ADDENDUM- CEWG Demonstration Projects

The Visceral Leishmaniasis Global R&D and Access Initiative

*"Authors must send an **addendum** to their project which describes, where relevant, how the project:*

1. *Intends to delink the price of the final product from the cost of the R&D.*
2. *Utilizes collaborative approaches, including open knowledge innovation approaches.*
3. *Utilizes licensing approaches that secure access to your research outputs and final products.*
4. *Proposes and fosters financing mechanisms including innovative, sustainable and pooled funding.*
5. *Fosters effective and efficient coordination mechanisms amongst existing organizations/initiatives.*
6. *Strengthens capacity for research, development and production, including through technology transfer, in developing countries. "*

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How the project :	ADDENDUM- The Visceral Leishmaniasis Global R&D & Access Initiative (1583 words)
1. Intends to de-link the price of the final product from the cost of the R&D	To address identified VL R&D gaps (cf. proposal Questions 4 and 5), the VL Global Initiative (hereafter 'Initiative') requires innovative incentive mechanisms that de-link R&D costs from product price. **De-linkage** particularly applies to activities of moving a new chemical entity from product pre-clinical to clinical development (**Objective 1, Activity 2**); completing clinical development of an existing candidate up to registration (**Objective 1, Activity 3**); and developing a new treatment for PKDL (**Objective 3**). De-linkage is ensured through: 1. DNDi's **intellectual property (IP) policy adopted in 2004, based on two criteria**: ensuring that drugs are affordable and accessible in an equitable manner to patients who need them; and developing drugs as public goods whenever possible. This is the basis of contract negotiations with pharmaceutical partners to guarantee patient access to end products, in line with the Target Product Profile, which defines the ideal characteristics of the end product. Research and operations are not financed through IP rent revenues. 2. **Contractual provisions with pharmaceutical partners**. In practice, DNDi aims at securing licensing terms which ensure research and its outputs are considered public goods that advance public health. After ten years of experience, DNDi developed 6 new treatments and established 'Gold standard' licensing terms: - Perpetual royalty-free, non-exclusive, sub-licensable licenses - Worldwide research and manufacturing rights; - Commitment to make the final product available at manufacturing cost, plus minimal margin, in all endemic countries, regardless of

	income level; - Non-exclusivity, enabling technology transfer and local production to multiply sources of production and decrease cost of product. As an example of de-linkage, ASAQ-FDC for malaria, developed by DNDi and Sanofi (2007), is available at-cost plus a small margin (under USD 1 for adults; under USD 0.5 for children). 3. **PDPs as push mechanisms**: The last decade, with new public and private donor commitments, has seen new push mechanisms, including PDPs, to finance R&D and pull mechanisms to attract new stakeholders. PDPs, with a model such as DNDi's, by seeking diverse funding from private and public donors (cash donations, in-kind contributions, R&D grants), inherently de-link R&D expenditures from product price, financing R&D by sources other than IP rent revenues. For the Initiative, DNDi has already secured EUR 9 million of the EUR 36 million needed. To develop a diagnostic tool based on quantitative PCR (qPCR) (**Objective 2**) **a milestone or small end-stage prize** is a suitable incentive for partners to better evaluate VL transmission via asymptomatic carriers and PKDL patients. Because R&D incentives are weakened by insufficient market potential, they fail to stimulate innovation. A **milestone or small end-stage prize** would stimulate investments to rapidly adapt the existing qPCRs to specific transmission risk-assessment needs for the Initiative. The qPCR technique could help correlate parasite load with transmission risk in asymptomatic and PKDL patients. It detects and quantifies parasite DNA. Similar methodologies exist but show varying levels of sensitivity and specificity in clinical VL, CL, MCL and PKDL. Additional investments are needed to develop more accurate qPCRs adapted to the regional VL variations, sensitive enough to detect very low parasite DNA in asymptomatic, antibody-positive carriers. **The VL prize** would notably reward a group already invested in qPCR and stimulate developing countries' research orientations and researchers, thus strengthening capacities. A small prize, up to EUR 500 thousands would attract small organizations, and shift some costs of failure to the prize-funder rather than researchers. As highlighted by the CEWG report, the success of the prize will depend on the suitability of its design, including targeted cost and technical requirements (e.g. sensitivity) for the intended purpose. The Initiative steering committee and scientific advisory committee will define the design and rules for the prize following key principles of de-linkage (i.e. availability and affordable access) and compliance with the initiative's IP and licensing rules (including open source publication of findings).
2. Utilizes collaborative approach: including open knowledge innovation approaches	Neglected diseases, where traditional market mechanisms do not attract investments and with limited funding resources, require open models for sharing knowledge and research data, particularly for upstream research, to identify promising new technologies/compounds. The **Drug Accelerator Consortium** (hereafter 'Accelerator') proposed, based on current DNDi negotiations with several pharmaceutical companies, will be launched in 2014. It transcends existing approaches of bilateral agreements, and will pool resources, compounds, and expertise across companies,

	expediting identification and selection of candidates for promising new chemical entities from lead optimization to pre-clinical research (**Objective 1, Activity 1**). The Accelerator would collectively adhere to the licensing practices described above, and reduce costs and time of the discovery phase of R&D. Outcomes would be placed into the public domain (e.g. through the **EU Open PHACTS Discovery Platform)** to catalyse further research. Specifically, the Accelerator's activity would comprise searching and screening multiple libraries simultaneously and pooling capabilities of companies to identify more rapidly expanded hit series to quickly establish Structure-Activity Relationships that the Initiative could take through lead optimization and the full spectrum of R&D to implementation. It would provide access to state-of-the-art compound profiling assays and expertise with other leaders in NTD lead optimization (e.g. Drug Discovery Unit of Dundee University) to increase the capacity to identify a large number of top quality preclinical candidates and avoid duplication. The **Innovative Medicines Initiative (IMI),** a public-private partnership between the European Union and the European Pharmaceutical Industries and Associations with a EUR 2 billion budget, within the Horizon 2020 (EU Framework Program) would be an adequate mechanism to promote collaboration among pharmaceutical companies, academic groups, SMEs, and a PDP. Additional funding could be sought through this mechanism (see below). The Initiative will implement **a Data Sharing Platform** to identify determinants of treatment efficacy and effectiveness (**Objective 4**). Working with **WWARN**, it will develop, under the principles described above, an open clinical and biological database (including pharmacology, *in vitro* and molecular parameters) to resolve scientific questions emanating from single studies. This requires technical expertise and a legal-ethical framework to pool anonymized patient data for research. Such expertise has been extensively developed by WWARN and malaria partners.
3. Utilizes licensing approaches that secure access to research outputs, and access to final products	The Initiative will secure innovative licensing terms (see Question 1) to make research outputs global public goods. Timely access to newly-generated knowledge and data is crucial to neglected diseases with high mortality rates (e.g. VL). The Initiative will provide open access to knowledge generated, including that of the Accelerator. Data from the Initiative will be presented and published in open access journals and publicly accessible databases (e.g. ChEMBL; WIPO Re:Search). The Initiative will apply **an equitable access policy** to all new therapeutic and diagnostic tools, based on agreed-upon principles that ensure affordable pricing, sustainable production, and de-linkage (see Objective 1 Activity 2). To ensure sustainable access, the Initiative will regularly review and propose **enabling regulatory, financial, and procurement policies by engaging endemic-country regulators in to accelerate the registration.**
4. Proposes and fosters financing mechanisms including innovative, sustainable and pooled funding	Leveraging the EUR 9 million already secured by DNDi for the Initiative, other appropriate pooled mechanisms will be approached: - **European & Developing Countries Clinical Trials Partnership (EDCTP-2),** which expanded its scope to clinical trials in Africa for all Neglected Infectious Diseases (global budget: EUR 248 million, 2014-2015) (for clinical-trial activities).

	- **Innovative Medicines Initiative (IMI)** co-funded by the European Commission and the pharmaceutical industry (in-kind contributions; to support the Accelerator). - **Global Health Initiative Technology Fund,** initiated in 2013, co-financed by the Japanese government, the Japanese pharmaceutical industry and the Bill and Melinda Gates Foundation (global budget: USD 100 million, 5 years) for infectious disease R&D. - **Member States'** dedicated funding (including emerging economies that are endemic for VL, e.g. Brazil, India) for demonstration projects, managed as pooled funding for example via TDR. New innovative funding sources (e.g. UNITAID; FTT), which require Member State decisions, protect long-term product development from shifting individual donor circumstances and priorities. The Initiative aims to constructively feed, by example, ongoing Member State discussions on such mechanisms.
5. Fosters effective and efficient coordination mechanisms amongst existing organizations/initiatives	The Initiative aims to demonstrate that R&D projects can be effective while **strengthening coordination** among **multidisciplinary partners** and through innovative R&D financing and coordination mechanisms, notably as VL affects EURO, SEARO, EMRO, AFRO, and PAHO. Seeking rapid health impact and a sustainable public health solution necessitates an integrated model for North-South and South-South collaboration. Constant strong involvement of endemic countries to define priorities and facilitate implementation of new tools, and innovative alliances with pharmaceutical and biotechnology companies and academia, are vital. DNDi, with no laboratories or manufacturing facilities, functions thanks to engagement of public and private partners (academia; public research institutions, particularly in endemic countries; pharmaceutical and biotechnology companies; NGOs; PDPs; and governments) by leveraging their assets, capacities, and expertise. The Initiative will **partner with the LEAP clinical platform in Africa, EDCTP, IMI, CSIR and OSDD,** in addition to **DNDi's pharmaceutical and academic partners.** A **steering committee elected among multidisciplinary partners**, would embody these sectors.
6. Strengthens capacity for research, development and production, technology transfer in developing countries	- **Technology transfer:** Development of a new diagnostic technology for diagnosis of asymptomatics and PKDL patients by xenodiagnoses (Objective 2): Two steps: training courses and set-up of colony and infectivity experiments in Bangladesh, Sudan, India (2-year duration). - **Capacity Strengthening** via the Prize for qPCR to evaluate the role of transmission in asymptomatics and PKDL. A pre-requisite for receiving the qPCR diagnosis Prize would be **capacity-building**. - Clinical development of an existing drug candidate up to registration (Fexinidazole/VL2098) (Objective 1, Activity 3) with potential support of **EDCTP and endemic countries, will enhance clinical trial capacity** (including GCP, GLP, ethics, case management, regulatory capacity) **in Asia, Africa, and Latin America,** through DNDi's platforms and other research networks. Fexinidazole for VL is now in clinical trial, driven by LEAP. With wide-range disease strains, the same GCP-standard clinical trials in different regions will differentiate geographical immune responses.

Objectives	Activities	Incentive mechanisms	Partners (*pending until discussion and agreement from suggested partners*)	Region
Objective 1: Development of safe, effective, 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 optimization to pre-clinical phase (class of Oxaborole, class of Nitromidazole)**	**Open knowledge and open source, through Drug Accelerator Consortium**	**Drug Accelerator Consortium partners (pharmaceutical companies), OSDD/CDRI, Dundee/GSK consortium, IMI/EU**	**Global**
	Activity 2:Moving an NCE from pre-clinical phase to POC (VL2098)	**De-linkage principle**	**All**	**Global**
	Activity 3: Complete clinical development of existing candidates up to registration (Fexinidazole and combination)	**De-linkage principle, capacity-building, Collaborative coordination, Innovative Regulatory pathways**	**LEAP platform, EDCTP, ICMR, Fiocruz, pharmaceutical partners**	**East Africa, Latin America, Indian sub-continent**
Objective 2: Understanding of the role of asymptomatic and PKDL patients in the transmission of the disease	**Xenodiagnosis**	**Capacity-building; transfer of technology; collaborative coordination; data sharing**	**University Utrecht, Institute of Endemic Diseases, University of Caracas, Ferrer Group, Salpêtrière Hospital, Stiefel GSK, SGS**	**Sudan, Bangladesh, India**
	Quantitative PCR	**De-linkage principle; milestone and/or small end prize; capacity-building**	**All**	**Global**
Objective 3: Development of safe, effective and field-adapted 1st-line treatment for PKDL patients	**Research on skin penetration of existing drugs – clinical development**	**De-linkage principle; capacity-building; collaborative coordination**	**LEAP, EDCTP, ICCDRB, PATH, IMI**	**Sudan, Bangladesh, possibly later India**
Objective 4: Tools to monitor the development of resistance to existing treatments	**Build up a data sharing platform**	**Open source; data sharing**	**WWARN, MoHs, ITM-Antwerp, EDCTP/EU**	**Global**