



DNDi *o u t l o o k*

Drugs for Neglected Diseases *Initiative*

www.dndi.org

Financing & incentives for neglected disease R&D: Opportunities and challenges

Comments to the WHO Consultative Expert Working Group (CEWG) on Research & Development: Financing and Coordination – June 2011

Introduction: new R&D landscape for neglected diseases

Fifteen years ago, research and development (R&D) for neglected diseases was at a virtual standstill. Even as late as 2006, only 1% of new drugs approved were specifically for tropical diseases and tuberculosis, even though these diseases account for more than 11% of the global disease burden.¹ This “fatal imbalance”² triggered the creation of several initiatives, including product development partnerships (PDPs), to fill R&D gaps. PDPs research, develop and support accessibility of new health technologies that target diseases disproportionately affecting developing countries, “where disease burdens are highest and no viable commercial markets exist”.³ The R&D pipeline for neglected diseases is now beginning to be replenished, with PDPs managing almost 150 projects in pre-clinical and clinical development.⁴

The Drugs for Neglected Diseases *initiative* (DNDi), launched in 2003 by public and private institutions⁵, is a collaborative, patient needs-driven, non-profit R&D organization that is developing new treatments for malaria, leishmaniasis, sleeping sickness (human African trypanosomiasis) and Chagas disease, and recently expanded its portfolio to include paediatric HIV and helminth infections.

DNDi advocates for increased resources for neglected disease R&D and for new and sustainable mechanisms to support needs-driven R&D. In 2003, DNDi esti-

mated that approximately EUR 230 million would be needed to deliver 6 to 8 new treatments for sleeping sickness, leishmaniasis, Chagas disease, malaria and to establish a robust pipeline of promising compounds for future needs by 2014.

In fact, between 2003 and 2011, with approximately EUR 100 million, DNDi has already developed four new combination therapies by making major improvements in existing treatments⁶, and has also built a promising pipeline of new drug candidates. Even though it is difficult to directly compare cost of development within different business models, the PDP one seems to be cheaper than the traditional pharma one. Further assessment should be conducted considering the evolution of R&D pipelines of PDPs. In contrast, the pharmaceutical industry estimates that the average cost to develop *one* drug is more than USD 1.2 billion.^{7,8}

DNDi is an example of a new form of international collaboration in health R&D that has successfully attracted public and private funding to this field and delivered long awaited treatments at a fraction of the cost claimed by the pharmaceutical sector.

Although a comprehensive, sustainable solution to the problem of neglected disease R&D has not yet emerged, governments, experts, and industry have proposed in the past few years a number of new ideas, including both “push” mechanisms to finance R&D and “pull” incentives to spur private sector investment.

Although DNDi’s experience has to date

been limited to drug R&D for the most neglected tropical diseases, many lessons may apply to other diseases and product types. Based on DNDi’s experience, two key priorities are clear: (1) increase resources for neglected disease R&D, and (2) reduce R&D costs through knowledge-sharing, innovative intellectual property (IP) and regulatory strategies to ensure access for all patients in need.

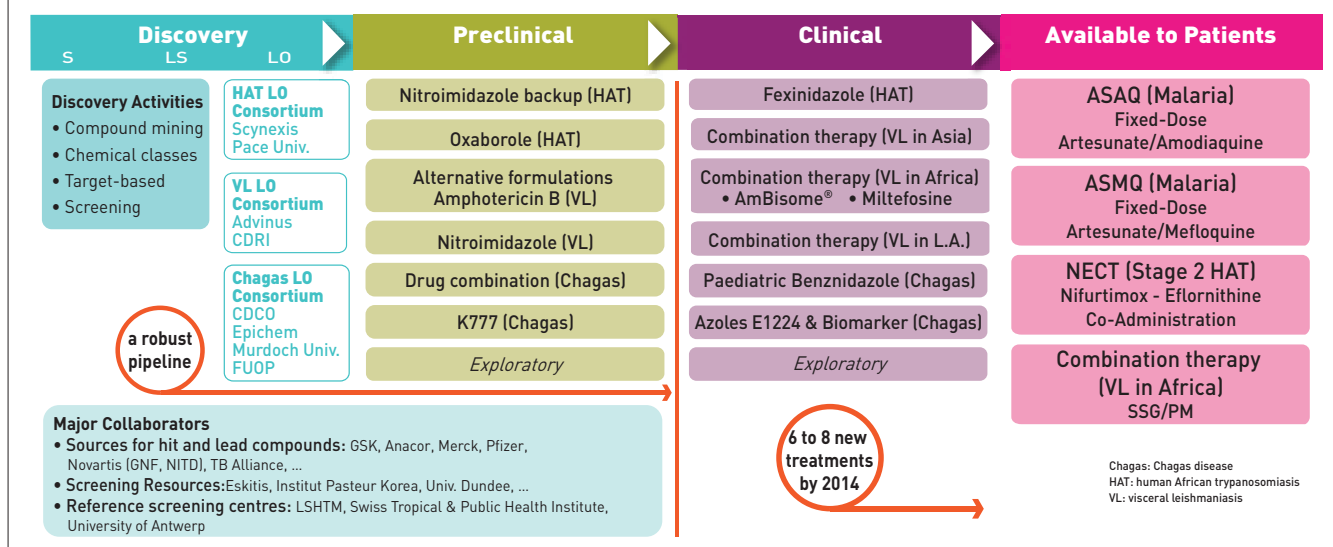
Increasing resources for neglected disease R&D

Despite significant efforts from donors in the last decade, funding for scientific and medical innovation for neglected diseases remains inadequate. Global neglected disease R&D funding in 2009 totalled USD 3.2 billion, (including malaria, tuberculosis, and HIV/AIDS)⁹ which is still insufficient. Of this amount, only USD 162 million – slightly over 5% – was spent on the kinetoplastid diseases (sleeping sickness, leishmaniasis, and Chagas disease).

Investigate innovative sustainable funding for product development and access

Activities related to product development and delivery, including large efficacy trials, manufacturing, registration and pharmaco-vigilance, indisputably constitute the most costly steps of R&D. Traditional grant opportunities are seldom adapted to the financing constraints of these long-term activities requiring large and sustainable sources of funds.

DNDi PORTFOLIO: € 100M SPENT BETWEEN 2003 AND JUNE 2011



In considering innovative and sustainable financing mechanisms for health R&D, the CEWG and WHO Member States should build upon the successes of existing international organisations and mechanisms that are already addressing market and public policy failures, such as UNITAID. Airline ticket and other indirect tax proposals on financial transactions, as suggested by the European Parliament¹⁰ or digital and mobile phone taxes, could be designed to raise predictable and sustainable funds for health and development priorities, including neglected disease R&D.

The allocation of new sources of financing should be determined according to global public health priorities, with the explicit involvement of disease endemic countries. WHO's leading role in the process is essential because of its political legitimacy, technical expertise, and mandate, but also in light of its role in translating R&D efforts into treatment recommendations for use at country level.

Although UNITAID does not currently fund R&D, late-stage product development and activities related to delivery would be a logical expansion of its mandate, enabling it to fill gaps in the portfolio of products that it supports, to influence product design and costs, and to integrate support for registration, introduction, purchase, and delivery. In the field of neglected diseases, and particularly the most neglected diseases, the existence of a stable, subsidised market is crucial to enlisting a manufacturer and to sustaining adequate supply of a new product at the lowest possible price.¹¹

In addition to new sustainable funding for product development and access, new

incentives need to be piloted to stimulate additional early-stage discovery of compounds candidates for neglected diseases.

Pilot milestone prizes to stimulate discovery of new clinical candidates

Discovery is an important gap in the current neglected disease R&D system. To date PDPs have focused to a substantial extent on "low-hanging fruits": drugs licensed for other indications, shelved product candidates, and new combinations and formulations of existing drugs. But attrition and development of resistance require replenishing pipelines with a continued supply of new drug candidates.

Biotechnology companies constitute a promising source of new compounds potentially active against neglected diseases, but solid incentives are needed to engage them in this field of R&D.¹²

Substantial rewards, ranging from EUR 5 to 20 million, for attaining specified milestones along the path to a new drug or other health technology could be a useful incentive to engage biotech companies in screening their compounds for neglected disease applications. For instance, DNDi spent approximately EUR 11 million on discovery and preclinical activities related to the Oxaborole project for sleeping sickness. These activities included hit identification, animal model testing, synthesis of approximately 400 compounds, and screening of an additional 330 compounds. One of these compounds, SCYX-7158, will enter into clinical development in 2011 and will be DNDi's first new chemical entity obtained from lead optimization activities carried out in collaboration with the biotech industry.

As with other pull mechanisms, prizes have the advantage that sponsors pay only for success. Moreover, they offer a way to support progress toward a clear goal without specifying the particular route that it should take. This is particularly appropriate for early-stage R&D, when the best approach may not be known and when the most likely innovators cannot always be identified in advance.

Milestone prizes also promise far earlier pay-outs than advance market commitments, priority review vouchers, or prizes for licensed products, and are thus more likely to attract new actors such as biotech. At the same time, prizes of this type could be a way to test important features, such as IP management and access provisions, for more ambitious and potentially transformative prize mechanisms, including final product prize funds that would reward innovation in proportion to health benefit.¹³

Reducing the costs of R&D for neglected diseases

The lack of funding and incentives for neglected disease R&D requires an open model of sharing knowledge and data to create a more enabling research environment. The DNDi model aims to reduce the costs of R&D through greater sharing of research knowledge and faster registration of needed products in endemic countries.

IP management, open innovation and sharing of knowledge

DNDi's experience in licensing agreements and IP management is driven by

two fundamental principles: (1) the need to ensure that treatments are ultimately affordable to patients and that access is equitable; and (2) the desire to develop drugs as public goods when possible, through dissemination of the results of DNDi's research work as widely as possible to encourage the research community to engage in additional or follow-on research.¹⁴

> Accessing compounds and annotated data

Because DNDi operates on a virtual basis, it negotiates sub-licensable licensing rights to have access to compounds, knowledge and data, and to coordinate R&D activities on a worldwide basis. Securing access to compound libraries of pharmaceutical or biotech companies, including unpublished data and focused knowledge about the compounds, is therefore key as it jumpstarts the expensive and time-consuming discovery phase.

As non-profit entities, PDPs are well-positioned to share knowledge and avoid duplication in research, thereby ensuring reduced costs, greater speed, and increased efficiency. DNDi has signed agreements with several pharmaceutical companies, a handful of biotechs, and other PDPs for access to compounds and related data with therapeutic potential for neglected diseases.

The DNDi partnership agreement with the Global Alliance for TB Drug Development (TB Alliance) for leishmaniasis treatment is a good illustration of the benefits of such open innovation practices. Under the agreement, TB Alliance granted DNDi access to a selected library of about 70 nitroimidazoles belonging to four chemical subclasses. The TB Alliance also shared its scientific expertise and specific knowledge of the drug class, gained through ongoing work with these compounds. These molecules were tested for their potential anti-leishmanial activity at the Central Drug Research Institute in India, under DNDi coordination, some of which demonstrated significant activity against leishmania parasites. The active compounds are expected to enter into clinical phase soon.

> Negotiating freedom to operate, paving the way for access

DNDi does not seek to finance its activities through IP revenues. As the IP generated in partnerships may be individually or jointly owned by DNDi and/or its part-

ners, DNDi secures non-exclusive, sub-licensable, royalty-free licenses on the IP generated from the research partnership to keep control of the outcome of the joint research in the field of neglected diseases. The licenses should ideally provide DNDi with freedom to coordinate R&D and manufacturing activities globally with third parties.

Furthermore, the license should also secure DNDi's right to have the final product distributed and sold in all endemic countries on an affordable and equitable basis. To that end, DNDi negotiates sustainable manufacture and distribution of the product at the lowest possible price in the public sector in endemic countries. Because for neglected diseases competition between manufacturers hardly exists, affordability can be reached through agreements with industrial partners committing to producing at the lowest possible cost, but including a reasonable margin in the price to ensure long-term production, thereby delinking the costs of R&D from the final price of the product.

The successful example of partnership between DNDi and Sanofi for a fixed-dose combination of artesunate (AS) and amodiaquine (AQ) to treat uncomplicated malaria (ASAQ) made this product available throughout sub-Saharan Africa. ASAQ is one of four artemisinin-based combination therapies recommended by WHO since 2001 to thwart the emergence of resistance. ASAQ is an innovative product which is adapted to patient needs of all ages and follows WHO recommendations for being easy to manage (once a day), accessible as a non-patented drug, affordably priced, and appropriate in terms of quality and storage (e.g. 3-year shelf-life).

DNDi coordinated the development of ASAQ through collaboration with various public and private partners while keeping the ownership of the related IP. DNDi then licensed its IP to Sanofi for the industrial production, registration and distribution of the FDC in African and other developing countries. Under the DNDi/Sanofi agreement, Sanofi has committed to supply the FDC to the public sector in endemic countries at a no-profit-no loss maximum price of USD 1. In the private sector, Sanofi is free to sell the FDC at market price and is paying a small royalty back to DNDi, which is reinvested in additional studies. DNDi and Sanofi agreed not to file any patent on the new FDC, which can therefore be freely produced and distributed by any other pharmaceutical company in the world.

The results of this approach are conclusive: ASAQ is registered in 30 sub-Saharan countries and India, and prequalified by WHO. To date, over 80 million treatments have been distributed in 21 countries. In addition, DNDi is currently facilitating technology transfer to ensure production of ASAQ by an African manufacturer.

> Pushing for transparency and sharing of knowledge

The lack of funding and incentives for neglected disease R&D requires new, open models for sharing knowledge and research data. From the Pool for Open Innovation against Neglected Tropical Diseases to the Medicines Patent Pool Foundation for HIV/AIDS, initiatives for open innovation are emerging, and while it may be too early to evaluate the impact, they are a clear illustration of a trend toward a more open environment to boost innovation.

Part of DNDi's mission is to make the results of its work available to the research community to engage in additional or follow-on research in the field of neglected diseases. Thus DNDi restricts confidentiality clauses only to information reasonably critical for the business activities of the industrial partner. Although DNDi has published widely in scientific journals since its creation, making available research outputs though open access scientific databases could further facilitate and stimulate neglected disease R&D.

To test this further, DNDi has recently released pre-clinical datasets related to fexinidazole, a clinical candidate for the treatment of sleeping sickness, on the Public Library of Science-Neglected Tropical Diseases (PLOS-NTD) website, in support of the scientific article.¹⁵ In addition, DNDi is analysing what types of screening data could be made available on public databases.

Innovative regulatory pathways to expedite access in endemic regions and strengthening local regulatory capacity

Historically, most new drugs for neglected diseases have been submitted to western regulatory authorities such as the U.S. Food and Drug Administration, the European Medicines Agency, or SwissMedic, either for routine regulatory review or under specific pathways such as orphan drug legislation or expedited approval mechanisms.

Nevertheless, this regulatory process has drawbacks: “[I]t delays access for African patients since African Medicines Regulatory Agencies often wait for the Western MRA decision before commencing action, and it puts neglected disease product decisions in the hands of regulators who have less experience in tropical disease products, presentations, and epidemiology, and who are not accountable for the needs and safety of target African patients”.¹⁶

What would therefore be the best registration strategy for the approval of a new drug to treat sleeping sickness, for example, which primarily affects neglected patients in Central and West Africa? What would be the best way to support African regulatory authorities in their evaluation of new drugs developed to treat their own populations? How should essential standards for the conduct of clinical trials be defined?

These are some of the issues addressed in the DNDi-commissioned report “Registering New Drugs: The African Context”, by the George Institute for International Health. Experts involved in this study expressed that African regulators have a crucial role to play in assessing health tools being used to respond to specific patient needs in their countries. The report issued the following key recommendations to strengthen regulatory authorisation processes in Africa for new drugs against neglected diseases:

> Ensure closer collaboration between developing and developed countries by involving regulators of endemic coun-

tries in regulatory assessments of new drugs for neglected diseases;

> Extend WHO’s role in the prequalification process of new tools against neglected tropical diseases, in addition to HIV/AIDS, malaria, and tuberculosis; and

> Strengthen regulatory capacity in Africa through the creation of Regional Centres of Excellence in each of Africa’s main sub-regions.

Towards a global public health & equitable access framework for R&D

R&D for neglected diseases suffers from various gaps along the R&D process including (1) new knowledge on drug targets and lead compounds may be published but pre-clinical research does not begin; (2) validated candidate drugs may not enter clinical development because of commercial company choices; and (3) new or existing drugs may not reach patients due to economically unsustainable production or high prices, lack of registration in all endemic countries, or lack of adapted formulations to the local conditions of use.

Several types of incentives and financing mechanisms tailored to particular stages of R&D, types of diseases and health technologies will therefore be necessary to address these various gaps and the unmet needs of neglected patients. Based on the WHO Global Strategy on Public Health, Innovation and Intellectual Property, these mechanisms should promote R&D according to public health needs, build and im-

prove innovative capacity in developing countries, including through transfer of technology, ensure delivery and access to populations in need, and manage IP in a manner consistent with all these objectives.

WHO and its member states will need to play a central role in setting public health R&D priorities, consistent with global public health needs, with strong participation from endemic countries.

Finally, the difficult challenges associated with provision of and access to medicines in developing countries, particularly in the case of neglected diseases, requires that access be addressed as a fundamental goal of any R&D incentive or financing mechanism. A comprehensive access strategy should ensure that new products, developed as public goods whenever possible, will be manufactured at the lowest possible cost in accordance with quality standards, but should also support registration in all endemic countries and ensure sustainable supply in the necessary volumes.

The urgency of providing the necessary health tools to address the global neglected disease burden requires an expeditious and efficient response from all actors.

At a time when many new actors, new policy proposals, and new funding initiatives have emerged in the field of health R&D, this process lead by WHO could mark a turning point. Policymakers have the mandate to design a sustainable strategy and plan to empower existing initiatives and design better policies to boost innovation and ensure equitable access to the fruits of this innovation. ■

NOTES

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- Since 2007, DNDi has delivered two fixed-dose anti-malarials: ASAQ and ASMQ, a combination treatment for the advanced stage of sleeping sickness, NECT

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 - In the field of neglected diseases, affordability can only be ensured through delinking the cost of R&D from the price of the final product. In cases where the market is too small to stimulate competition, ND products will need to be supplied at cost, or at a price corresponding to a small margin above the lowest manufacturing costs to ensure sustainability of production.

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