



Transforming Individual Successes into Sustainable Change to Ensure Health Innovation for Neglected Patients:

WHY AN ESSENTIAL HEALTH R&D CONVENTION IS NEEDED



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*“To make a real difference in the lives of the poorest and most neglected populations – to bring the best science to the most neglected – we must go beyond individual success stories and move toward sustainable change... We need both strong coordination of programs to treat patients today and a **new global framework for R&D under the leadership of WHO** to ensure R&D priority setting according to needs, secure sustainable financing, and establish an enabling policy environment that guarantees both innovation and access for neglected patients.”*

Dr Bernard Pécoul,
Executive Director, DNDi



BACKGROUND & SCOPE

Twelve years ago, research and development (R&D) for poverty-related, neglected diseases¹ was at a virtual standstill. Even as late as 2006, only 1.3 % of new drugs approved were specifically for neglected diseases, even though these diseases accounted for more than 11% of the global disease burden.² As acknowledged in the landmark 2006 report of the World Health Organization (WHO) Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH):

“[w]here there is no purchasing power [t]he market alone, and the incentives that propel it, such as patent protection, cannot by themselves address the health needs of developing countries. [W]e do all agree on the urgent need for action to generate more and sustainable funding for R&D to address the health needs of developing countries, and to engage governments in this endeavor more than has been the case to date.”³

Recognition of this ‘fatal imbalance’⁴ triggered a need for new approaches and alternative models to address market and policy failures. It led to the creation of new initiatives, including not-for-profit product development partnerships (PDPs), such as the Drugs for Neglected Diseases initiative (DNDi), to fill R&D gaps. It prompted the mobilization of additional resources from public and private actors for neglected disease R&D. It also kick-started an international policy process led by the WHO,⁵ which is now at a crucial turning point:

In April 2012, the report of the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) made a major recommendation for consideration at the World Health Assembly in May 2012:⁶

“[T]he time has now come for WHO Member States to begin a process leading to the negotiation of a binding agreement on R&D relevant to the health needs of developing countries, and this would be under Article 19 of the WHO Constitution.”

Since its creation in 2003, DNDi has advocated for increased public responsibility and a more enabling environment in which to carry out needs-driven R&D. This policy brief reviews the evolving landscape for neglected disease R&D over the past decade and explains why, from DNDi’s perspective, a new global framework for essential health R&D is needed. It outlines lessons learned from DNDi’s first-hand experience as a not-for-profit R&D organization dedicated to developing new treatments for the most neglected patients.

¹ Hereafter, the terms poverty-related diseases and neglected diseases are used interchangeably (with the corresponding term ‘R&D for neglected diseases’). Both ‘neglected diseases’ and ‘poverty-related diseases’ refer to ‘diseases that disproportionately affect developing countries’ which fall within the Type II and Type III disease classification (for further details see Footnote 6). The scope of the CEWG mandate is broader and also includes the specific R&D needs of developing countries in relation to type I diseases.

² Chirac P., Torreele E. Global framework on essential health R&D. *Lancet* 2006; 367: p. 1560.

³ Public health, innovation and intellectual property rights – report of the Commission on Intellectual Property Rights, Innovation and Public Health, World Health Organization 2006, pp. 17. <http://www.who.int/intellectualproperty/report/en/>

⁴ ‘Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases’. MSF Campaign for Access to Essential Medicines and Drugs for Neglected Diseases Working Group. Geneva, 2001.

⁵ Key outputs from this policy process include the 2001 Report of the WHO Commission on Macroeconomics and Health, the 2006 report of the Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH), the 2008 Global Strategy and Plan of Action on public health, innovation and intellectual property (GSPA), and the recent recommendations from the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG).

⁶ The Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) was established by the World Health Assembly Resolution 63.28 of May 2010 to deepen the analysis of the previous Expert Working Group (EWG) on ‘current financing and coordination of research and development, as well as proposals for new and innovative sources of financing to stimulate research and development related to Type II and Type III diseases and the specific research and development needs of developing countries in relation to Type I diseases’. Type I diseases are incident in both rich and poor countries, with large numbers of vulnerable populations in each. Type II diseases are incident in both rich and poor countries, but with a substantial proportion of the cases in poor countries. Type III diseases are those that are overwhelmingly or exclusively incident in developing countries. <http://www.who.int/phi/en/>

OVER 1 BILLION PEOPLE, INCLUDING 500 MILLION CHILDREN, IN THE POOREST REGIONS OF THE WORLD ARE AFFECTED BY NEGLECTED DISEASES.



Pamela, her husband Charles, and their two-year old son **Pascal** are all HIV positive. They live in Homa Bay, in western Kenya. Pascal used to have to take four to five different syrups a day. This was not an easy task as some of the syrups have a high percentage of alcohol, giving them a horrible taste for children.

“It was a real struggle getting Pascal to take the syrups every day. He didn’t like the taste. Sometimes we had to hold him down and force him.”



Fatima Puntano lives in the suburban area of Salta, Argentina, where Chagas disease is common. She is one of many who were born with Chagas and have passed it on to their children at birth without knowing it.

“I was diagnosed with Chagas disease when I became pregnant. I didn’t know I had it. My mother had Chagas. They found out my baby was infected when she was born.”

For Fatima, there are only two drugs for her longstanding disease – already in the chronic stage – neither of which is sufficiently safe or effective. Even if treated, there is currently no adequate way to tell whether she is definitely cured.



Rinku Devi is 26 years old. She lives in Muzzafarpur in Bihar State, an endemic area for kala azar in India.

“I delivered a baby two weeks ago. Four days later, I was admitted to the hospital because I had been having fever and body pain for more than two months.”

Luckily for Rinku, the hospital can provide free intravenous treatment. But millions of others in the kala azar disease epicenter are not so fortunate.

EVOLVING LANDSCAPE FOR NEGLECTED DISEASE R&D

Over the past decade, there have been several important trends with respect to neglected disease R&D. Many of these developments are promising while others still need to be evaluated:

- A steady increase in resources for global health has also included increased funding for R&D, with contributions from new R&D actors such as PDPs and new donors, notably Médecins Sans Frontières (MSF) and the Bill & Melinda Gates Foundation in addition to Organization for Economic Cooperation and Development (OECD) countries.
- New interest in more open models for innovation to maximize sharing of research knowledge and increase access, such as the Open Source Drug Discovery (OSDD) consortium in India, the Medicines Patent Pool (MPP) for HIV/AIDS, and the World Intellectual Property Organization (WIPO) Re:Search database.
- New incentive mechanisms to address market failures, such as the US Food and Drug Administration (FDA) priority review voucher, the US Patent and Trademark Office's 'Patents for Humanity' initiative, the pneumococcal vaccine advance market commitment, and several prize competitions.
- New R&D initiatives that have been launched by a broad range of stakeholders, e.g.:

- Academic groups such as the Consortium for Parasitic Drug Development or the Drug Discovery Unit of University of Dundee;
- Emerging economies such as the Oswaldo Cruz Center for Technological Development in Health in Brazil, the Council of Scientific and Industrial Research in India, and the Institut Pasteur Korea;
- Pharmaceutical companies such as the Novartis Institute for Tropical Diseases or the GlaxoSmithKline Tres Cantos Open Lab;
- Specific programs supporting neglected disease R&D from OECD governments such as the European and Developing Countries Clinical Trials Partnership (EDCTP) and the Therapeutics for Rare and Neglected Diseases (TRND) program of the US National Institutes of Health, now part of the National Center for Advancing Translational Sciences (NCATS).

Successes have emerged from this trend, but they are by and large individual and limited advances that would have greater overall impact if they were part of a coordinated global framework for R&D.

Looking at PDPs, which 'play a dominant role in neglected disease R&D, managing around 42% of

global grant funding for neglected disease R&D',⁷ can be illustrative. Even though 16 new products for neglected diseases have been launched by 15 PDPs,⁸ these are largely incremental improvements. Major scientific 'breakthroughs' will still be needed to fundamentally transform the trajectory of certain neglected diseases and enhance chances of disease control and elimination.

While the R&D pipeline for neglected diseases is now beginning to be replenished with over 150 products in pre-clinical and clinical development,⁹ promising candidates will not progress through the pipeline and generate public health breakthroughs without increased and sustained funding, new incentives and innovative collaboration models to ensure further development, and a solid strategy for patient access, including delinking the costs of R&D from the price of products.

Neglected disease R&D still relies too heavily on a few OECD donors, certain philanthropic actors, and some company corporate social responsibility policies. Financing is guided by individual donors' priorities, with no overarching identification of needs and objectives.

New partnerships established to strengthen research capacities in neglected-disease endemic regions require long-term commitments. Overcoming regulatory barriers at all stages requires not only policy change and new regulatory pathways but also

MAIN CHALLENGES FOR NEGLECTED DISEASE R&D SUSTAINABILITY

adequate and sustainable funding.

Despite the promise and success of some PDPs, they do not and cannot constitute the only solution to the systemic problem of lack of R&D to address the needs of patients without significant purchasing power. Only governments can provide massive, reliable, additional, and sustainable financing in support of a new framework that redefines the 'rules of the game' to enable the development and delivery of new and adapted health technologies for patients in developing countries. While the private sector is a key actor, it is not appropriate for industry to define R&D health priorities.

While the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA)¹⁰ made major inroads into identifying the gaps and future directions that essential health R&D should take, a more ambitious – and, importantly, binding and sustainable – framework is critically needed.

⁷ Moran M, Guzman J, Abela-Oversteegen L, Liyanage R, Omune B, Wu L, et al. GFINDER Report 2011: Neglected Disease Research and Development: Is Innovation Under Threat? Sydney: Policy Cures; 2011.

⁸ Source: B&MGF, 2011.

⁹ Global Health Primer <http://www.bvgh.org/Biopharmaceutical-Solutions/Global-Health-Primer.aspx>.

¹⁰ Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. Resolution 61.21, World Health Assembly, Sixty-first Sess. (2008).

In its nearly 10 years of experience in drug R&D for neglected diseases, DNDi has encountered both successes and challenges, from which important lessons can be learned that may apply to other diseases and product types.

DNDi's collaborative model has shown that enhanced and sustained R&D that addresses the needs of developing countries requires two policy moves that must occur simultaneously within a global framework:

- Increased financial and technical resources (with new incentives and funding mechanisms).
- Reduced R&D costs through open innovation mechanisms, pro-access intellectual property (IP) management, harmonized regulatory strategies, and transparency of R&D costs.



LESSON 1

SUCCESSFUL COORDINATION OF R&D REQUIRES STRONG ENDEMIC COUNTRY INVOLVEMENT

BACKGROUND

In the past, few health R&D initiatives have been conducted under the leadership of endemic countries. This is starting to change, as illustrated by a handful of initiatives, most notably antiretroviral formulations for HIV/AIDS developed by Indian generic manufacturers and the Meningitis Vaccine Project, which involved partners from African endemic countries strategically and the Serum Institute of India in the manufacture of the vaccine, under coordination of WHO and the Program for Appropriate Technologies in Health (PATH).¹¹

In 2001, the WHO Commission on Macroeconomics and Health argued that investing in indigenous health R&D capabilities could play a critical role in improving health outcomes and therefore promoting economic and social

development.¹² Leaders of the Federative Republic of Brazil, the Russian Federation, the Republic of India, the People's Republic of China and the Republic of South Africa confirmed this engagement at the Fourth BRICS Summit in India on 29 March 2012.¹³ This points to the importance of, among other things, encouraging and reinforcing scientific knowledge of diseases, strengthening clinical research and manufacturing capacities, and supporting regulatory reform. The sustainability of essential health R&D critically depends on developing countries' involvement and leadership in defining needs and setting R&D priorities under WHO coordination. It also depends on their active role in conducting research and designing adequate national policies to ensure treatment access for patients.



DNDi EXPERIENCE

ENSURING ENDEMIC COUNTRIES ARE PARTNERS AT ALL LEVELS IS CRUCIAL TO SUCCESS

Four out of six of DNDi's founding members are research institutions from neglected-disease endemic countries, namely the Oswaldo Cruz Foundation from Brazil, the Indian Council of Medical Research, the Kenya Medical Research Institute, and the Ministry of Health of Malaysia. With this solid basis, DNDi's policies and practices have been embedded in an endemic-country approach.

DNDi utilizes and strengthens R&D capacity in endemic countries through regional disease-specific platforms,¹⁴ which bring together key regional actors from ministries of health, national control programs, regulatory authorities, academia, and civil society, as well as clinicians and health professionals. These platforms have been instrumental to DNDi's successes. For example:

- The Leishmaniasis East Africa Platform (LEAP) was critical to making available DNDi's first new treatment for visceral leishmaniasis (VL) in Africa – sodium stibogluconate & paromomycin combination therapy (SSG&PM). It brought together scientists from five countries to design and conduct a common Phase III multicenter study in accordance with Good Clinical Practice (GCP) standards, with recruitment of more than 1,000 patients, and facilitated implementation of WHO's 2010 recommendation of SSG&PM as first-line treatment for VL in the region.
- The Human African Trypanosomiasis (HAT) Platform for sleeping sickness was instrumental in developing and facilitating implementation of and

access to DNDi's 2009 nifurtimox-eflornithine combination therapy (NECT), the first improved treatment for sleeping sickness in 25 years, in all endemic countries. National authorities play a particularly important role in the platform.

- In addition, experts from endemic countries play a major role in the definition of DNDi's disease-specific 'target product profiles' (TPPs), together with other international experts. The TPP, which drives all DNDi R&D activities, is the description of the 'ideal' treatment that an R&D project is pursuing (e.g. target indication, population, clinical efficacy, safety and tolerability, stability, route of administration, cost, etc). Sound knowledge of patients' needs is essential to a credible TPP. The Chagas Clinical Research Platform (CCRP), created in 2009, was instrumental in the review and update of the TPP for Chagas disease.

DNDi is committed to transferring industrial development and other

R&D know-how to partners in endemic regions. To date, DNDi has actively participated in the process of technology transfer between Farmanguinhos (Brazil) and Cipla (India) for one of its fixed-dose combination (FDC) antimalarials (artesunate/mefloquine or ASMQ), which was completed in 2010, and is currently involved in the transfer of technology to an African manufacturer partner, Zenufa, for ASAQ (artesunate/amodiaquine, the first DNDi antimalarial FDC, which was developed with Sanofi).

When discussing the regulatory strategy with its industrial partners, DNDi promotes pathways that involve neglected disease-endemic countries' participation and assessment of the risk/benefit equation (see Lesson 4).

Developing countries, particularly emerging economies with strong innovation capacity, offer increasing opportunities for conducting R&D through international collaborations with public and private actors.¹⁵ However, a more enabling framework coupled with new incentives to ensure both innovation and access is needed in developing countries.

WHY A CONVENTION?

An R&D convention would engage Member States' public responsibility in defining R&D priorities, based on patients' needs in developing countries and allocating adequate resources to priority R&D projects. The convention would also establish WHO's key coordinating role in guaranteeing endemic country involvement.

¹¹ <http://www.meningvax.org/partners.php>

¹² Macroeconomics and health: investing in health for economic development. Report of the Commission on Macro-economics and Health. Geneva, World Health Organization, 2001, p.8.

¹³ In paragraph 43 of the Fourth BRICS Summit - Delhi Declaration, State leaders declared: 'we have taken note of [...] the growing capacities for research and development and innovation in our countries. We encourage this process both in priority areas of food, pharma, health and energy as well as basic research in the emerging inter-disciplinary fields of nanotechnology, biotechnology, advanced materials science, etc. We encourage flow of knowledge amongst our research institutions through joint projects, workshops and exchanges of young scientists.'

¹⁴ <http://www.dndi.org/index.php/overview-sc.html>

¹⁵ A Business Plan To Help The 'Global South' In Its Fight Against Neglected Diseases by Frew S.E, Liu V.Y, and Singer P.A., Health Affairs, 2009, Vol. 28, 6:1760-73

LESSON 2

INCREASED AND SUSTAINABLE FINANCING IS NEEDED FOR ESSENTIAL HEALTH R&D

BACKGROUND

The so-called '10/90 gap', illustrating the fact that only about 10% of all health research is devoted to the health problems of 90% of the world's population, remains largely unchanged since 1990, despite recent initiatives. While the absence of data renders accurate and comparative analysis difficult, it can be noted that global health research spending amounted to approximately US\$ 160 billion (in 2005),¹⁶ whereas just US\$ 3.2 billion was spent on neglected disease R&D (in 2010).¹⁷

Moreover, public funding for neglected disease R&D from the world's richest nations fell by 6% in 2010 and there is a need for additional and more sustainable sources of funding.

Building upon the successful model of UNITAID, which is financed through airline ticket taxes, indirect tax proposals on financial transactions, or sectorial taxes such as tobacco, digital, or mobile phone taxes could constitute the type of innovative and sustainable funding mechanisms that are needed. The idea of a European financial transaction tax (FTT) is being discussed by G20 leaders and already has support from France, Germany, and Ireland, for example, as well as key civil society groups, and business and philanthropic leaders such as Bill Gates.¹⁸ In addition, endemic countries, and particularly emerging economies, also have a responsibility to contribute to increased financing of essential health R&D.



DNDi EXPERIENCE

R&D COSTS CAN BE REDUCED THROUGH MORE OPEN, COLLABORATIVE MODELS, AND NEW AND SUSTAINABLE FUNDING NEEDS REMAIN CRITICAL

DNDi is an example of a new form of international collaboration in health R&D that has successfully attracted public and private funding and delivered new treatments at a fraction of the cost generally reported by the pharmaceutical sector for drug development. Within nine years and with US\$ 160 million, DNDi has developed six new treatments for neglected diseases, which significantly improve upon existing treatment options, and has built a promising pipeline including 11 new chemical entities.

To develop an additional five to seven new treatments – to reach DNDi’s objective of developing 11 to 13 new treatments in total by 2018, including at least one new chemical entity – and to continue building a robust pipeline, DNDi estimates in total US\$ 525 million will be needed.¹⁹ So far, DNDi estimates its costs of development to range from US\$ 15-50 million for improved treatments, and US\$ 130-200 million for a new chemical entity.

Although it is difficult to compare costs of development between different business models, preliminary data indicate that the PDP model is far more efficient than the traditional pharmaceutical business model. This may be explained by the more open, collaborative modus operandi of PDPs and the fact that they are addressing unmet medical needs and abandoned gaps. A deeper analysis of these costs and an effort to fairly quantify in-kind contributions of all partners is urgently required to

estimate the overall funding needed for neglected disease R&D.

So far, funding is far from being secured for all R&D stages, but particularly for clinical development and implementation

of promising product candidates, including large efficacy trials, manufacturing, registration and pharmacovigilance, which constitute the most costly steps of R&D.

WHY A CONVENTION?

A binding R&D convention could engage governments’ public responsibility, both in developed and developing countries, to compensate for the market failure in drug development for diseases that disproportionately affect the poor. It could provide adequate funding on a sustainable basis, as a proportion of GDP, or of health development aid. Such a convention could also secure a portion of innovative financing mechanisms, such as an international financial transaction tax, for essential health R&D. In addition, a more cost-effective and efficient model for conducting essential health R&D would benefit all countries.



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¹⁶ In 1990, the Commission on Health Research for Development estimated that only about 5% of the world’s resources for health research (which totaled US\$ 30 billion in 1986) were being applied to the health problems of low- and middle-income countries, where 93% of the world’s preventable deaths occurred. <http://www.globalforumhealth.org/about/1090-gap/>

¹⁷ Moran M, Guzman J, Abela-Oversteegen L, Liyanage R, Omune B, Wu L, et al. GFINDER Report 2011: Neglected Disease Research and Development: Is Innovation Under Threat? Sydney: Policy Cures; 2011.

¹⁸ ‘A financial transaction tax (FTT) has been widely advocated as a good way of raising additional resources for development. FTTs already exist in many countries, where they generate significant revenue, so they are clearly technically feasible... Some modeling suggests that even a small tax of 10 basis points on equities and two basis points on bonds would yield about USD 48 billion on a G20-wide basis... It is critical that a portion of the money raised be reserved for investments in development.’ Cited in *Innovation With Impact: Financing 21st Century Development* (a report by Bill Gates to G20 leaders), Cannes Summit, November 2011.

¹⁹ DNDi 2011-2018 Business Plan.

LESSON 3

OPEN INNOVATION AND PRO-ACCESS IP MANAGEMENT IS NECESSARY TO DEVELOP GLOBAL PUBLIC GOODS FOR NEGLECTED PATIENTS

BACKGROUND

Health R&D to address the needs of developing countries requires new and open models for sharing knowledge and research data. As demonstrated by the Open Source Drug Discovery consortium in India,²⁰ ChEMBL-NTD,²¹ WIPO Re:Search,²² the Medicines for Malaria Venture's open access Malaria Box,²³ GSK's Open Lab²⁴ and the Medicines Patent Pool,²⁵ initiatives for open innovation are flourishing, and while it may be too early to evaluate their impact, they are a clear illustration of a trend toward a more open approach to boosting innovation.²⁶



DNDi EXPERIENCE

AN OPEN INNOVATION MODEL, WHICH REDUCES R&D COSTS, COMBINED WITH SECURING PATIENT ACCESS IS NOT ONLY POSSIBLE, IT IS IMPERATIVE

In order to deliver major scientific breakthroughs for neglected diseases, DNDi has gained increased access to patented or unpublished compounds from pharmaceutical companies, biotech companies, and other PDP libraries. When positive hits are identified through screening and before engaging financial resources into expensive lead optimization and development activities, DNDi negotiates research and license agreements to gain access to annotated data and focused knowledge about promising compounds and to secure the necessary freedom to operate. Access to such information is key as it jumpstarts the expensive and time-consuming discovery phase, avoids duplication in research, reduces overall R&D costs, and therefore increases efficiency.²⁷

In accordance with its IP policy,²⁸ DNDi negotiates terms with partners to ensure that they will not use their IP 'in a manner that impedes equitable and affordable access to the products of the research, or that impedes additional or follow-on research by DNDi, its partners and other researchers, especially those undertaking research on neglected diseases.' In addition, various provisions aim at delinking the cost of R&D from the price of the product, which is essential to ensure affordable and equitable access for patients in developing countries.

DNDi has managed to negotiate favorable licensing terms with several pharmaceutical companies, and after a number of years of experience in such negotiations, has come to define a 'gold standard' of licensing terms, which can be summarized as follows:

- Perpetual royalty-free non-exclusive sub-licensable licenses in the specific disease areas determined in the contract;
- Worldwide research and manufacturing rights;
- Commitment to make the final product available at cost, plus a minimal margin, in all endemic countries, regardless of income level;
- Non-exclusivity enabling technology transfer and local production.

With these objectives in mind, the six new treatments DNDi has developed

that are easier-to-use, non-patented, field-adapted, and affordable have been made available as public goods,²⁹ with no IP barriers. For example, the antimalarial ASAQ was developed as a public good in order to have the product accessible on the widest scale possible. This 'public good' driving principle also supported technology transfer to an African manufacturer to secure a second manufacturing source, strengthening production capacity in one of the highest malaria-burden regions and potentially driving prices further down through competition.

However, while the 'gold standard' may be achieved on a case-by-case basis through bilateral negotiations, in the absence of a global framework, there is no sustainable way to systematically ensure that the treatments developed for the poorest populations of the world can and will be delivered as public goods.

WHY A CONVENTION?

Consolidating and improving upon the various current 'open source' initiatives, an R&D convention could create a sustainable and enabling normative framework linking innovation of and access to new health products (and delinking the cost of R&D from the price of end products). Moving into an open source model of R&D supported by public funding requires the adoption of fundamental principles tying publicly funded R&D to guarantees of equitable access and affordability of the end products, as global public goods.

²⁰ The OSDD consortium launched in September 2008 has more than 5,500 registered users from more than 130 countries around the world, and has emerged as the largest collaborative effort in drug discovery. Launched on the three cardinal principals of Collaborate, Discover & Share, it is a community driven open innovation platform to address the unmet need of research and development of drugs for diseases that affect the developing world. <http://www.osdd.net/about-us>

²¹ The ChEMBL - Neglected Tropical Disease archive is a repository for Open Access primary screening and medicinal chemistry data directed at neglected diseases. The primary purpose of ChEMBL-NTD is to provide a freely accessible and permanent archive and distribution center for deposited data. ChEMBL-NTD is a subset of the data in the free medicinal chemistry and drug discovery database ChEMBL. <https://www.ebi.ac.uk/chemblntd>

²² Re:Search is a World Intellectual Property Organization (WIPO) initiative to create an open innovation platform – in the form of a searchable public database – to make intellectual property (IP), including compounds and regulatory data, for neglected disease innovation available for licensing. <http://www.wipo.int/research/en/>

²³ In a bid to catalyze malaria and neglected disease drug discovery, MMV and SCYNEXIS, Inc. have assembled a Malaria Box of 400 carefully selected commercially available compounds with antimalarial activity and will provide it to researchers at no cost. <http://www.mmv.org/malariabox>

²⁴ The Tres Cantos Open Lab Foundation aims to accelerate the discovery and development of medicines to tackle diseases of the developing world in an open collaborative way. <http://www.openlabfoundation.org/default.aspx>

²⁵ The Medicines Patent Pool Foundation aims at increasing access to appropriate medicines for people living with HIV in low and middle-income countries by negotiating with patent holders to share their IP with the Pool, and then licensing it to other producers to facilitate production of affordable generic medicines, well-adapted for use in resource-poor settings. <http://www.medicinespatentpool.org/>

²⁶ 'The most urgent need in the fight against neglected tropical disease is in even newer and better medicines and vaccines. And for that we need to think differently about how we do R&D. Given the scale of the task we all face, that means finding new ways of industry, academia, NGOs and governments working together. We call this the "open innovation agenda," and it has three parts: The first is greater flexibility around intellectual property; the second is creating new, broad-based partnerships where researchers have access to our industrial-scale expertise, processes, facilities and infrastructure, not just our know-how or IT; and third, and perhaps most interesting, is access to new compounds.' Extract from an interview of Andrew Witty, Executive Officer, Glaxosmithkline, Council on Foreign Relations, January 20, 2010, NY.

²⁷ DNDi reached out to pharmaceutical companies for access to their compound libraries after 3 years of work with public libraries of compounds, which led to the identification of only one promising candidate for sleeping sickness. <http://www.dndi.org/portfolio/fexinidazole.html>

²⁸ DNDi IP policy is routed in two major principles: to ensure that treatments developed by DNDi are affordable and that access is equitable, and to develop public goods whenever possible. DNDi IP policy is available at <http://www.dndi.org/index.php/ip-policy.html>

²⁹ Two antimalarial fixed-dose combinations, new combination therapies for the treatment of sleeping sickness and visceral leishmaniasis, and a new paediatric formulation for the treatment of Chagas disease. <http://www.dndi.org/index.php/overview-treatments.html>

LESSON 4

INNOVATIVE REGULATORY PATHWAYS ARE NEEDED TO EXPEDITE RESEARCH AND ACCESS

BACKGROUND

Even though the CEWG did not consider ‘regulatory harmonization’ as ‘a proposal principally directed at enhancing R&D for neglected diseases’, the regulatory environment is a major component of any discussion related to the political economy of pharmaceutical innovation. DNDi strongly recommends the inclusion of a regulatory component in an R&D convention to expedite access for patients, reduce the costs of R&D and ultimately strengthen developing countries’ regulatory capacity.

In addressing developing countries’ health needs, the argument that Western regulatory authorities are the only certified sources to evaluate the quality, safety, and efficacy of medicines should be challenged, in particular for assessing the risks and benefits of health products for diseases predominant in developing countries, for which therapeutic options are often severely limited.

However, obtaining necessary approvals by regulatory authorities in many developing countries is a long and costly process that ranges from ethics approval, to conducting a clinical trial, up to the full registration of the product, which can considerably delay patient access to essential medicines. To take the example of neglected diseases, most new drugs have been first assessed by well-resourced regulatory authorities before being approved for use in endemic countries. But with around 150 new products for neglected diseases in development, developing countries’ regulators have a crucial role to play in assessing the benefits and risks of these new health tools developed to respond to specific patient needs in their own countries.

It is therefore urgent to strengthen capacities of poorly-resourced regulatory bodies in endemic countries notably through enhanced formal collaboration with regulatory bodies of well-resourced and experienced endemic countries or of ‘stringent’ countries, in partnership with WHO. It is fundamental to stimulate, support, and promote regional initiatives that aim at accelerating scientific risk/benefit adjusted reviews and rationalize mutual recognition of regulatory policies within regional zones where disease prevalence is similar. Innovative regulatory pathways are needed to expedite access to essential medicines in developing countries, while ensuring that new treatments are safe, effective and of quality, and reduce costs linked to regulatory approvals, while strengthening local regulatory capacity.³⁰



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DNDi EXPERIENCE

COUNTRIES WHERE DISEASES ARE ENDEMIC ARE IN THE BEST POSITION TO ASSESS RISKS AND BENEFITS FOR THEIR POPULATIONS, WE JUST NEED THE RIGHT REGULATORY FRAMEWORK

The example of SSG&PM is illustrative: even though this new treatment for visceral leishmaniasis is recommended by WHO as first-line treatment, the lack of a harmonized regulatory environment in East Africa results in various, and sometimes different, regulatory processes in each country to include the treatment in national protocols and to register one of the two components of the treatment. Time, money, and lives could be saved if such processes were part of a global R&D framework.

DNDi has used various strategies to jointly involve regulators from endemic countries – who have the best knowledge of the diseases, patients’ needs, and the responsibility to assess the benefit/risks for their own populations – and regulators from developed countries, with experience in the approval of new drugs. For example:

- A DNDi regulatory file was offered as a case study in a training of the WHO Prequalification Program. The ASAQ dossier was reviewed for

a ‘virtual approval’ by participants from developing countries, with support from WHO and European Medicines Agency (EMA) experts.

- DNDi’s ASMQ regulatory file was jointly assessed by a group of regulators from ASEAN (Association of Southeast Asian Nations) countries.
- Following review by WHO, the eligibility of fexinidazole (a new drug candidate for sleeping sickness) for an evaluation through Article 58 of the EMA has been confirmed. In 2011, DNDi and Sanofi received a joint EMA and FDA scientific advice on the

clinical development plan.

In 2012, DNDi with administrative support from WHO, organized an international ethics workshop with representatives from endemic and non-endemic countries in Africa and a French Ethics Committee to review its pivotal clinical study of fexinidazole for late-stage sleeping sickness.

- In the case of the pediatric dosage form of benznidazole, DNDi hopes to have the new formulation registered in endemic countries based on the first registration by the Brazilian regulatory agency, Anvisa.

WHY A CONVENTION?

DNDi strongly recommends the inclusion of a regulatory component in an R&D convention to facilitate timely patient access to medicines, reduce costs of R&D, and ultimately strengthen developing countries’ regulatory capacity.



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³⁰ Moran M, Guzman J, McDonald A, Wu L, Omune B (2010) Registering new drugs: the African context. London: Health Policy Division, The George Institute for International Health. <http://www.dndi.org/index.php/regulatory.html>

CONCLUSIONS

TIME FOR AN ESSENTIAL HEALTH R&D CONVENTION

The neglected disease R&D landscape has evolved within the last decade, with important advances having been made during this time. However, it is now time to transform individual successes into sustainable change.

An essential health R&D convention would ensure that public leadership channels the efforts of all actors and initiatives towards a common goal.

Based on DNDi's experiences and lessons learned, a binding R&D convention under WHO leadership as recommended by the CEWG, could:

- Enable the **definition of R&D priorities** based on patients' needs in developing countries and allocate adequate resources to priority R&D projects;
- **Estimate and raise adequate levels of financial resources** through innovative funding mechanisms and new commitments from both 'traditional' donors and emerging economies;
- **Address the various R&D gaps** (discovery, development, implementation³¹) through several types of incentives and financing mechanisms tailored to particular stages of R&D, types of diseases, and health technologies;
- **Design adequate minimum standards** and principles concerning the availability, scope, and use of research tools and related incentives to ensure innovation of and equitable access to new essential health products;

- Support **international collaboration and strengthening of regulatory capacity** in developing countries to streamline clinical development and marketing authorization of new products for diseases that disproportionately affect developing countries; and
- **Coordinate with relevant international procurement organizations** and national control programs to ensure timely delivery and access in developing countries.

As the sole legally mandated intergovernmental agency responsible for public health, WHO can and should lead this process.

Today, there is a unique opportunity to alleviate human suffering and prevent needless deaths in developing countries in a sustainable manner.

DNDi supports the CEWG conclusion that 'a binding instrument on R&D is necessary to secure appropriate funding and coordination to promote R&D needed to address the diseases that disproportionately affect developing countries and which constitute a common global responsibility.'³²

³¹ Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases. MSF Campaign for Access to Essential Medicines and Drugs for Neglected Diseases Working Group. Geneva, 2001.

³² http://www.who.int/phi/CEWG_Report_5_April_2012.pdf (see p.120)

Regional Offices

DNDi AFRICA

c/o Centre for Clinical Research
Kenya Medical Research Institute
PO Box 20778
KNH 00202 Nairobi
Kenya
Tel: +254 20 273 0076

DNDi LATIN AMERICA

Jardim Botânico-Rio de Janeiro
Rua Santa Heloisa 5
Rio de Janeiro, RJ 22460-080
Brazil
Tel: +55 21 2215 2941
www.dndi.org.br

DNDi INDIA

c/o Indian Council of Medical Research
2nd Campus – Room No 3, 1st Floor
TB Association Building
3, Red Cross Road
New Delhi 110-001
India
Tel: +91 11 2373 1635

DNDi JAPAN

3-1-4 Nishi-Shinjuku
Shinjuku-ku Tokyo 160-0023
Japan
Tel: +81 3 6304 5588
www.dndijapan.org

DNDi MALAYSIA

Administration Building, IPHarm-MOSTI
Blok 5-A, Halaman Bukit Gambir
11700 Pulau Pinang
Malaysia
Tel: +60 4 657 9022

Project Support Office

DNDi DRC

04 av. de la Révolution
Quartier Socimat
Commune de Gombe
Kinshasa
Democratic Republic of the Congo
Tel: +243 81 011 81 31

Affiliate

DNDi NORTH AMERICA

40 Wall Street, 24th Floor
New York, NY 10005
USA
Tel: +1 646 616 8680
www.dndina.org