDi's accounts in 2013.

This data shows that, while DNDi remains dependant on 2-3 funders for at least half of its funding, it has managed to diversify its donor base, reduced this dependency significantly, and de-risked its income to some extent.

[34] Source: DNDi Annual Reports 2009 – 2013.

Table 13: DNDi - Principal Funders 2009-2013[35]

(EUR mill)	2009	2010	2011	2012	2013
Public Sector					
DFID (UK)	5.017	6.221	7.559	7.325	6.601
DGIS (Holland)	0.482	0.068	2.000	4.000	4.000
SDC (Switzerland)		1.467	0.837	0.902	2.289
BMBF/BMZ (Germany)	0.676		0.401	2.000	2.000
MAEE/AFD (France)	2.641	1.025	0.585	0.190	1.010
UNITAID					0.607
Norway					0.593
European Union	0.076	0.090	0.326	0.238	0.414
Geneva Canton	0.132	0.149	0.161	0.166	0.135
NIH/NIAID (USA)	0.244	0.209	0.326	0.346	0.132
MoH Brazil					0.032
AECID (Spain)	2.500	2.500	1.000	1.000	
Global Fund (AMFm)	0.134	0.161	0.258	0.113	
Total	**11.902**	**11.890**	**13.453**	**16.280**	**17.813**
Private					
Gates Foundation	4.996	8.984	7.088	7.218	5.469
Medicins sans Frontières	3.492	3.630	3.956	4.750	4.949
Wellcome Trust			0.719	1.084	1.185
BBVA					0.400
Medicor Foundation	0.405	0.305	0.359	0.232	0.377
Moreau Family					0.329
UBS Optimus Foundation	0.180				0.197
Rockefeller Foundation					0.111
Starr International Foundation	0.141			0.079	0.076
Sandoz Family Foundation					
GHIT					
Others		0.071	0.097	0.116	0.106
Total	**9.214**	**12.990**	**12.219**	**13.479**	**13.199**
Grand Total	**21.116**	**24.880**	**25.677**	**29.759**	**31.011**

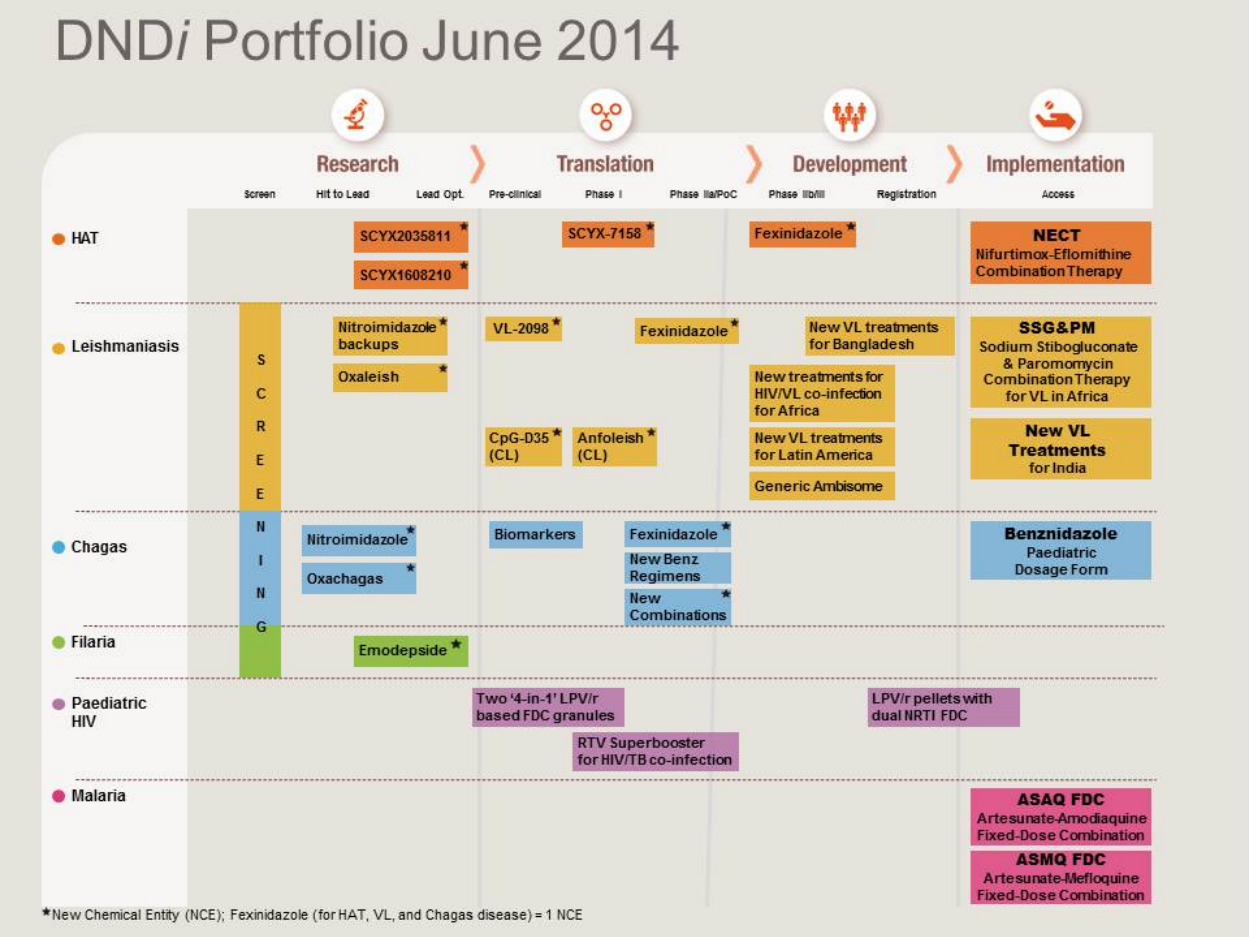
[35] DNDi Annual Reports 2009 – 2013. Donations are shown as per the Statement of Operations for each year, reflecting the income recognised for that year.

11.2.3 DNDi Income and Expenditure Statement 2009-2013[36]

(EUR mill)	2009	2010	2011	2012	2013
Income					
- public sector	11.77	11.89	13.46	16.28	17.81
- private sector	6.01	9.41	8.32	8.76	8.25
- founders	3.49	3.63	3.96	4.75	4.95
Total Income	21.27	24.93	25.83	29.85	31.24
Social Mission Expenditure					
- R&D Coordination	1.63	1.69	2.02	2.58	2.66
- HAT projects	6.00	7.31	5.79	3.49	5.30
- Leishmaniasis projects	4.07	4.68	4.47	4.35	3.93
- Chagas disease projects	1.40	2.36	3.81	2.33	2.63
- Other projects	2.45	2.22	2.40	3.62	3.23
- Portfolio Building	0.85	1.56	1.60	6.42	5.46
Total R&D	16.39	19.81	20.08	22.79	23.21
- Capacity Strengthening	1.32	1.41	1.46	1.63	1.73
- Advocacy	1.19	0.94	0.87	1.45	1.88
Total Social Mission	18.91	22.17	22.41	25.87	26.81
Other Expenditure					
Fundraising	0.89	1.17	1.48	1.48	1.52
General & Admin	1.31	1.54	2.14	2.54	2.68
Total Expenditure	21.11	24.88	26.03	29.90	31.01
Operating Surplus	0.16	0.06	(0.20)	(0.05)	0.23
Other income (net)	0.33	0.50	0.28	0.12	(0.12)
Surplus before allocations	0.49	0.55	0.08	0.07	0.23
Other Expenditure/Income	10.3 %	10.9 %	14.0 %	13.5 %	13.4 %

[36] DNDi Annual Reports 2009 – 2013.

11.2.4 DNDi Project Portfolio[37]



11.2.5 DNDi Achievements

DNDi's summarises its achievements since its launch as follows[38]:-

R&D Portfolio

DNDi has been building a strong R&D portfolio with the objective to deliver a total of 11 to 13 new treatments by 2018 for leishmaniasis, sleeping sickness, Chagas disease, malaria, paediatric HIV, and specific helminth infections, as is summarised in the previous section.

Malaria

ASAQ – fixed-dose combination of artesunate and amodiaquine for use in sub- Saharan Africa; launched in March 2007 in partnership with Sanofi; obtained WHO prequalification in October 2008; registered in 31 African countries, India, and Colombia; more than 280 million treatment courses delivered.

[37] DNDi website (http://www.dndi.org/diseases-projects/portfolio.html)

[38] DNDi website (http://www.dndi.org/about-us/overview-dndi/key-accomplishments.html)

ASMQ – FDC of artesunate and mefloquine for treatment in Latin America and Asia; registered in Brazil in March 2008 in partnership with Farmanguinhos/Fiocruz and in India in 2011 with a South-South technology transfer to Cipla Ltd.

Human African Trypanosomiasis

NECT – Nifurtimox-Eflornithine Co-administration Therapy was included in the WHO Essential Medicines List in 2009 and added to the WHO Essential Medicines List (EML) for Children in 2013. This is the first new improved treatment in 25 years for stage 2 HAT. Available in 12 African countries, covering 99 % of reported HAT cases. More than 90 % of stage 2 HAT patients treated with NECT in 2013 replacing toxic melarsoprol use, which dropped from 36 % to less than 1 %.

Fexinidazole – First success of compound mining from DNDi's nitroimidazoles project. Entered clinical development in 2009. In May 2009, Sanofi and DNDi signed agreement to develop and deploy. Phase II/III studies are ongoing in 9 clinical trial sites in the Democratic Republic of Congo and Central African Republic.

Oxaborole (SCYX-7158) – DNDi, Anacor Pharmaceuticals, and SCYNEXIS Inc. completed very promising pre-clinical studies for oxaborole, the first new oral drug candidate discovered specifically to combat HAT in June 2011. Phase I human clinical trials are ongoing in Grenoble.

Leishmaniasis

Visceral Leishmaniasis combination trials in Africa, Asia and Latin America have been implemented for evaluating safe and short-course combination therapy, using existing drugs, in three regions to stave off parasitic resistance and provide a shorter, more effective treatment course;

SSG&PM (Africa) – Combination Treatment of sodium stibogluconate and paromomycin launched by DNDi in 2010. Combination is now recommended by the WHO Expert Committee as first-line treatment for VL in East Africa.

New VL treatments (Asia) – In 2010, a study investigating the three possible 2-drug combinations of AmBisome®, miltefosine, and paromomycin was completed in India. All three combination treatments were shown highly efficacious (> 97.5 % cure rate). A WHO Expert Committee recommended these treatments to be used preferentially to current established monotherapy treatments for VL in South Asia. DNDi is working with TDR and One World Health to facilitate their introduction and support VL elimination strategies.

Chagas Disease

Paediatric Benznidazole –The only currently available Chagas treatment for children. Developed with Laboratório Farmacêutico do Estado de Pernambuco Governador Miguel Arraes (LAFEPE), the paediatric formulation of benznidazole was granted registration in Brazil in December 2011. Paediatric benznidazole was added to the WHO Essential Medicines List for Children in 2013.

Discovery & Screening Activities

DNDi has consolidated these activities, with strategic focus on compound collection, target identification, target validation, assay development, high-throughput screening, hit identification, and hit-to-lead selection. High-throughput screening is available for VL and Chagas (Institut Pasteur Korea) and for HAT (Eskitis).
DNDi is working closely with Swiss TPH, Dundee University, and London School of Hygiene & Tropical

Medicine, University of Antwerp, as well as developing synergies with Medicines for Malaria Venture and TB Alliance. DNDi has established working relations with GSK, Sanofi, Merck, Novartis, Pfizer, and many others.

Strengthening Research Capacities

Three regional networks for research capacity strengthening have been established:-

Africa – the **HAT Platform** and the **Leishmaniasis East Africa Platform** (LEAP). Main activities have included GCP, ethics, and trial-monitoring training: establishment and training of data safety monitoring boards: workshops on clinical trial methodology: information sharing on recent clinical research developments.

Latin America – the **Chagas Platform**. The main objective is to facilitate clinical research by creating a forum for technical discussions, to develop a critical mass of expertise, and to strengthen institutional research capacities.

11.3. FIND Annexes

11.3.1 FIND Business Model

11.3.1.1 Outline of FIND's New Five-Year Strategy 2015 - 2020

FIND identifies **four strategic goals** and specifies the **objectives** and the **indicators** for future success:

1. **Catalyze development**: Identify needed diagnostic solutions and remove barriers to their development.

Objectives:

- Shape a robust, global product pipeline towards defined diagnostic needs
- Maximize chances of success for diagnostics most likely to meet defined needs

Indicators of success:

- Availability of products: number of commercially available products to which FIND has contributed that meet priority needs

2. **Guide use & policy**: Lead products through the clinical trials pathway to global policy on use and market entry.

Objectives

- Reduce the time from development to market for diagnostic solutions meeting global health needs
- Create solid understanding of if, how and where to use diagnostic solutions in preparation for uptake

Indicators of success

- Availability of global policies: number of global policy recommendations that FIND has enabled
- Efficient and effective evidence generation: Average time from first registration to public sector introduction in a relevant country for FIND- supported solution

3. **Accelerate access**: Support uptake and appropriate use of diagnostics to achieve health impact.

Objectives

- Support rapid translation of global pol-icy into relevant and actionable country plans
- Enable quality-assured scale-up and use of proven diagnostic solutions

Indicators of success

- Speed of country adoption: number of countries with FIND support to Ministries of Health that introduce diagnostic products within 2 years of global guidance
- Coverage: % of target population tested with appropriate diagnostics for diseases & countries within FIND's focus
- Quality assurance: % of FIND-supported rollouts accompanied by a quality assurance plan

4. **Shape agenda**: Improve understanding of diagnostics' value and strengthen commitment to their funding and use.

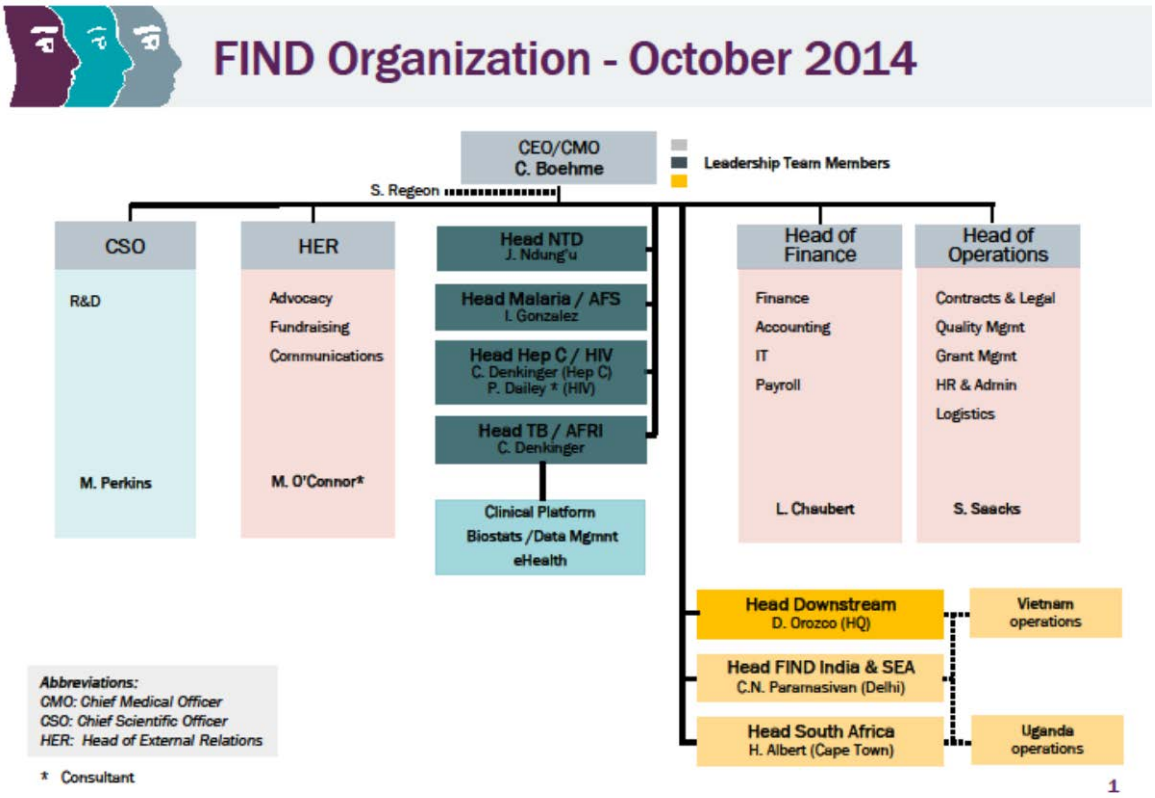
Objectives

- Champion the role of diagnostics as an essential ingredient to good healthcare
- Shape the diagnostics ecosystem to foster industry investment and country willingness to support

Indicators of success

- FIND thought leadership: Number of diagnostics-related articles published by FIND and collaborators that reach a relevant and wide audience
- Funding: % total USD and % of total health resources contributed to diagnostics for diseases in FIND's portfolio

11.3.1.2 FIND Organogram 2014

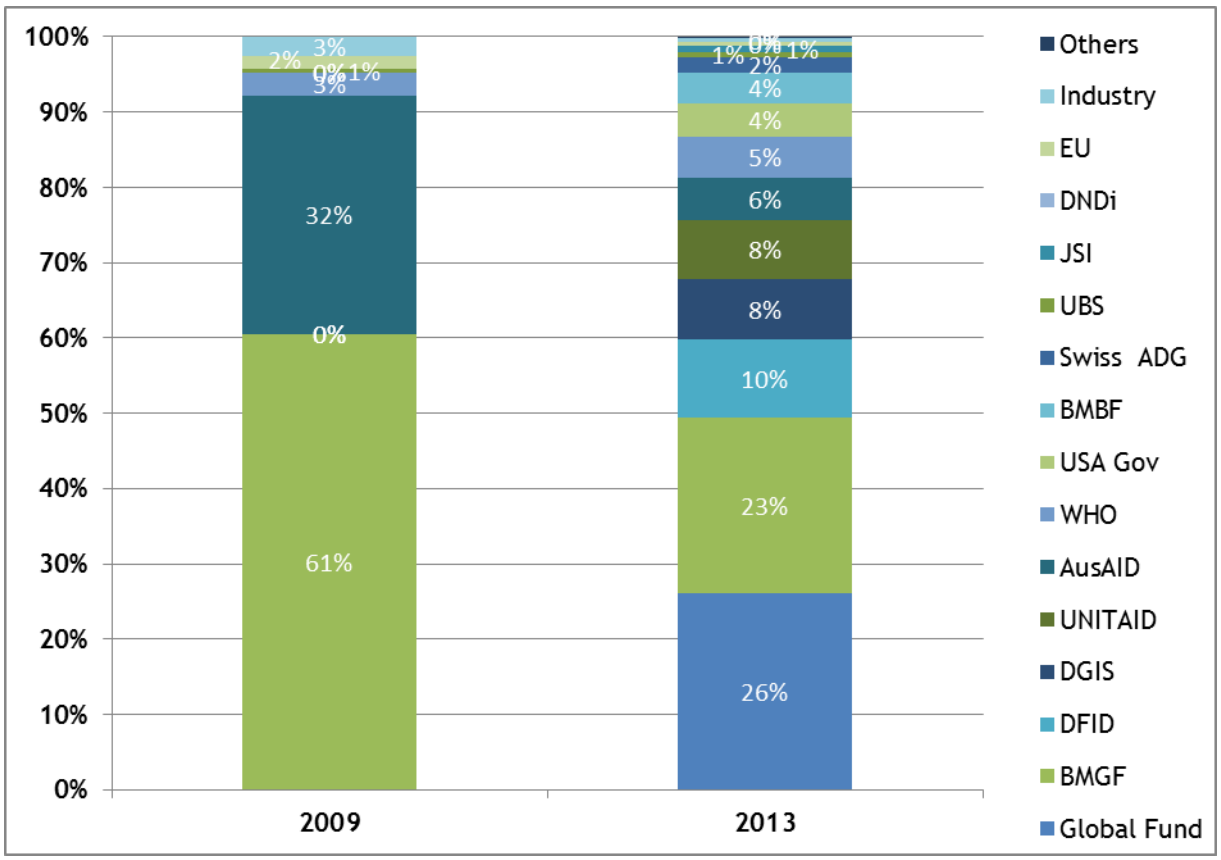


11.3.2 FIND Funders

11.3.2.1 FIND Funders

FIND's principal funders in 2009 (the first year of the evaluation) and 2013 (the final year) are shown in the figure below:

Figure 2: FIND - Income by Funder (percentage)



In the period under review, FIND has increased its funding from EUR 19 mill in 2009 to EUR 42 mill in 2013. It has also diversified its donors from 4 major donors (individually identified in its Annual Report) to 17 donors in 2013. In 2009, the largest donors were BMGF (61 %), AUSAID (32 %), and WHO (3.2 %). By 2013 the largest funders were Global Fund (26 %), BMGF (23.6 %), and DFID (10 %), DGIS (8 %), and UNITAID (8 %). BMBF is supporting a 4-year FIND programme with a total of EUR 7.45 mill FIND has recognized in their accounts EUR 3.1 mill (13 % total) in 2012 and EUR 1.8 mill (4.2 % total) in 2013.

This data shows that, while FIND remains dependant on 2-3 funders for at least half of its funding, it has managed to diversify its donor base, reduced this dependency significantly, and de-risked its income.

Table 14: FIND - Contributions received 2009-2013

EUR mill	2009	2010	2011	2012	2013	Total
The Global Fund to Fight AIDS, TB and Malaria	-	-	2.135	0.135	11.143	13.414
The Bill and Melinda Gates Foundation	11.553	17.460	7.708	10.884	9.867	57.474
Department for International Development (DFID), UK	-	3.189	2.681	2.544	4.467	12.883
Dutch Ministry of Foreign Affairs (DGIS), Netherlands	-	3.006	3.514	1.785	3.419	11.725
UNITAID	-	9.377	0.365	-	3.345	13.088
Australian Department of Foreign Affairs and Trade	6.064	-	-	-	2.408	8.472
WHO	0.556	0.485	1.265	1.545	2.390	6.243
Government of the United States	-	0.178	0.921	2.210	1.880	5.192
Federal Ministry of Education And Research (BMBF)	-	-	-	3.133	1.767	4.901
Swiss Agency for Development and Cooperation	-	-	-	-	0.892	0.892
UBS Optimus Foundation, Switzerland	0.149	-	0.180	0.491	0.322	1.143
JSI Research & Training	0.021	-	0.125	0.275	0.254	0.675
TI Pharma	-	-	0.009	0.091	0.150	0.252
Republic and Canton of Geneva	-	-	-	-	0.064	0.064
Intellectual Ventures Management LLC	-	-	-	-	0.046	0.046
DNDi	-	0.055	-	-	0.039	0.094
European Union	0.344	0.044	0.403	0.001	0.019	0.813
Global BioDiagnostics	-	-	-	0.005	-	0.005
Becton Dickinson and Co	0.050	0.125	0.195	0.015	-	0.385
Government of Ireland	-	-	-	-	-	-
Total cash contributions	18.740	33.923	19.506	23.120	42.480	137.770

In addition FIND has received in-kind contributions from industry partners and collaborators of EUR 5.0 mill 2011 -2013.

11.3.2.2 Types of restricted funding in FIND

FIND defines the different levels of restriction as follows:

Highly restrictive conditions: Grants that lack the flexibility that would allow the recipient to terminate projects without losing the funding might prolong the work, which may not be the optimal use of funds. In this case, while the use of funds still fits the scope of work, there is increased risk that projects may not reach the desired impact and therefore are usually not best value for money (scientific funders such as US NIH, UK Medical Research Council or European Commission funding mechanism are examples of donors using these types of restrictions). The other issue is that requesting changes or adjustments of scope require time from both the donor and grantee. It is unclear whether there is always a good return on investment by imposing these processes when factoring in the costs of filing a change of scope, of assessing the request at the donor's end, re-negotiating and re-drafting funding agreements, which adds to the cost of doing business for all parties involved (this is usually the case with US government institutions and with donors such as UNITAID and Global Fund).

Multiplication of audits, financial restrictions, and reporting: These types of restrictions have been expanding for most donors. Although a healthy level of reporting and oversight is most beneficial of the sector as a whole, these measures present challenges for non-profit organizations when combined with unrealistic staff and overhead expectations. Donors should have an understanding of the impact of the requirements they impose and ensure that there is a good balance between requirements resources allowed to meet these requirements while still offering enough funding to reach project goals.

Softer restrictions such as timeframes or portfolio funding (as used by DFID and KfW): These softer restrictions can be managed more efficiently and usually have the benefit of allowing the grantee to meet their own goals, interests or obligations. This usually results in increased funding capacity from the donor side and is possible for the grantee to manage more easily.

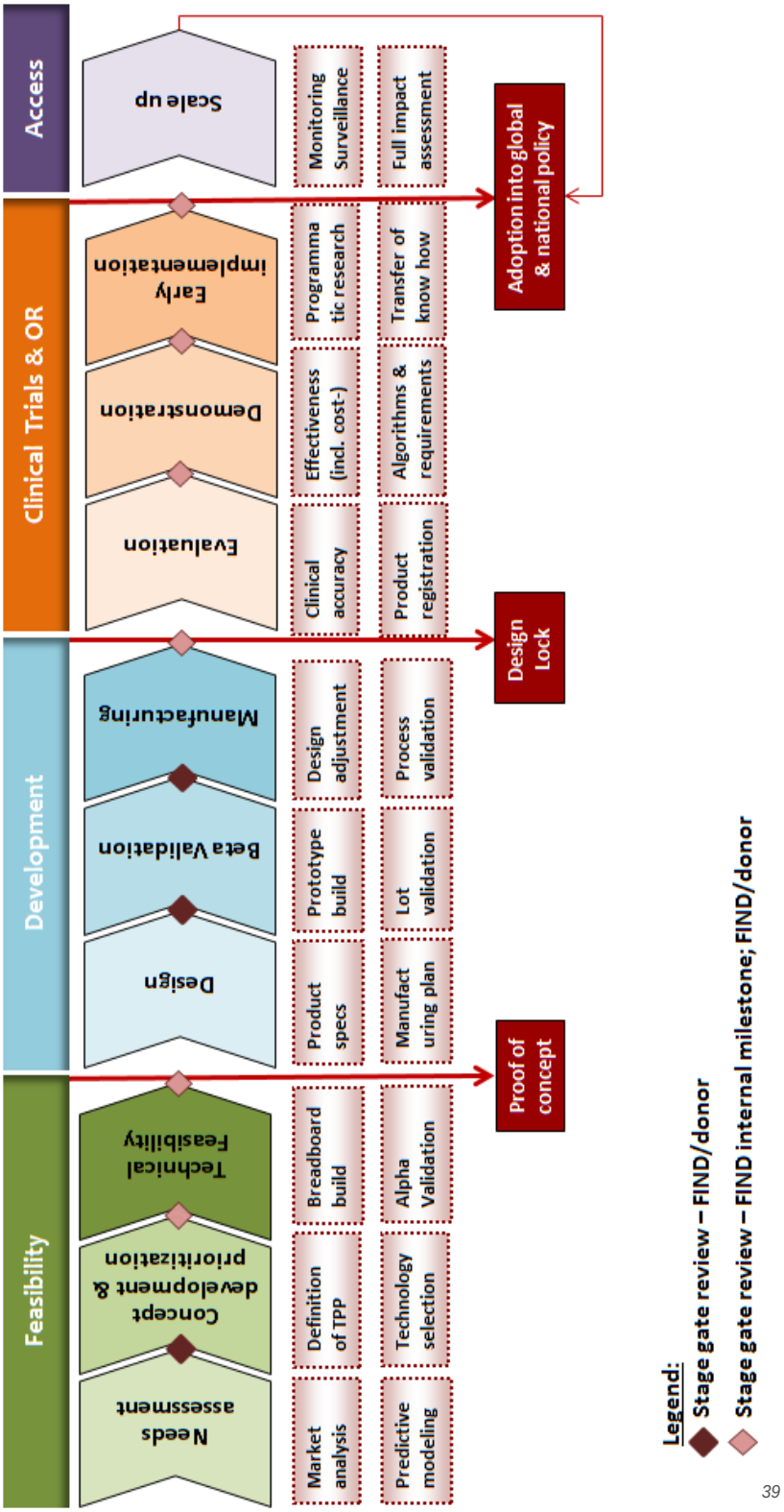
11.3.3 FIND Income and Expenditure Statement 2009 – 2013

Table 15: FIND - Income and Expenditure Statement 2009-2013

STATEMENT OF REVENUE AND EXPENDITURE FOR THE YEAR ENDED 31 DECEMBER					
All amounts in mill US dollars. Figures are restated to the new disease structure					
REVENUE	**2009**	**2010**	**2011**	**2012**	**2013**
Grant revenue	24.5	27.4	29.3	33.1	32.3
Sundry income	0.1	0.2	0.2	0.1	0.2
Total revenue	**24.6**	**27.6**	**29.5**	**33.2**	**32.5**
EXPENDITURE					
Tuberculosis and Acute Febrile Respiratory Illness	15.1	14.8	17.2	14.8	15.5
Neglected tropical diseases	4.3	3.5	2.8	3.8	3.5
Malaria and Acute Fever Syndrome	3.4	3.1	2.8	3	4.4
Hepatitis and Human Immunodeficiency Virus	0.1	0.5	3.5	1.3	1.4
Cross disease	-	-	0.2	1.5	2.2
Total programme services	**22.9**	**21.9**	**26.6**	**24.4**	**27.1**
Total supporting services	**3.5**	**3.8**	**5.6**	**4.4**	**3.1**
Total expenditure	**26.4**	**25.7**	**32.2**	**28.8**	**30.2**
Excess (deficit) of revenue over expenditure for year	**-1.7**	**1.9**	**-2.6**	**4.4**	**2.3**
Accumulated surplus (deficit) brought forward	2.3	0.5	2.4	-6	-1.6
Adjustment for change in revenue recognition policy	-	-	-5.8	-	-
Accumulated surplus (deficit) carried forward	**0.5**	**2.4**	**-6**	**-1.6**	**0.7**

11.3.4 FIND Project Portfolio

11.3.4.1 Diagnostics Development Phases



39

[39] Breadboard build: A breadboard (or protoboard) is a construction base for prototyping of electronics

Definitions of phases (phase end-points are in bold text):

Feasibility: Diagnostic needs (the gap) are assessed and best option for addressing that need identified; **proof of principle** for that option validated against TPPs (or Feasibility Target Specifications, which is what FIND used to define before the current approach, which is to have consensus-based TPPs); to provide justification for initiation of product development (a costly phase); and to select partner/s for development and manufacturing.

Development: Product developed against specifications, final prototype validated. Development studies are for performance testing of the final prototype ("Alpha"-trial) against targets in defined Product Specification that are based on TPPs. If targets are met, product can be **design-locked** and manufacturing scaled-up for the next phase, e.g. Evaluation study ("Beta" trial).

Evaluation: To show that **product specifications can be proven in target patients** and settings; to produce data suitable for use in applications for **product registration** with regulatory bodies. The major activity of this phase is conducting an Evaluation study to prove performance of design locked IVD (e.g. zero series of production or already commercial IVD), and compare results with the Product Specification. The IVDs must have been manufactured in compliance with GMP-IVD standards or quality controlled manufacturing conditions.

Demonstration: To demonstrate clinical utility and health economic impact (effectiveness) in settings of intended use. Demonstration studies have 3 phases: 1) Validation phase, comprising observational studies to validate proficiency of training and comparison of test results from new technology with gold standard methods; 2) Implementation phase, which has interventional design. Test results of new technology are used to manage patients. 3) Continuation phase, where the new technology is used for laboratory routine diagnosis in programmatic settings – this phase is effectively early implementation.

Demonstration must produce high quality data along the line of the GRADE (Grading of Recommendations Assessment, Development and Evaluation), which is the grading system recognized by the WHO. These studies are conducted within the level of health care system for which the new technology is intended. Data are presented to the relevant **WHO** group (e.g. the Strategic and Technology Advisory Group for TB diagnostics, STAG) for **endorsement**, which is necessary in order for the tests to be entered on to the UN procurement lists. At the same time, strategies to engage managers from national disease control programmes, senior policy makers in Ministries of Health of endemic countries, civil society, and donors have to take effect in order for the FIND-supported IVD to be adopted and included in national health policies and guidelines.

Global access: Activities for global access is started in the early project phases (during Development phase) as these include pricing negotiations; defining IPR, if any; developing strategies to engage NTP managers/MoH/civil society; planning for distribution and after sales support etc.

Laboratory strengthening: Laboratory support projects, including laboratory strengthening and accreditation, are planned and initiated during the Demonstration phase. These projects greatly facilitate scale-up and contribute to sustainability after implementation projects have ended.

11.3.4.2 FIND Project Portfolio Development and Achievements over Time

Programme / Product					
TB	2009	2010	2011	2012	2013
Liquid culture MTB and DST	5 Implementation	5 Implementation	5 Implementation	5 Implementation	5 Implementation
Rapid speciation	5 Implementation	5 Implementation	5 Implementation	5 Implementation	5 Implementation
Line probe assay	5 Implementation	5 Implementation	5 Implementation	5 Implementation	5 Implementation
LED FM	4 Demonstration	5 Implementation			
Ag detection LAM	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility
Lateral flow sensitivity increase	1 Feasibility	1 Feasibility			
Antigen discovery	1 Feasibility	1 Feasibility	1 Feasibility		
VOC	1 Feasibility	1 Feasibility	1 Feasibility		
Tr DNA	1 Feasibility	1 Feasibility	1 Feasibility		
Antibody detection	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility
IGRAs for latent TB	3 Evaluation	3 Evaluation			
Xpert MTB/Rif	4 Demonstration	4 Demonstration	5 Implementation	5 Implementation	5 Implementation
MDR-XDR colour test	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility
LPA 2nd line		3 Evaluation	3 Evaluation	3 Evaluation	
Beta lactamase detection				1 Feasibility	1 Feasibility
Molecular DST				1 Feasibility	1 Feasibility
Microimaging					1 Feasibility
Reducing reporting times – eHealth				1 Feasibility	1 Feasibility
Treatment monitoring				1 Feasibility	1 Feasibility
Next gen molecular				1 Feasibility	1 Feasibility
Xpert HIV-VL			1 Feasibility	1 Feasibility	2 Development
NTDs	2009	2010	2011	2012	2013
HAT LAMP	2 Development	2 Development	3 Evaluation	3 Evaluation	4 Demonstration
LED fluorescence microscopy (method)	3 Evaluation	4 Demonstration	4 Demonstration	4 Demonstration	4 Demonstration
Antigen Detection	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility
Antibody Detection (1st Gen RDT)	1 Feasibility	2 Development	2 Development	3 Evaluation	4 Demonstration
Staging markers (CSF)	1 Feasibility	2 Development	2 Development	2 Development	2 Development
Staging Markers (blood)			1 Feasibility	1 Feasibility	1 Feasibility
Chagas LAMP			1 Feasibility	1 Feasibility	1 Feasibility
Leishmaniasis LAMP			1 Feasibility	1 Feasibility	1 Feasibility
Leishmaniasis ELISA			1 Feasibility	1 Feasibility	1 Feasibility
HAT Advocacy	5 Implementation	5 Implementation	5 Implementation	5 Implementation	5 Implementation
Malaria	2009	2010	2011	2012	2013
Positive Control Wells	1 Feasibility	1 Feasibility	2 Development	2 Development	3 Evaluation
Malaria LAMP	1 Feasibility	2 Development	2 Development	3 Evaluation	4 Demonstration
Malaria HTP LAMP				1 Feasibility	2 Development
Blood Transfer		1 Feasibility	2 Development	3 Evaluation	4 Demonstration
QC of malaria RDTs	5 Implementation	5 Implementation	5 Implementation	5 Implementation	5 Implementation
Reagents for improved RDTs	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility	1 Feasibility
Darker fields indicate further advanced development stages					

11.3.5 FIND Achievements

11.3.5.1 FIND Achievements

TB: During the observation period FIND has worked on **21 diagnostic projects** related to TB.

- 14 projects focused on the early feasibility research of innovative DNA, antigen or antibody detection methodologies or drug susceptibility testing or treatment monitoring approaches.
- 1 project was in the development stage, 2 projects in the evaluation stage and 5 in the demonstration / implementation stage.

Selected Achievements:

Xpert® MTB/RIF (Xpert)

- **Xpert** is a new cartridge-based assay used in a multi-disease testing platform that simplifies molecular testing by integrating and automating the three processes required for real-time PCR-based molecular testing. The support of the development of the Xpert can be regarded as one of the most significant contributions of FIND and has been identified by several interviewees as a game changer that has revolutionized the management of TB in many countries.
- Xpert has experienced a broad uptake globally with over 5 million cartridges procured in the public sector of 80 low- and middle-income countries. Country data has confirmed significant increases in case detection and reductions in time to treatment and misdiagnoses for TB and MDRTB. Previously it has estimated that the implementation of Xpert would avert around 130,000 TB cases and around 180,000 TB deaths in southern Africa over the 10 y following introduction. This would reduce prevalence by 28 % (14 %-40 %) by 2022, with more modest reductions in incidence[40]. Health system costs are projected to increase substantially with Xpert, by USD 460 mill (294-699 mill) over 10 years. In 2013 the WHO recommended that Xpert also be used for diagnosing TB in paediatric and HIV patients, where diagnosis of TB can be rather difficult.
- The introduction of Xpert has revitalised a previously “dead” market and stimulated interest by other developers. Although the Xpert is a large step forward, it does not fill the current gap for reliable Point-of-Care (PoC) TB case detection[41].

TB LPA 2nd line

- **TB LPA 2nd line** is a molecular line probe assay (LPA) technology for detection of tuberculosis and its resistance to second-line drugs fluoroquinolones, aminoglycosides / cyclic peptides, ethambutol and streptomycin. Based on data submitted by FIND on the utility of the LPA 2nd line assay, the WHO has recommended its use as a rule-in test for extreme drug resistant TB (XDR-TB) and is expected to make a full recommendation soon. Continuing work toward more efficient infection control and programmatic management of drug resistant TB, FIND and academic partners have developed reagents for DST testing for pyrazinamide, fluoroquinolones and aminoglycosides that can be adapted to any appropriate instrument platform.

[40] PLoS Med. 2012;9(11). Epub 2012 Nov 20., Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. Menzies NA1, Cohen T, Lin HH, Murray M, Salomon JA.

[41] Work over the last 2 years is expected to result in technologies by 2016 that can be as transformational as Xpert, yet can be used one level down in the health system to reach more patients and close the 3M gap in detection that still exists.

EXPAND-TB

- **EXPAND-TB**: FIND is collaborating with UNITAID, WHO, GLI and STOP TB in the EXPAND-TB Project. This has addressed one of the key obstacles to the scale-up of MDR-TB care, by accelerating access to new and rapid diagnostic technologies within appropriate laboratory services at country level, and ensuring that these new technologies are properly transferred and integrated within TB control programmes.
- FIND has acted as the main implementing agency and was responsible for training and project management, including support for procurement and logistics.
- By the end of 2013, 92 of the 100 targeted laboratories were fully operational and reporting MDR-TB cases. Training on LPA, liquid culture, DST, rapid speciation and GeneXpert had been provided to nearly 2,300 laboratory staff, managers, physicians and nurses, making a significant contribution to improving diagnostic capacity in the target countries. The cumulative number of MDR-TB cases detected reached 71,824 at the end of 2013, which represents 62 % of the overall project target (see Figure 3 in Annex 11.3.5.2 MDR-Tuberculosis (TB) Detection using MGIT, LPA and Xpert). In India alone 90 % of all reported MDR TB cases in 2013 were diagnosed through the Expand TB programme.

Malaria: During the evaluation period FIND has worked on **6 diagnostic projects** related to Malaria.

- 3 projects moved from feasibility testing through development to evaluation / demonstration, focusing on detection of DNA, positive control wells and easier blood-transfer.
- 1 project evaluated a broad selection of commercially available rapid diagnostic tests for their utility in the field and 2 projects are in the early stages.

Selected achievements:

- **Malaria LAMP:** The loop-mediated isothermal amplification test (LAMP) for malarial DNA, developed by FIND and partners, allows for the first time molecular diagnosis and detection of very low parasite density infections outside of high-capacity laboratory facilities. This LAMP test has potential applications both as reference standard for other diagnostics, for primary diagnosis of returned travellers in non-endemic countries, and as a tool for population screening in malaria elimination campaigns. A high-throughput assay suited to large-scale screening studies is in development.
- **Blood Transfer Device:** RDTs are increasingly used by personnel with little or no training in laboratory techniques. The correct transfer of blood from a patient to a point-of-care test is vital to both accuracy of the diagnosis and the safety of the health care worker. FIND has developed improved blood transfer devices that meet the needs of health care workers and reduce risk of blood exposure and improve the consistency in the blood volume transferred. These devices are now also included in malaria RDT kits and by the end of 2013, over 100 million devices had been procured for use worldwide. It has been adopted for use with HIV RDTs as well.
- **Quality Control of Malaria RDTs:** FIND has collaborated with WHO to carry out independent, laboratory-based evaluations of RDTs for malaria. Evaluations demonstrated marked variability in in the specificity and sensitivity of commercially-available tests: some performed exceptionally well in endemic country conditions and were capable of detecting even low parasite densities in blood samples, while other tests were only able to detect high parasite densities. FIND and WHO, in collaboration with national reference laboratories, have been developing tools and protocols to routinely lot-test RDTs, to verify their quality when procured.

Kinetoplastids (HAT, Chagas and Leishmaniasis): During the evaluation period FIND has worked on **10 diagnostic projects** related to kinetoplastids.

- 3 projects focused on the feasibility of HAT antigen detection and disease staging test from blood and CSF.
- 3 projects moved through development and evaluation to demonstration: A 1st generation HAT antibody test, LED fluorescence microscopy for HAT and an innovative HAT LAMP test.
- 1 project has engaged in the advocacy for the implementation of HAT diagnostics implementation.
- 3 projects have evaluated the feasibility of the LAMP technology for Chagas and Leishmaniasis and the ELISA technology for Leishmaniasis.

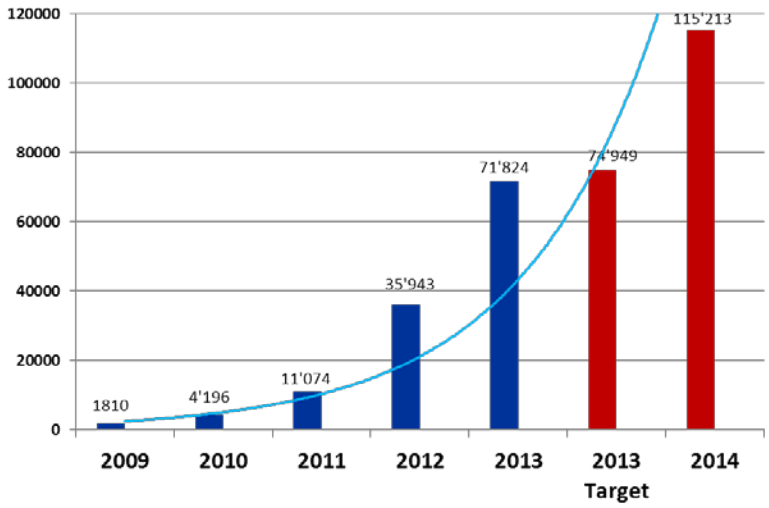
Selected achievements:

- **RDT for HAT:** this first ever RDT for HAT (using lateral flow format) was launched in December 2012. The test is cheaper ($ 0.50), more cost-effective and more sensitive than the traditionally used card agglutination test for trypanosomiasis (CATT), both in active and passive screening, and is being used in 5 out of 7 projected countries (currently in 166 health facilities) to accelerate elimination of the disease.
- **The HAT LAMP kit** for confirmatory diagnosis of HAT was developed and launched in 2011. Studies in 2012 confirmed that the test is highly sensitive and specific in detection of T.b. rhodesiense patients. The test is versatile and can be performed on blood samples collected and stored for up to 10 weeks when dried on filter papers. This allows for samples which are being collected from patients by mobile teams or in remote rural health centres to be sent to a central laboratory for testing and represents a major step forward towards the elimination of this disease and a practical step towards realizing the intentions of the London Declaration.

HAT diagnostics implementation: one of the approaches that FIND has taken is to combine 3 tools – the HAT RDT, LAMP HAT, and ultra-sensitive method for fluorescent microscopy using the iLED microscope. This approach is designed to accelerate the elimination of the disease, particularly as the 2nd generation of the RDT will be rolled out in conjunction with a new drug from DNDi (and in partnership with them) and is expected to enable elimination by 2020.9.3.1

11.3.5.2 MDR-Tuberculosis (TB) Detection using MGIT, LPA and Xpert

Figure 3: FIND - Cumulative MDR-TB cases detected 2009-2013 and FIND targets 2013-2014



11.3.5.3 Annual Sales of FIND supported Products 2009 – 2013

Product type	Contract executed	WHO Approval	Annual Sales in EUR				
			2009	2010	2011	2012	2013
Xpert	2006	2010	-	40,790	488,560	1,200,000	3,300,000
***** LPA**	2006	2008	100,000	150,000	300,000	400,000	500,000
*** Liquid Culture (BD data)**	2004	2007	4,000,000	5,200,000	5,900,000	5,000,000	5,100,000
**** Rapid Speciation**	2006	2007	33,500	34,000	70,000	60,000	50,000
****** Fluo Microscopy**	2007	2009	50	100	150	150	100

* World-wide sales, not only FIND markets Financial year is end November; Xpert takes market share in SA after 2011
** TAUNS only till 2010 then plus XPAND TB/SD; after 3010 only XPAND TB - sales numbers drop; BD selling minimal numbers due to cost
*** Based on DH's comments and same ratio Public/Private as Xpert. XPAND TB is ca 10 % of total units
**** Carl Zeiss made 900 units in 2009 - have not manufactured any more since then- did not win any big tenders

11.3.5.4 FIND Value for Money Indicators and Drivers

Criteria	Potential Indicator Metrics
Economy Getting the best value from inputs	• Proportion of co-funding/ in-kind contributions leveraged from partners • Evidence of leveraging of other PDPs for drug or vaccine trial platforms (usually by "piggy-backing" on trials or by adding critical mass, so metric would be number of trials we can "top up" or share) • Cost reduction in FIND target markets compared to high income countries • Proportion of programmatic spend out of total spend (consistently lean with regard to running/admin costs)
Efficiency Maximising the outputs for a given level of inputs	• Number of biomarker- and product development and validation projects enabled through use of FIND clinical platform (incl. specimen banks) and mentorship programme • Number of products successfully developed (meeting target product profiles) • Number of technologies assessed through systematic technology scouting and selection process • Number of tests approved by WHO or regulatory authorities
Effectiveness Ensuring that the outputs deliver the desired outcome	• Number of national programmes that are implementing FIND co-developed tests in disease control or elimination efforts • Number of co-developed tests sold in disease endemic countries (uptake) • Shortened time to treatment • Quality assurance data informs procurement leading to use of higher quality tests (extent to which large scale global health programmes procure tests based on whether or not they have been quality assessed through FIND-partners processes) • Number of cited open access research publications with FIND authorship
Cost-effectiveness	• High cost-effectiveness of new tools and reduction of transmission/incidence demonstrated through mathematical modelling and large scale trials • Proportion of donor and national funding devoted to implementation of FIND co-developed products • Money saved through avoidance of misdiagnosis and overtreatment • Number of patients appropriately treated per dollar of donor funding

11.4. EVI Annexes

11.4.1 EVI Activities[42]

Vaccine development

Development of vaccines is inherently risky, with vaccine candidates potentially falling at every hurdle. Vaccines also take years to develop and test. EVI funds and actively maintains a diverse vaccine portfolio targeting various stages in the development pipeline.

Coordination (Europe and global)

EVI brings together and coordinates a large number of diverse individuals and organisations from academia, industry, regulatory bodies, governments, and the public arena. EVI's coordination activities unite these stakeholders in order to achieve goals that aim to strengthen efforts to expedite the acquisition of safe and efficacious vaccines.

Harmonisation

Research on vaccines for diseases of poverty has historically been fragmented, leading to difficulties when comparing experimental vaccines from different labs. EVI is working across Europe to harmonise specific aspects of such work, including adjuvant testing and numerous assays commonly used in determining experimental vaccine efficacy.

Services

R&D groups seeking to progress new vaccine candidates are often confronted with a disparate group of those providing services in vaccine development. EVI provides services to accelerate R&D of vaccine candidates, so helping to address these structural weaknesses.

Capacity strengthening

Specialist expertise and facilities to carry out vaccine R&D are a limiting factor in the development of vaccines for diseases of poverty. EVI works in many ways within both Developing Countries and Europe, directly and by funding others, to strengthen capacity to develop and assess vaccine candidates.

Policy

As an important part of achieving its mission, EVI is actively involved in policy activities surrounding vaccine Research and Development (R&D) and vaccination, as well as issues linked to global health at large. Part of these activities is for example, the development of roadmaps and research agendas, as well as advocacy for sustained support for global health R&D. In the context of our policy activities we engage with major policy makers, funders, civil society, policy leaders, the scientific community and other stakeholders on national, European and international levels.

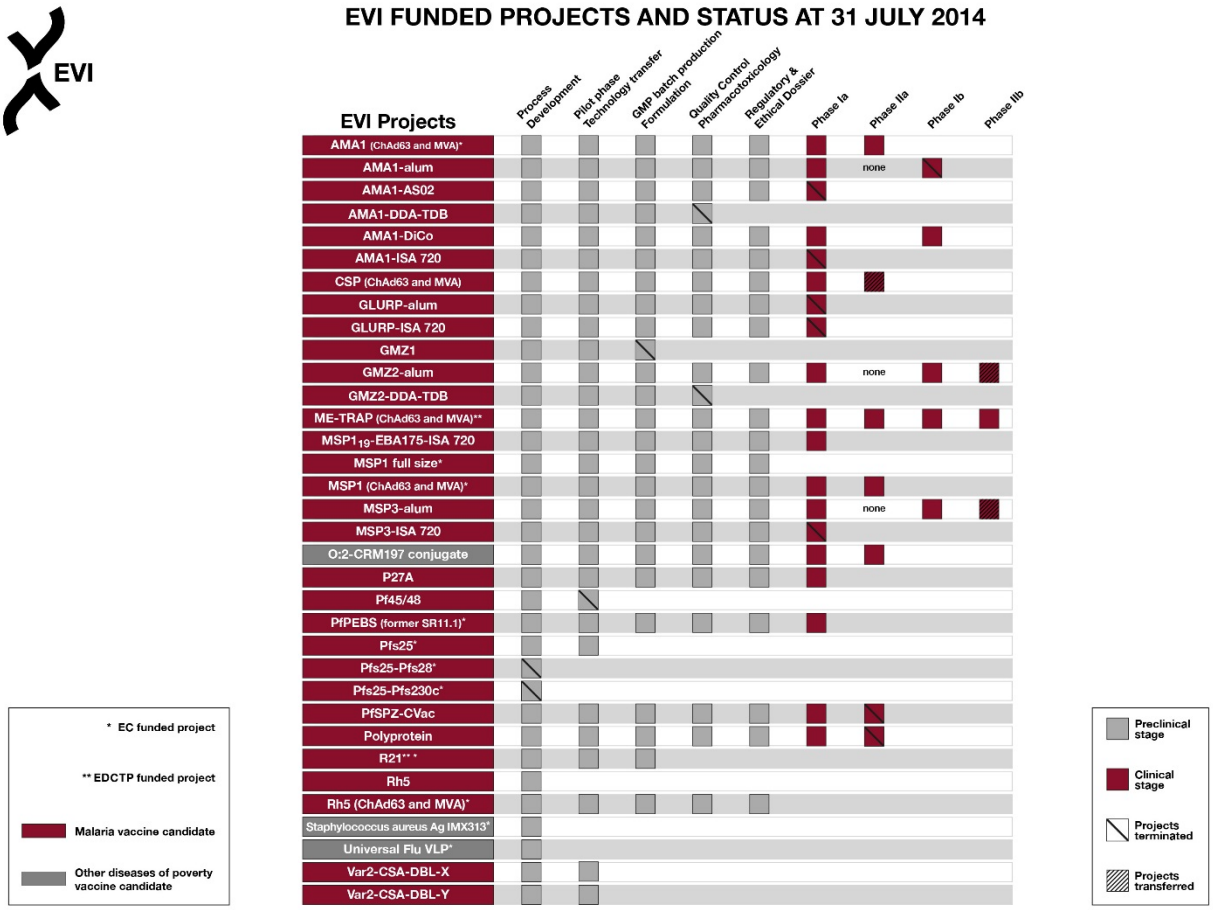
[42] http://www.euvaccine.eu/portfolio

11.4.2 EVI Profit and Loss 2010 to 2013

EUR mill	2010	2011	2012	2013
Income Realized				
Total contributions, Grants and other Support	12.887	11.256	7.737	9.696
Revenue from indirect contributions			0.267	0.491
National Government agency grants			4.063	2.570
EU Grants			2.109	4.432
EDCTP Grants			1.564	2.203
Earned revenues	0.001	-	0.009	0.013
Total Income Realized	*12.888*	*11.256*	*8.013*	*9.709*
Direct and Indirect Project expenditures				
Grants contracts & direct assistance	10.483	9.064	0.509	7.066
Salaries & wage expenses	1.185	1.414	1.444	1.254
Contract service expenses	0.509	0.159	0.147	0.145
Facility & equipment maintenance expenses	0.040	0.079	0.032	0.053
Equipment hardware & software	0.014	0.017	0.003	0.020
Travel & meetings expenses	0.284	0.311	0.277	0.322
Indirect business expenses	0.559	0.416	0.145	0.400
Other direct expenses	0.020	0.034	0.061	0.056
EVI Board BoS & SAC expenses	0.030	0.035	0.029	0.008
EC ESAC SAC SC expenses	0.000	0.010	0.023	0.004
Total expenses	*13.125*	*11.538*	*7.252*	*9.330*
Other interest and income	0.237	0.282	-	-
Net result			**0.761**	**0.391**

*Management informed American Appraisal (AA Evaluation 2013, page 14) that part of the grants received from EC/ECDTP is earmarked for indirect, project development or overhead cost. If parts of these earmarked cost budgets remain unused by EVI, the unspent part will be accounted for as net income/equity. In 2012, an amount of EUR 0.75 mill (built up over the years 2009-2012) was accounted for as net profit as advised for by Falk & Co.

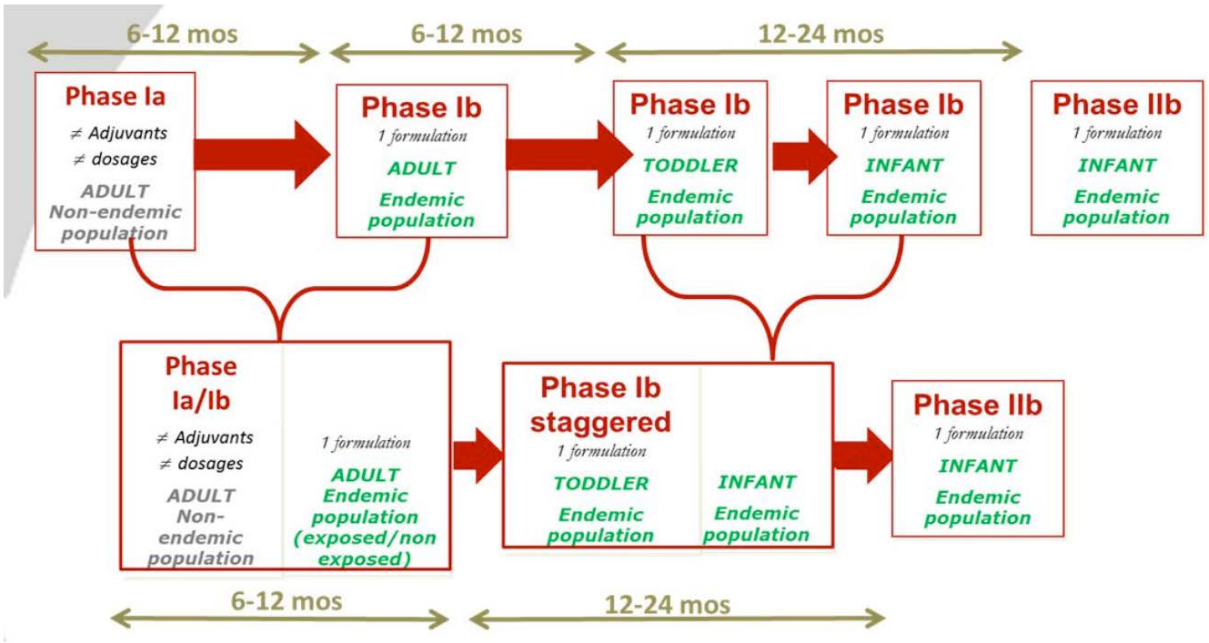
11.4.3 EVI Project Portfolio July 2014



List of Abbreviations of EVI Portfolio

Ad	Adenovirus
Ag	Antigen
AMA1	Apical Membrane Antigen 1
ChAd63	Chimpanzee Adenovirus 63
CSP	Circumsporozoite Protein
DiCo	Diversity Covering
EBA	Erythrocyte-Binding Antigen
EC	European Commission
EDCTP	European and Developing Countries' Clinical Trials Partnership
GMP	Good Manufacturing Practice
ME-TRAP	Multiple Epitope Thrombospondin-Related Adhesion Protein
MSP	Merozoite Surface Protein
MVA	Modified Vaccinia Virus Ankara
P27A	Fragment P27A of the novel malaria protein PFF0165c
Pf	*Plasmodium falciparum*
PfPEBS	*Plasmodium falciparum* Pre-Erythrocytic and Blood Stage
R21	Circumsporozoite protein particle
Rh5	Reticulocyte-binding Protein Homologue 5
VLP	Virus-Like Particle

11.4.4 Classical Clinical Development Path and EVI Fast-Track Clinical Development Path



The fast-track EVI strategy allows to assess the candidate vaccine in the same protocol, for both safety and immunogenicity in European and African populations.

This staggered approach has been successfully implemented for the AMA1-Dico project and the P27A projects, with approval from Regulatory and Ethics Authorities in both European countries (France and Switzerland), and African countries (Senegal and Tanzania).

11.4.5 EVI Partnerships

Figure 4: EVI - Partnerships Public and Private in Developed and Developing Countries