

# Making drugs accessible to poor populations: a funding model

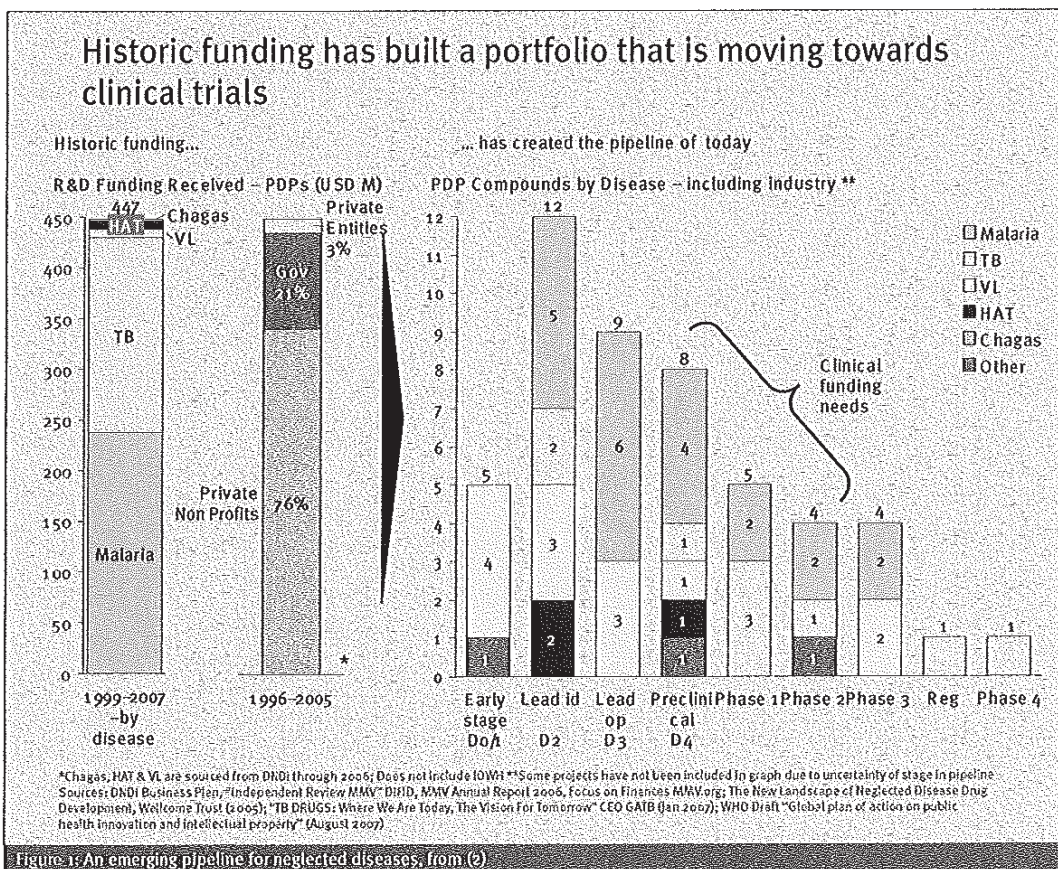


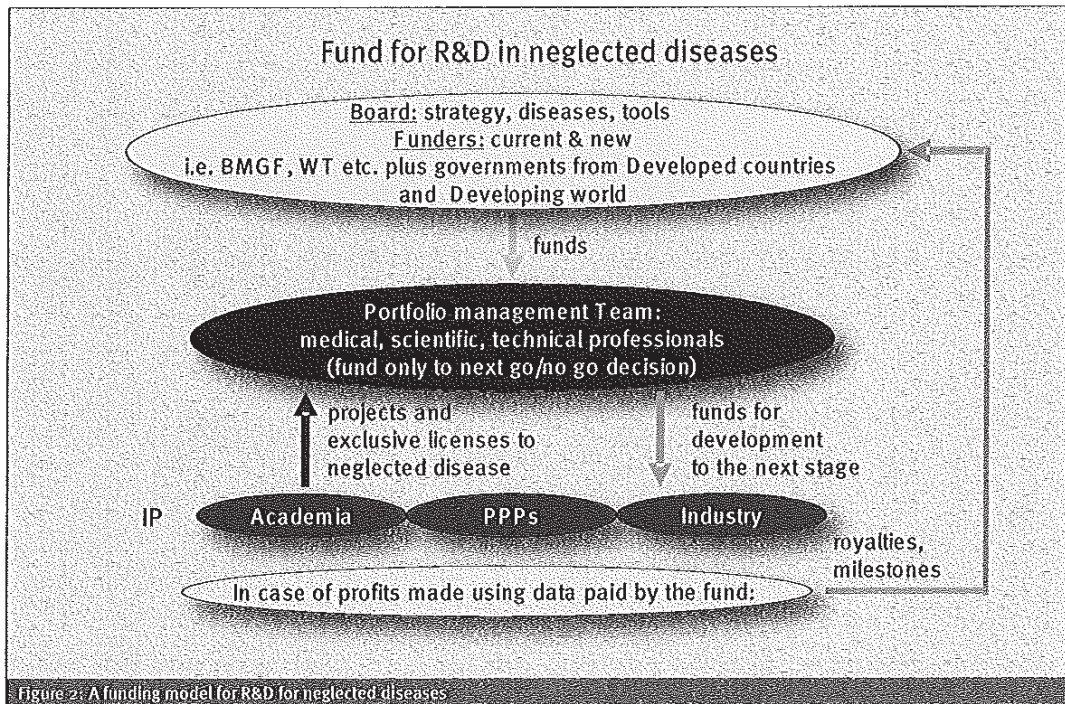
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According to a recent publication by Mary Moran et al<sup>1</sup>, public-private partnerships (PPPs) or product development partnerships (PDPs) involving non-governmental organizations (NGOs), academia and the pharmaceutical/biotech industry have generated a growing early pipeline of new drug therapies for neglected diseases such as malaria, tuberculosis, Dengue and parasitic diseases such as Leishmaniasis, human African trypanosomiasis and Chagas disease. This activity resulted in about 63 projects in

2005<sup>1</sup>, several of which are in early clinical testing. A more recent survey is shown in Figure 1.

Despite the high attrition rate it is expected that several of these projects will approach full development towards registration with costs of several hundred million US dollars per project. A study by Dalberg, commissioned by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and Novartis<sup>2</sup> estimates that US\$ 6–10 billion will be needed for that purpose in the next 10 years.





In comparison, in the same study the estimated cost of building this early pipeline was around US\$ 0.5 billion, allocated by a variety of private and public donors to PDPs. There is no indication that the current donors could generate sufficient funds for full development of the neglected diseases pipeline. There is a danger that a very unfortunate situation will arise where innovative compounds for neglected diseases in the pipeline that show a promising proof of concept in early human studies will stall in further development for lack of funding.

The model proposed (see Figure 2) describes a possible way to address this situation that attempts to take into account the needs of all stakeholders. It has been discussed with several pharmaceutical companies and representatives of NGOs such as Médecins Sans Frontières, Oxfam and the World Health Organization, who have all indicated that they had no fundamental objections and encouraged us to further develop it. The model is complementary to others such as Advanced Marketing Commitments and Prizes and the differences will be discussed.

**A model to fund R&D for neglected diseases (Fund for R&D in Neglected Diseases, FRIND).** The model (Figure 3) is designed to apply only to disease areas with large medical need but where no commercial returns can be expected and where normal market mechanisms therefore do not apply and where pharmaceutical and biotech companies can only invest very limited R&D funds. Examples are the 10 diseases on the TDR list<sup>3</sup>.

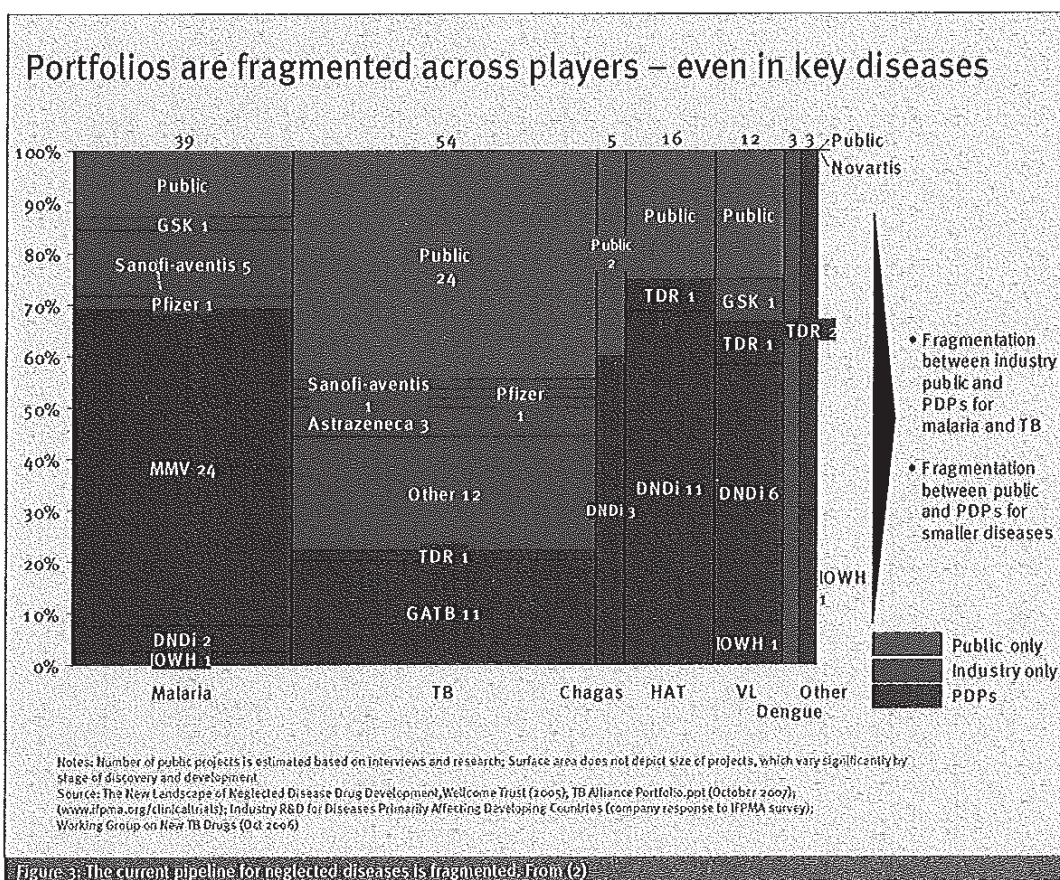
**Funding and governance.** The fund can be financed by the current donors to PDPs but in view of the magnitude envisaged governments of both developed and developing

nations will have to contribute. Representatives of the donors would constitute the Board of the fund in which the disease scope, product scope (e.g. medicines/vaccines only, or to include diagnostic methods etc.) and the strategy would be defined. The Board would not be involved directly in the portfolio management within the strategy. The mission of the fund must include the obligation to make available the therapies it funds to poor patients in the developing world for free or at an affordable price, or at least at no profit (if a profit can be made, then the normal market mechanisms will be applicable). FRIND would only finance the R&D component and would need partners/other donors for manufacturing and distribution.

**Potential applicants.** Any entity, academic, biotech/pharmaceutical company or PDP with a therapeutic/diagnostic project fulfilling a medical need for a neglected disease within the scope of FRIND can apply to the fund.

**Portfolio management team/scientific advisory board.** The members of the portfolio management team should have the same profile and skills found in large pharmaceutical companies' portfolio decision teams, i.e. scientific-, medical, technical-R&D, regulatory-, economics- experts familiar both with the therapeutic area and the environment in which the new drugs should be applied (field experts).

**Prioritization and allocation principles.** The portfolio decisions should be made exclusively on scientific, medical, technical and economic criteria excluding political factors as much as possible. To reduce potential waste of resources it is essential to apply a fund allocation rule where having estimated the totality of funds required for the entire development of the product, the portfolio team would then only allocate the funds



needed to reach the next decision point. At this stage the new results would be evaluated and a new decision to continue funding to the next stage or stop would be made.

**Overcoming the fragmentation of the neglected disease portfolio.** An analysis of the current neglected disease portfolio<sup>2</sup> indicates that even within single diseases there are several actors working in parallel and with limited communication between them (Figure 3).

It is expected that the fund under discussion would become the major source of funds for R&D for neglected diseases and one consequence would be that the portfolio management team would eventually see most projects within a disease area which would allow them to compare them, invest in the best ones or combine them.

**Intellectual property protection.** Intellectual property protection is essential for fostering investments in research for new medicines worldwide and should not be an impediment to access to medicines in the developing world<sup>4</sup>. In the context of FRIND, intellectual property could be handled as follows:

The inventors of the new product to be funded by FRIND (academic institutions, biotech companies, PDPs or pharmaceutical companies) would usually patent their inventions and retain ownership. If any of the entities above apply to FRIND for funding of their project in R or D they in

return would allocate an exclusive licence to the fund for the particular neglected disease within the mission of FRIND. The inventors would retain the rights for all other applications. This is important because nature does not distinguish between diseases of the rich and poor. For instance, a compound developed for Dengue fever, a neglected disease of increasing impact, might very well show useful activity in hepatitis C, an indication with commercial blockbuster potential, because both the Dengue virus and the hepatitis C virus (HCV) are genetically close because both belong to the genus *Flaviridae*. The inventor might very well want to develop the commercial application (HCV) using their own funds to later sell it with profit where a commercial market exists. If, however, the entity marketing such a therapy uses data that has been elaborated in a FRIND funded activity, royalties and/or milestones should be due to the fund to reimburse their expenses for the data generation.

### Discussion

There are several alternative models in discussion to stimulate R&D in neglected diseases, e.g. Advance Market Commitments (AMC)<sup>5</sup> or Prize mechanisms as proposed by James Love<sup>6</sup>. The current FRIND proposal overcomes a major drawback of the two models discussed above. Any entity that wants to access either AMC or Prize money needs to invest at

risk in the full development of its product for neglected disease and as about 7 out of 10 projects in clinical phase one fail before registration all that investment would be lost. This is a major disincentive not only for pharmaceutical companies but is outright unaffordable for many PDPs, academic institutions or small biotech firms. In addition since many advances in the treatment of disease are incremental, the concept of a "prize" for the first successful product is inappropriate and might be a disincentive to parallel activities. In contrast the current FRIND model would fund the individual R&D phases upfront and would bear the risk. An additional benefit is that through FRIND a portfolio management approach across different players might be established that allows more optimal allocation of (scarce) donor resources to the most promising R&D projects.

The model proposed here and AMCs or Prizes are not mutually exclusive but rather complementary to increase the probability of the creation of urgently needed new therapies for neglected diseases. The brief description of the model in this paper is intended to stimulate discussion and to evaluate its acceptance from the main stakeholders and potential donors. It has already received constructive contributions

from NGOs such as MSF, representatives from WHO, Oxfam and other pharmaceutical companies and is currently being presented to national governments. If sufficient support for this concept can be generated a more detailed model will be elaborated in a second phase. □

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#### References and abbreviations

- <sup>1</sup> Moran M. A breakthrough in R&D for neglected diseases: New ways to get the drugs we need. *PLoS Medicine* 2005; 2:828-831.
- <sup>2</sup> Feasibility study for a fund for R&D for neglected diseases. Dalberg Global Development Advisors. Commissioned by IFPMA and Novartis International AG, 2008.
- <sup>3</sup> <http://www.who.int/dp/diseases/default.htm>

- <sup>4</sup> Herrling P. Patent sense. *Nature*, 2007; 449:174-175 (2007).
- <sup>5</sup> <http://www.vaccineamc.org/mechanism.html>
- <sup>6</sup> Love J. The big idea: prizes to stimulate R&D for new medicines. Knowledge Ecology International, Tim Hubbard, Wellcome Trust Sanger Institute. Revised March 2007.

#### Abbreviations

AMC:	advanced market commitments	HAT:	human African trypanosomiasis
BMGF:	Bill & Melinda Gates Foundation	HCV:	hepatitis virus C
DO:	drug discovery phase 0, target finding	IFPMA:	International Federation of Pharmaceutical Manufacturers & Associations
D1:	drug discovery phase 1, high throughput assay formulating	IOWH:	Institute for One World Health
D2:	drug discovery phase 2, high throughput screening, hit finding	MMV:	Medicines for Malaria Venture
D3:	drug discovery phase 3, lead optimization, medicinal chemistry for small molecules	NGO:	nongovernmental organization
D4:	drug discovery phase 4, late preclinical phase	R&D:	research and development
DNDi:	Drugs for Neglected Diseases Initiative	TB:	tuberculosis
FRIND:	Funding Model for R&D in Neglected Diseases	TDR:	WHO special programme for research and training in tropical diseases
GATB:	Global Alliance for Tb Drug Development, Tb Alliance	VL:	Visceral Leishmaniasis
GSK:	GlaxoSmithKline	WT:	Wellcome Trust

## Financing R&D for neglected diseases

There has recently been a welcome increase in R&D activity to provide much-needed new drugs for neglected diseases of the developing world. This activity has resulted in an early stage pipeline of potential medicines that will require significant new funding if they are to progress to registration — a need that might be addressed by a novel type of funding body.

Providing new medicines for neglected diseases of the developing world is a key global health issue. For some diseases, such as malaria, existing medicines are encountering increasing resistance, whereas for others, such as the kinetoplast parasitic diseases, the existing drugs have unacceptable side effects, or no drugs at all are available, as is the case for dengue fever.

Responding to this need, there has been a welcome boost to R&D activity in this field in the past few years, catalysed by public–private partnerships (PPPs) between academic institutions, pharmaceutical companies, charities and governments, as well as by increased funding. These activities, which have consumed about US\$500 million so far, have resulted in ~60 projects for a range of neglected diseases, most of which are at an early stage<sup>1,2</sup>.

However, a critical concern for these projects is becoming increasingly apparent. An estimate taking into account historical attrition rates indicates that it will take a further investment of at least ~\$1 billion per year in the next 10 years to generate the data required for successful compounds in this portfolio to be registered<sup>3</sup> [OK?]. Currently, no source of funding of this magnitude exists that would invest in R&D for medicines for diseases for which no commercial returns are to be expected.

With these challenges in mind, it has recently been proposed that a new fund for R&D for neglected disease should be established with governments of developed and developing countries, charities and other entities as donors<sup>3</sup>. This fund — the fund for R&D in neglected diseases (FRIND) — would allocate resources using a modification of the process applied by large pharmaceutical companies, without the aspects of high commercial returns, but within the existing patent system. It would be overseen by a board designated by the donors, and its task would be purely strategic: it would focus on ensuring accessibility to poor patients, defining fundable diseases and nominating a portfolio management team.

This team, which is crucial to maximizing output from the resources available, must include the following expertises: first, basic scientists knowledgeable in the diseases of interest, pharmacologists, molecular biologists, medicinal chemists and so on; second, development experts versed in technical, chemical and safety issues; third, medical

doctors with experience in epidemiology, clinical research and in the countries where the diseases are endemic; and fourth, economists and public health experts. The team would then evaluate projects originating from academic institutions, PPPs or pharmaceutical companies at any stage during the R&D process against appropriate target product profiles, as well as competing projects.

If the project is deemed viable, the portfolio team would allocate sufficient resources, but only up to the next decision point. The project originators would then present the new data obtained with the FRIND money, and on the basis of this data the team would decide whether to continue to the next stage or not. With regard to patenting, the project originators would usually patent the molecules they propose to FRIND, but in return for the money received, they would allocate an exclusive license for the neglected disease indication to FRIND. The originators, however, would keep the ownership for composition of matter and any other indications for which a commercial return might be expected for their own development.

This model has several advantages. First, by funding projects only from one decision point to the next, waste of resources is minimized. Second, as it is expected that several entities working in the same neglected disease would at one point apply to the fund, FRIND experts could directly compare projects in the same indication and promote only the most viable ones, which is more difficult to achieve with the current fragmented state of the pipeline. Third, this proposal works within the existing global intellectual property model of the developed world, but ensures that patents are not used to prevent affordable access to patients in developing countries. Finally, in contrast to other models such as prizes, advanced marketing commitments or vouchers — in which all the failure risk remains with the originator, representing a major disincentive to invest — the FRIND proposal shifts this risk to the fund. This could encourage many entities to bring forward their solutions for neglected diseases that otherwise would not.

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