DNDi
Drugs for Neglected Diseases initiative

'Demonstration projects' in the framework of the follow-up of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG)

December 2013

Background: 'CEWG Demonstration Projects'

This year, during the 66th World Health Assembly (WHA), Member States adopted the resolution 66.22[1] on the follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG),[2] which resulted from an intergovernmental meeting in November 2012.[3] While any discussion of a research and development (R&D) Convention was to be postponed until 2016, Member States decided on two significant action points: (1) establishing a Global Health R&D Observatory under the auspices of the World Health Organization (WHO), and (2) requesting the WHO Director General to set up several 'demonstration projects'. The main objective of the overall 'CEWG process' is to get Member States to agree on innovative mechanisms to fund and coordinate public health R&D to address unmet medical needs of developing countries.

The decision point A66/B/Conf./2 adopted at the 66th WHA specifies that demonstration projects should, in particular, ***'utilize collaborative approaches, including open knowledge approaches for R&D coordination; promote the de-linkage of the cost of R&D from product price; and propose and foster financing mechanisms including innovative, sustainable and pooled funding.'*** In addition, ***'[t]he demonstration projects should provide evidence for long term sustainable solutions.'***

The mid-term and final outcomes of the demonstration projects could help to pave the way towards concrete actions for a sustainable global framework.

'Demonstration Projects': Process and Principles

1. Process

Through WHO regional consultations, each of the WHO regions selected a maximum of four projects. These projects will be presented and discussed during the **technical meeting organized by the WHO for Member States with selected experts** from 3 to 5 December 2013. The objective of the December meeting is to propose a priority list of projects for consideration by Member States. A report of the meeting, as well as descriptions of the priority projects, will be submitted by the WHO Secretariat for consideration of the 134th WHO Executive Board (EB; 20-25 January 2014) and the 67th World Health Assembly in May 2014.

2. Principles

a) Overall principle

The goal of the demonstration projects process is **to identify projects that address research gaps, ensure effective coordination at all levels, and secure needed resources for implementation in order to develop and deliver health products.**

Since the actual process of the demonstration projects is an **outcome of the CEWG follow-up**, as mentioned above, each of the projects should integrate one or several of the mechanisms elaborated in the CEWG report (listed below), and which could be designed in various ways to meet the decision point criteria depending on diseases, technologies, state of science, funding opportunities, etc.

While Member States, experts, and relevant stakeholders will review the selection of projects, it is essential to link the process with its ***raison d'être*** and background, which is to provide and demonstrate evidence for discussions on **a sustainable global framework as described in the CEWG report.**

b) WHA A66/B/Conf./2 principles -

For a project to be selected, the following principles should be fulfilled:

I. **Address diseases/conditions that disproportionately affect people in low- and middle-income countries**, particularly the poor, and where immediate action can be taken at various stages of discovery or development based on an analysis of **identified R&D gaps in product pipelines.**

II. **Utilize collaborative approaches, including open knowledge approaches for R&D coordination:**

Various types and combinations of collaborative approaches to R&D could be considered for demonstration projects and could be designed in such a way as to promote open knowledge innovation, including direct grants, patent pools, pre- (or 'non-') competitive R&D platforms, open access schemes, or open source reward systems (e.g. a discretionary

[1] Full resolution text available at http://apps.who.int/gb/ebwha/pdf_files/WHA66/A66_R22-en.pdf
[2] Full report available at http://www.who.int/phi/cewg_report/en/index.html
[3] For a full background WHO PHI web site http://www.who.int/phi/en/

sum of resources can be allocated to reward researchers whose open sharing of knowledge has proven to be a critical step in the development of innovation. Such a reward could be awarded retrospectively).

III. **Promote a mechanism that allows for de-linkage of the cost of R&D from product price:**

The de-linkage of the cost of R&D from the product price can only be ensured when the cost of R&D is paid for (or 'recouped') through mechanisms other than the sales revenues of the product. This can be done through a range of mechanisms with contractual commitments for access, affordability, and non-exclusive licensing provisions. It would entail transparency related to the costs of R&D, manufacturing, and delivery of the final products.

- **Prizes** are a clear example of the type of incentive mechanism that can de-link the cost of R&D from the product price, through contractual commitment to the winner. With end-stage prizes, substantial awards could be granted to developers who come up with technologies or products that meet clear specifications or target product profiles (TPPs),[4] awarding innovators for added value to public health-orientated innovation. Milestone prizes could be awarded to projects that achieve pre-determined milestone thresholds throughout the drug, diagnostic, or vaccine development pathway. For example, this mechanism could be put in place for one of the demonstration projects below with rewards for each critical step. The end sum for the accumulated milestone prizes would be comparable to an end-stage prize.
- In addition, de-linkage of R&D cost from product price can also be implemented with any type of **grant** through provisions/clauses in grant contracts to ensure access and affordability of the final products.
- **Patent pools** can also promote the de-linkage of R&D costs from product price by encouraging competitive pricing of end products. In order to ensure equitable access, the terms of the licenses should include the widest possible geographical scope in low- and middle-income countries.
- Finally, the concept of de-linkage is also useful to promote the rational introduction and responsible marketing of new medical tools. As the incentive for R&D is not linked to the sales revenue from the new product, not only are prices lower, but there is no perverse incentive to aggressively promote and market the tools.

Illustration through the DND*i*'s proposed CEWG demonstration projects

With support of Member States, DND*i* submitted two candidate demonstration projects with the aim to demonstrate that projects can be optimized through guiding principles such as **cross-regional collaboration** of existing networks, **open-innovation and knowledge sharing**, **equitable access** to new products, and **sustainable funding** secured through existing and new funding mechanisms. DND*i* is also partner in another candidate demonstration project, on cutaneous leishmaniasis, submitted by the US Food and Drug Administration and Osaka University.

Chagas R&D Accelerator Initiative: A coordination mechanism to accelerate the development and delivery of new tools to treat and control Chagas disease based on open innovation and access principles

Endemic throughout Latin America and the leading parasitic killer of the Americas, Chagas disease (American trypanosomiasis) is a highly important but little-addressed public health issue, not only in Latin America but increasingly in non-endemic, developed countries, due to globalization and population flows. Urgently needed new public health tools consist of the following: 1) Improved and better-tolerated treatments: the only two drugs available to treat Chagas disease are therapies of long duration that are poorly tolerated, especially in adult chronic Chagas disease patients; 2) Tests for therapeutic response: tests are needed to assess patient cure and accelerate clinical trials for drugs by reducing time and costs.

The Chagas R&D Accelerator Initiative is a mechanism for targeted coordination (portfolio management) of promising R&D approaches, which seeks to identify and prioritize projects from any organization with the highest chances of new-tool delivery; expedite their development by applying new incentive mechanisms; quantify and secure innovative financing through national, regional, and international initiatives; and ensure commitments for open innovation and patient access to new products.

Guiding principles of the Initiative:

- **Open knowledge and innovation:** Institutions, companies, and researchers would sign a formal agreement ensuring open knowledge sharing, data transparency, and publication of results (whether positive or negative).
- **Sustainable funding:** Members of the Initiative's committee, principally governments, would commit to secure the necessary funding through different mechanisms, including in-kind resources such as expertise and facilities. The coordination of the Initiative could bring public and private funding into a virtual fund to support priority projects, which could be taken forward at national and multinational levels. The Initiative would provide an opportunity to test new ways to target and leverage existing funds in the region, for example by using financial instruments that support socially responsible projects, innovation, and national industries.

[4]The TPP is a succinct description of the ideal specifications needed for a treatment in order to best respond to the needs of patients. TPPs are developed with leading experts from endemic countries, researchers, clinicians, and disease control programs.

- **Equitable access and de-linkage:** The Initiative would implement a policy of equitable access to new therapeutic and diagnostic tools, with commitments for production and supply at cost plus a minimal margin, registration and availability in all endemic countries, and open licensing of intellectual property (IP) with the possibility of technology transfer, thus supporting de-linkage of R&D costs from final product prices. Funding and use of resources would be tied to agreements by the recipients to the open innovation and access policies. To ensure sustainable access, the coordination mechanism would regularly review and propose enabling regulatory, financial, and procurement policies.
- Promote and support a range of **new incentive mechanisms.** As a first step, the use of a milestone prize for biomarkers would be explored.

The goal would be to accelerate R&D for Chagas disease and deliver new tools for the treatment of people living with Chagas disease within five years in four areas: 1) new treatment options: delivering proofs of concept of alternative treatment regimens of existing drugs as well as a new chemical entity, ending with at least one new treatment option; 2) field-friendly point of care diagnostic kit (using polymerase chain reaction – or PCR); 3) creation of a biobank portal and establishment of two biobanks in endemic countries; and 4) new qualified biomarkers for assessing treatment response. Such new tools would be used to support control of Chagas disease worldwide.

Governance

The coordination Initiative would be composed of representatives of the scientific community, key Latin American governments, PAHO/WHO, TDR, DND*i*, treatment providers, and the International Federation of People Affected by Chagas Disease (FINDECHAGAS), and would be supported by a secretariat hosted by an existing institution. It proposes a deliberate regional focus and a key role for Latin American governments. Few health R&D initiatives have been conducted under the leadership of endemic countries, yet the sustainability of essential health R&D critically depends on developing countries' leadership. It would demonstrate that countries in Latin America can collaborate on R&D priorities based on open innovation principles, focused on a disease of regional importance. It would also demonstrate that endemic countries can collaborate on funding directly, and through in-kind access to facilities and expertise, such an R&D collaboration, including with stakeholders and public and private funders from any region. This would establish an important precedent within the region and internationally, and provide opportunities to evaluate whether such collaborations would be of benefit in other disease areas and regions.

Visceral Leishmaniasis Global R&D and Access Initiative

Visceral leishmaniasis (VL) is generally fatal without treatment. VL occurs on five continents with endemic transmission reported in 98 countries. VL is **one of the most neglected tropical diseases** despite the fact that it is the most deadly parasitic disease after malaria. A worldwide disease, in southern Europe, up to 70% of cases of VL in adults are associated with HIV infection; India is an important endemic country with 60% of all cases occurring in Bihar state; around 20,000 cases are estimated in the East Africa region, which is prone to devastating outbreaks; and in Sudan more than half of patients develop post kala-azar dermal leishmaniasis (PKDL).

Although the number of treatment options for VL has increased in the past decade, the **existing therapies for VL have serious drawbacks** in terms of safety, resistance, stability, and cost, and have low tolerability, long treatment duration, and difficult administration in field settings. The disease remains a challenging public health problem in the endemic regions, and an increasing health burden in other regions such as Europe (e.g. Spain), where the disease appears to be re-emerging.

Guiding principles of the Initiative:

- **Sharing knowledge and open innovation:** The establishment of a Drug Accelerator Consortium as an open knowledge platform – which could be supported by the Innovative Medicines Initiative (IMI)/Horizon 2020 – would be a key asset to speed up upstream research, avoid duplication of research and decrease cost of R&D. Partners within the Drug Accelerator would agree to screen their libraries together, increasing the chance to identify hits for later optimization. Other institutions and researchers from different initiatives and networks would agree to open knowledge sharing, similar to the Open Source Drug Discovery (OSDD) set up in India as part of the Council of Scientific and Industrial Research (CSIR).
- **Sustainable funding:** In addition to existing resources committed to the support of VL, new funding mechanisms would be needed to increase resources. These could include: the European and Developing Countries Clinical Trials Partnership (EDCTP 2), Innovative Medicines Initiative (IMI), contributions from emerging-economy countries and regions affected by the disease (Brazil, India, Middle East and North Africa) and prizes.
- **Exploring innovative incentives mechanisms:** The Initiative would explore innovative mechanisms such as a milestone prize for xenodiagnoses and quantitative PCR.

- **Equitable access**: To ensure affordable access, the Initiative would emulate collaboration with industrial partners similar to that between DND*i* and Sanofi for fexinidazole, a new drug being tested against the disease. Such agreements would make available, as public goods, any new therapeutic and diagnostic tools developed, as well as making them available at affordable prices.
- **Coordination through a collaborative approach**: The VL Global R&D & Access Initiative would be set-up in partnership with the existing VL consortia and research platforms from the different relevant regions.

The goal of the project is to address some of the critical R&D gaps in order to provide supporting tools to meet the WHO elimination goals for VL, which focus on the Indian sub-continent, by working on asymptomatic cases and PKDL patients, as well as to address the urgent treatment needs for East Africa and Latin America (new treatment options).
The overall project, which addresses the identified gaps of VL R&D requires **different innovative incentive mechanisms to fill R&D gaps,** to increase knowledge, decrease the risk of failure, raise the resources needed, capitalize on existing resources, and develop affordable drugs applying **the principle of de-linkage**.

The VL Initiative would consider the following innovative incentive mechanisms according to the R&D gaps targeted and the related treatment limitation:

Objectives	Topic	Incentives mechanisms	Partners (*pending until discussion and aggreement from suggested partners*)	Region
Objectives 1: effective, safe and field-adapted 1st line treatments for East Africa and Latin America (and 2nd line for the Indian sub-continent),	Activity 1 : Identifying new compounds from lead optimisation to pre-clinical phase (class of Oxaborole, Dundee/GSK, class of Nitromidazole) Activity 2:Moving a NCE from pre-clinical phase to POC (VL 2098)	Open knowledge, Drug Accelerator and Open source Grant with access clause	OSDD/ CDRI, Drug Accelerator partners, IMI	Global
	Activity 3: Development during clinical trials (Fexinidazole and Combinaison)	Capacity building, Collaborative coordination, Innovative Regulatory pathways	LEAP, EDCTP, Fiocruz, ICMR,	East Africa, Latin America, India
Objectives 2: understanding of the role of asymptomatic and PKDL patients in the transmission of the disease	Xenodiagnosis and quantitative PCR	Capacity building, Collaborative coordination, data sharing, Milestones Prizes	University Utrecht, Institute of Endemic Diseases, University of Caracas, Ferrer Group, Salpêtrière Hospital, Stiefel GSK, SGS	Soudan, Bangladesh, India
Objectives 3: safe, effective and field-adapted 1st line treatment for PKDL patients	Research on skin penetration of existing drugs – clinical development	Open knowledge, Drug Accelerator and Open source	LEAP, EDCTP, ICCDRB, PATH, IMI	Sudan, Bangladesh, possibly later India
Objectives 4: tools to monitor the development of resistance to existing treatments	Build up database and tools	Open source , data sharing	WARRN, MoHs , ITM, EDCTP (www.leishrisk.net)	Global

Governance

One of the main objectives of the VL Global Initiative would be to demonstrate that R&D projects can be optimized by strengthening coordination with **multidisciplinary partners** and through innovative mechanisms to finance and coordinate R&D. To this end, the Initiative would be composed of a **steering committee,** selected among the representatives of the scientific community, key governments, main R&D partners, relevant regional WHO offices (SEARO, PAHO, EURO, AFRO), DND*i*, and existing VL initiatives (Leishmaniasis East African Platform (LEAP); Consortium for VL Treatment in India and Bangladesh; Consortium on HIV/VL in East Africa; Consortium on PKDL) and would be supported by a **secretariat** hosted by an existing institution.

The Initiative, based on a strong coordination with relevant partnerships and through the steering committee elected from multidisciplinary partners, would catalyse the existing and future expertise and networks in the VL R&D area, in order to accelerate the delivery of tools to treat VL patients and to prevent VL transmission.