Ideas in Progress

Paper Number 58

Orphan and rare diseases in context

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The series constitute ‘ideas in progress,’ after the notion described by I.J. Good in ‘The Scientist Speculates.’ Good also describes ideas about ideas as ‘partly baked ideas’ believing that “… it is often better to be stimulating and wrong than boring and right.” While the papers do not take this tenet as an excuse for licence at the expense of rigour, they are exploratory and the ideas may change as a theme is developed over time.

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Introduction

Orphan and rare diseases, including neglected tropical diseases (NTDs), have been of long running concern, sometimes turning to acrimony in which science and industry have been castigated for placing financial gain ahead of the relief of human suffering. However, the complexity of these situations cannot be reduced to simple declarations, a feature that in the last few years has been revealed as pharmaceutical companies (large and small) and many other prestigious organizations have come together, in permissible ways, to ameliorate what is a dynamic situation. It is an area that we (the authors) tip-toe into hesitantly. One of us became interested, at arms length, in controlled delivery of drugs in the 1970s while our combined interest has grown through diagnostics which, when combined with controlled delivery, may have an important part to play in disease characterization, methods of treatment and the specification of treatments themselves. For us this will be a matter of learning, the language in particular, to enable an appreciation of the field. In that sense our aims are modest and relate particularly to NTDs. We rate our current level of expertise in the field as at the lower end of ‘familiar’ regarding the main themes involved (the ‘self assessment of expertise’ is explained in an Appendix 2).

A Background to Orphan and rare diseases

Orphan and rare diseases are real enough but behaviourally tend to be in the 'eye of the beholder', making their prioritization and definitions a matter of preference and political geography rather than scientific exactness. Individual diseases have been identified but the situations in which they are embedded are complex. These situations arise through combinations of social need, the individual sciences of the diseases themselves, the economics of the invention and widespread dissemination of the treatments, all of which are influenced by local and global politics and their interaction with belief and value systems that dominate polities. The geographies and their related ecologies associated with each of the diseases in question, particularly NTDs, create multiple complex situations related to their control in as much as that is possible. But what are orphan and rare diseases?

Orphan diseases are often associated with poverty whereas rare diseases are not inevitably so. Both groups present difficult choices for the creation and implementation of treatment(s) for each one. Because orphan diseases are very much in the 'eye of the beholder' some definitions have a distinct financial orientation while others are quite the reverse: for that reason we shall not spend time on the academic penchant for all embracing definitions, but instead will focus on the geography and ecology of orphan diseases.

For example, an orphan disease may be one that has not been "adopted" by the pharmaceutical industry because the financial incentives are regarded as too low for the private sector to make and market new medications to treat or prevent it. For example:

1. According to US criteria, an orphan disease is one that affects fewer than 200,000 people. (There are more than 5,000 such rare disorders)

2. A common disease that has been ignored (such as tuberculosis, cholera, typhoid, and malaria) because it is far more prevalent in developing countries than in the developed world.

To quote, “The US Orphan Drug Act of 1983 offered tax incentives on clinical trials and 7 years of marketing exclusivity for drugs developed for conditions that occur only rarely in the US. Since then, more than 200 orphan drugs have been approved by the US Food and Drug Administration (FDA) and are on the market. Similar legislation has been adopted in Japan and Australia. In the year 2000, the European Union adopted "orphan medicinal products" legislation modeled on the US law, but including tropical diseases and other disorders prevalent only in the developing world. The EU law provides for 10 years of marketing exclusivity, but no tax incentives (because there is no centralized EU taxation system)”. In contrast the European Medicines Agency (EMA) uses the following guidelines; again we quote:

“A medicinal product is designated as an orphan medicinal product if:

1. It is intended for the diagnosis, prevention or treatment of a life-threatening or chronically de-
ilitating condition affecting no more than five in 10,000 persons in the European Union at the time of submission of the designation application (prevalence criterion), or;

2. It is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and without incentives it is unlikely that expected sales of the medicinal product would cover the investment in its development, and;

3. No satisfactory method of diagnosis, prevention or treatment of the condition concerned is authorised, or, if such method exists, the medicinal product will be of significant benefit to those affected by the condition”

In both examples there is an emphasis on the number of people affected by the disease in question, but this is a questionable base-line especially for NTDs. However, these two examples give an indication of different ways of thinking about the incidence of these diseases which is what we turn to next.

‘Diseases of poverty’, mostly but not inevitably NTDs, inflict ‘avoidable’, where avoidable is dominated by lack of resources, misery on the poorest people in the world wherever they live. By contrast, rare diseases and conditions (for an example see Stix, G. 2011, The Tale of Two Patients Tackling a Mystery Disease, Scientific American, Nov. 14 regarding the work of William A. Gahl, head of the National Institute of Health’s Undiagnosed Diseases Program), whilst they occur anywhere, are not in the sense used above ‘avoidable’ but are intractable currently because science (of all kinds) does not know how to, or cannot at present, provide safe or successful paths of treatment. These diseases and conditions might reasonably be characterized as ‘known unknowns’ in taxonomy of ignorance (see Appendix 4). For completeness, there are new diseases which, up to their point of discovery, have never been foreseen and might be classified as ‘unknown unknowns’.

Some classifications indicate that there are ‘5,000 rare diseases’ within their stipulated criteria: various sources are more selective. The sixth Millennium Development Goals lists HIV, Malaria and Tuberculosis in particular along with 13 other infectious conditions nominated as NTDs. All are major disabling conditions and are amongst the most common infections amongst 2.7 billion people who live on less than $2 per day. NTDs include, by prevalence: Ascariasis, Trichuriasis, Hookworm infection, Schistosomiasis, Lymphatic filariasis, Trachoma, Onchocerciasis, Leishmaniasis, Chagas’ disease, Leprosy, Human African trypanosomiasis, Dracunculiasis and Buruli Ulcer (Hotez, Molyneux et al. 2007).

Other databases, notably from WIPO Re:Search, list similar sets of diseases including: Buruli ulcer; Chagas disease (American trypanosomiasis); Cysticercosis; dengue/dengue haemorrhagic fever; Dracubculiasis (guinea-worm disease); Echinococcosis; Endemic treponematoses (Yaws); Footborne rematode infections (clonorchiasis, Fascioliasi, Opisthorchiasis, Paragonimiasis); Human African trypanosomiasis; Leishmaniasis; Leprosy; Lymphatic filiarisis; Malaria; Onchonciasis; Podoniosis; Rabies; Schistosomiasis; Snakebite; Soil transmitted helminthiasis; Trachoma and Tuberculosis.

The second of these databases has arisen from the recent formation of WIPO Re:Search which is to quote "composed of intellectual property assets, including compounds, enabling technologies, know-how, and other information that Providers have chosen to make available in WIPO Re:Search. All the information is publicly available and can be accessed without registration". The database arises from "a collaboration between WIPO, BIO Ventures For Global Health (BVGH), pharmaceutical giants, nonprofits, and universities, is offering up a searchable database of intellectual property from drug companies that can aid in the treatment of diseases …. (NTDs) ….. The initiative will also facilitate partnerships between participating organizations to speed up research and development". The declared purpose of WIPO Re:Search is to enable new approaches to "One of the world’s great global health challenges … to overcome the impact of neglected tropical diseases,……. These diseases negatively affect the lives of more than one billion people, many of whom live in the world’s least developed countries. WIPO Re:Search aims to stimulate more research and development for new and better treatment options for those suffering from these conditions".

WIPO Re:Search’s partner is BIO Ventures for Global Health (BVGH) and is advised on technical matters by the WHO: its database provides access to "intellectual property for pharmaceutical compounds, technologies, and – most importantly – know-how and data available for research and development for neglected tropical diseases, tuberculosis, and malaria. By providing a searchable, public database of available intellectual property
assets and resources, WIPO Re:Search facilitates new partnerships to support organizations that conduct research on treatments for neglected tropical diseases, ultimately improving the lives of those most in need”.

Unsurprisingly, access, browsing and/or use of the WIPO Re:Search Database is governed by specified Terms of use. Acceptance of these Terms of use by an investigator, acknowledges that the Intellectual Property detailed in the database is offered for possible license, individually negotiated, under terms to be agreed with the indicated owner of that Intellectual Property. No license is implied, under listed Intellectual Property, from access to the database.

Each of the NTDs listed is described briefly in an Appendix 1. Ebola (a haemorrhagic fever) is not included but is described along with the others.

It is hoped that the formation of WIPO Re: Search may accelerate attention to NTDs. However, prior to the formation of WIPO Re:Search, the Millennium Development Goals called for a dramatic reduction in poverty and a marked improvement in the health of the poor. Simultaneously, the World Health Organisation (WHO) advocated an increase in basic and applied research aimed at specific diseases (WHO 2001). These institutional commitments were followed by public initiatives and public/private collaborations, aimed at improving the treatment of diseases in Developing Countries that cause and are consequences of poverty. The Millennium Development Goals and the WHO highlighted the need for more basic and applied research aimed at HIV/AIDS, Tuberculosis, Malaria and other infectious diseases in Developing Countries (WHO 2001). Since 2001, other international organizations, publicly funded initiatives and public-private partnerships have embarked on technological development to combat these diseases (Hotez, Molyneux et al. 2007). However, there are hurdles to be overcome as there is a:

1. “Drug gap”: less than ten percent of the global health research spending is dedicated to diseases that primarily afflict the poorest ninety percent of the world’s population (Oxfam International 2008)

2. “Knowledge gap”: research for diseases of poverty is under-funded

3. “Policy gap”: public health initiatives have not been able to tackle the problem of access to medicines in the developing world (Trouiller, Olliaro et al. 2002). The Doha Declaration reaffirmed some flexibility in the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), enabling the possibility of compulsory patent licenses for medicines in cases of national emergency, but access to pharmaceuticals in the developing world is still challenging.

The formation of WIPO Re:Search is aimed at these three hurdles to create an effective research, production and delivery model to which poverty-related diseases could adhere.

The drug creation process

In the developed countries the model for the creation of a new medicine follows the basic principles set out below:

- Basic and applied research identify new drug targets
- Development of potential drug candidates
- Clinical trials that prove safety and efficacy
- Regulatory approval mechanisms that guarantee market access
- Compliance with reimbursement policies that assure market demand

In developed country practice these steps, and those discussed below, are well known to be lengthy and costly (Di Masi, Hansen et al. 2003). For example, for one drug to be approved by the US Food and Drug Administration (FDA), a firm typically screens 5,000-10,000 compounds. From these an average of 250 survive pre-clinical testing; only five reach clinical testing and only one gains FDA approval. The average time required to take a product from the start of clinical testing to regulatory approval is 7 years (Kaitin and DiMasi 2011). The associated, basic research on health conditions is often funded by the public sector, while clinical testing and drug development are financed by the private sector. Globally, of the total investment in R&D, governments contribute about 44% of the total development cost; the phar-
The pharmaceutical industry contributes about 48% and nonprofit, and university funds make up the remaining 8% (Levine 4, 5)

**The global drug gap**

The above drug development and approval process has led to the neglect of certain classes of diseases as indicated earlier. Less than ten percent of the spending on health research globally is dedicated to poverty related diseases ($6 billion of a total of $100 billion annually) that afflict the poorest ninety percent of the world’s population (Oxfam International, 2008). The 10/90 ratio is the consequence of a number of market and government (and governance) failures as well as huge income differences (Reich 2000). All of these failures lead to important deficiencies in acquiring the knowledge needed to foster technological developments in vector control; early diagnosis; disease surveillance; preventive chemotherapy; drug treatments and vaccine development. Commercial investments in R&D are heavily influenced by the size of the market (Levine date). From the 1,223 new drugs brought to market between 1975 and 1997, only 13 (less than 1%) were targeted at NTDs; of these, only 4 were the direct result of R&D investment from the pharmaceutical industry (Levine 12)

**The role of philanthropy and public-private partnerships**

In the Developing Countries philanthropic organisations have been a great source of funding for research into tropical diseases. However, their funding cannot cover the costs of the whole process of bringing a new drug to market along with the development of manufacturing capacity (Levine, Kremer et al. 2005). Private companies, are strengthening their R&D effort into tropical diseases using open innovation approaches (Kar 2010) but so far this reorientation of R&D effort has not yet been sufficient for the magnitude of the problem, which may be ameliorated through the recent creation of WIPO Re:Search.

In the 1990s, the Product Development Public-Private Partnership concept (PDP) emerged as a way to channel philanthropic funding. The WHO defines these public-private partnerships as “a wide variety of ventures involving a diversity of arrangements, varying from small, single-product collaborations with industry to large entities hosted in United Nations agencies or private not-for-profit organizations” (WHO 2011). PDPs now occupy an important place in the global R&D landscape for poverty related diseases (Moran, Guzman et al. 2010). The field of neglected tropical diseases is also starting to create PDPs aimed at accelerating the development of drugs, diagnostics and vaccines targeted at these diseases. The Rockefeller foundation and the Bill & Melinda Gates foundation have been instrumental in the development of the PDP concept and its implementation (Levine, Kremer et al. 2005). In 2007, the Bill & Melinda Gates Foundation provided 49.3% of PDP funding. The United States Agency for International Development (USAID), the UK Department for International Development (DFID), the Dutch Ministry of Foreign Affairs and Irish Aid completed the picture of the top five funders, each providing over US$20 million to PDP organisations in that year. Together, these five funders accounted for 77.1% of the global funding of PDPs. The “big three” diseases (HIV/AIDS, TB and malaria) received the largest amounts of funding in 2007 (Moran, Guzman et al. 2010).

Other organisations that have also been crucial in fostering research and product development in diseases of poverty include:

- **The Global Fund to Fight AIDS, Tuberculosis and Malaria** (created in 2002) is a partnership between governments, civil society, the private sector and affected communities: it is a new approach to international health financing dedicated to attracting and disbursing additional resources to prevent and treat HIV/AIDS, tuberculosis and malaria. The Fund has become the dominant financier of programs to fight AIDS, tuberculosis and malaria, with approved funding of US$ 21.7 billion for more than 600 programs in 150 countries (The Global Fund 2011).

- **Drugs for Neglected Diseases Initiative (DNDi)**, established in 2003 by five public sector institutions – the Oswaldo Cruz Foundation from Brazil, the Indian Council for Medical Research, the Kenya Medical Research Institute, the Ministry of Health of Malaysia; France’s Pasteur Institute; Médecins sans Frontières (MSF); and the UNDP/World Bank/WHO’s Special Programme for Research and Training in Tropical Diseases (TDR). DNDi is a, patients’ needs-driven, collaborative non-profit drug research and development (R&D) organization that is developing new
treatments for malaria, visceral leishmaniasis (VL), sleeping sickness (human African trypanosomiasis, HAT), and Chagas’ disease (DN-Di 2011)

**Task Force for Global Health** is a non-profit, public health organization created to serve as a Secretariat for a consortium of UNICEF, WHO, The Rockefeller Foundation, The United Nations Development Programme, and the World Bank. These organizations sought support for a collaborative effort to improve child wellness and survival strategies. Some of these collaborations are: the Centre for Global Health Collaboration, Children Without Worms, Global Polio Eradication, International Trachoma Initiative, Lymphatic Filariasis Support Centre, Mectizan Donation Program, Public Health Informatics Institute, Training Programs in Epidemiology and Public Health Interventions Network.

The recent (2010) creation of WIPO Re:Search must now be added to the above list.

Some of the main product development programmes in which pharmaceutical companies have been involved are:

- **African Programme for Onchocerciasis Control (APOC)**
- **Onchocerciasis Elimination Program of the Americas (OEPA)**
- **Global Programme to Eliminate Lymphatic Filariasis (elephantiasis)**
- **International Trachoma Initiative**
- **Children Without Worms (CWW) Initiative**
- **WHO Programme to Eliminate Sleeping Sickness**
- **Schistosomiasis Control Initiative**
- **Leprosy Drug Donation**
- **African Malaria Partnership (AMP) Programme**
- **Chagas Disease Treatment Tuberculosis (TB) Treatment**

More details of these programmes are given in Appendix 3. An alternative to the establishment of PDPs is the **generation of markets to encourage drug development**. The creation of incentives for commercial investments in R&D, where donors commit to pay for a new medicine only if, and when, it is developed, are fostering the creation of markets for medicines targeted to the poor (Levine, Kremer et al. 2005). These commitments are characterised by:

1. Technical specification in terms of outputs
2. Minimum price guarantee, available up to a fixed number of treatments
3. Guaranteed co-payments of products meeting the specifications, paid by sponsors and permitting eligible countries to buy medicines at affordable prices
4. Inclusion of performance incentives both at the supply side and at the demand side (Eicher, Levine et al. 2009)

These proposals may have an impact on access to medicines in the context of the Developing Countries. Again the modus operandi intended by WIPO Re:Search and its success will become obvious over time.

**Bridging the knowledge gap**

Multinational companies (MNCs) based in Africa are focused mainly on the development of generic drugs or on drug reformulations. Some developing countries are more advanced scientifically than others and are referred as **Innovative Developing Countries (IDCs)**. These countries are in favour of the development of pharmaceuticals for poverty related diseases. Health research in Developing Countries is close to the needs of the poor; it is conducted in the public sector and driven by public health goals. Some manufacturers in Developing Countries follow a business model in based on high-volumes at low-margins, which leads to low-cost products, often with the goal of distributing them to Developing Country markets (drug exports from India and Brazil are 67% and 74% respectively go to other developing countries. Conversely, 63% of Uganda’s drug imports and 54% of
Tanzania’s currently come from other developing countries (Moran 2005).

In 2008, the **African Network for Drugs and Diagnostics Innovation (ANDI)** emerged with the intention of strengthening research and development capacity in Africa and to foster African-led innovation through the discovery and development of affordable tools (e.g. natural product drug formulations) for diseases prevalent in the continent. The rationale for ANDI is the creation of incentives for African entrepreneurs to address diseases that are unattractive at a global level (Tom Mboya-Okeyo 2009).

The **South-South Initiative for infectious diseases of poverty (SSI)**, aims to promote research collaboration between investigators in Disease Endemic Countries (DECs) across Africa, Latin America and Asia, with an emphasis on infectious poverty related diseases while the **Global Network for Neglected Tropical Diseases** is an advocacy initiative led by the Sabin Institute and is dedicated to raising the awareness, political will, and funding necessary to control and eliminate the most common neglected tropical diseases. International research collaborations such as the **Malaria Genomic Epidemiology Network**, **MalariaGEN** are aimed at bringing together data and expertise from multiple investigators to achieve specific scientific objectives. Finally, in response to the need to identify drug targets, a number of parasite genome projects are in progress (El-Sayed, Myler et al. 2005; Morel, Acharya et al. 2005).

Much of the above ought to be augmented by the WIPO Re:search initiative referred to earlier.

**The Policy Gap**

In 1994 the World Trade Organisation (WTO) created the **TRIPS (Trade-Related aspects of Intellectual Property Rights) agreement**, which obligated WTO-members to recognise pharmaceutical product patents under the threat of trade sanctions (REF).

Numerous factors can affect the decisions that determine the extent to which firms pursue and succeed in the development of drugs in various therapeutic areas. These include (Kaitin and DiMasi 2011):

- Potential development and approval times
- Development-related costs
- Estimates of the likelihood of approvals
- Potential market sizes

Until recently the prevailing business model used by the large pharmaceutical companies, to justify their investments (Moran 2005), has been of the ‘blockbuster’ drug which seeks peak sales of around $500 million per year. These ‘blockbuster’ drugs make use of the advances in the science and technology of drug efficacy that stem from and can support applied research in ways that enable commercialisation where profitable markets exist (Smith, Correa et al. 2009). The blockbuster business model does not work for orphan and rare diseases, particularly the NTDs that prevail in the developing countries. Consequently, under the blockbuster business model the global pharmaceutical market have tended to become highly polarised, with North America, Europe and Japan accounting for 75% of sales (REF cited in Smith 2009). While Developed Countries produce and export high-value patented pharmaceuticals, developing countries import these products and often ‘reverse engineer’ them to produce equivalent low-priced generics. Malaria, for instance, is one of the world’s biggest killers and, an effective vaccine and/or treatment would have an enormous social value. However, few alternatives have been licensed over the past 20 years, or are in development (Klausner and Alonso 2004), although the eagerly awaited results from the world’s first large-scale trial of a malaria vaccine confirm a vaccine, called RTS,S, offers partial protection, cutting episodes of malaria in babies and toddlers in half. Although not nearly as impressive as most vaccines currently in use the vaccine could help curtail malaria’s massive death toll significantly (RTS,S was developed by GlaxoSmithKline (GSK) Biologicals in Rixensart, Belgium, in partnership with the PATH Malaria Vaccine Initiative (MVI). It contains an engineered protein that combines a protein fragment from the malaria parasite, *Plasmodium falciparum*, and a protein from the Hepatitis B virus that helps trigger a strong immune response (Ref)). The first field trial, in 2000 children in Mozambique, showed that RTS,S lowered the risk of developing malaria symptoms by 30%, with no severe side effects. Phase II trials in Mozambique, Kenya, and Tanzania have consistently shown that the vaccine can **cut the number of malaria episodes by between 35% and 53%**. The phase III trial enrolled more than 15,000 babies aged 6 to 12 weeks and toddlers between 5 and 17 months across sub-Saharan Africa. The part-
nership presented the first data at a meeting at the Bill & Melinda Gates Foundation, which supported the trial; the results were also published online by *The New England Journal of Medicine* (First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children, The RTS,S Clinical Trials Partnership, N Engl J Med 2011; 365:1863-1875)

Other reports from MVI Path indicate the level of attention now focused on achieving an anti-malaria vaccine for which a revised business model may be needed to achieve widespread use (ref http://www.malariavaccine.org/latest-news.php).

**Implications of the TRIPS agreement**

In 2001, the implications of the TRIPS agreement for the Developing Countries led to the Doha Declaration (WTO ministerial declaration on the TRIPS agreement and public health). Under article 8, WTO-members could “adopt measures necessary to protect public health and nutrition”. TRIPS allowed licenses to be granted compulsorily to enable third parties to produce or sell a drug, against payment of a royalty to the patent owner, when drugs are not available in sufficient supply, or are not affordable. The principle of the Doha Declaration was ratified at the 61st World Health Assembly (WHA). Resolution WHA 61:21, secured an enhanced and sustainable basis for needs-driven essential health R&D relevant to diseases that affect developing countries disproportionately (Smith, Correa et al. 2009). However, issuing compulsory licenses has often been difficult because:

(i) TRIPS allows companies to sue governments at the WTO

(ii) Data-exclusivity provisions of the bilateral agreements restrict the use of bio-equivalency for generic drugs because there are ethical problems in testing a generic equivalent drug versus placebo (Stiglitz 2009).

WHO defines essential drugs as “those that satisfy the health care needs of the majority of the population and should be available at all times in adequate amounts and in appropriate dosage forms” (WHO 2010). However, developing countries often do not have access to essential medicines. *Anti-retrovirals* reach the market fastest in the US and Europe (twice as fast as other drugs) (Kaitin and DiMasi 2011) but despite the rate at which the FDA grants approval for HIV drugs, the 33 million people living with HIV (22 million in sub-Saharan Africa), ten million people are in urgent need of treatment (Medicines Patent Pool 2011). Because of inequalities in market access, WHO has identified patent pools as one way to improve access to essential medicines in the Developing Countries. In the *patent pool model*, multiple patents are ‘pooled’ and licensed out by one entity in order to cut down on transaction costs for all the parties involved: this is particularly important in HIV treatments which comprise a number of drug combinations and allows more affordable drugs, as well as speeding up the process of improving access to urgently-needed, newer and improved HIV medicines (UNITAID 2011).

The EU has launched (2010), through an FP 7 project, the Access to Pharmaceuticals (ATP) consortium to promote *Socially Responsible Licensing* (SRL): what this means is not entirely clear but the intention is to promote means to improve and ensure the availability of essential medicines in the Developing Countries. The ATP consortium partners are the International Vaccine Institute (IVI), Oswaldo Cruz Foundation (FIOCRUZ), South African Medical Research Council (SAMRC), St George’s, University of London and the University of Neuchâtel (UNINE). The ATP consortium regards access to pharmaceuticals, particularly for NTDs as an 'essential human right'. As with most EU funded projects ATP is essentially an ongoing multidisciplinary academic study, whereas WIPO Re:Search has other practical purposes, though these have yet to be realized in practice. WIPO Re:Search's partners, as set out earlier, include the Developed World's major pharmaceutical companies, major Universities and BVGH. While ATP see Intellectual Property and product development as two issues the WIPO Re:Search consortium brings real development work to the business of addressing NTD issues. Briefly ATP’s aims are to foster and here we quote:

1. *Early Stage Research and Development*: To develop practical models and best practices for academic policy in IP management and licensing, to minimise barriers for the delivery of pharmaceutical innovation to populations in need. We will work with a variety of stakeholders including Technology Transfer Officers to develop practical and implementable best practices for identification and commercialisation of pharmaceutical innovations that
are of importance to health problems of disadvantaged populations

2. **Product Development**: To review existing and evolving practices in Public-Private or Product Development Partnerships (PDP) and to analyse their outcomes in terms of pharmaceutical development. We will identify and develop best practices for successful pharmaceutical partnerships in the commercialisation of therapies for needs that are inadequately met by traditional industry

3. **Commercial Access to Pharmaceuticals**: To identify problems and develop solutions aimed at simplifying processes and removing barriers to trans-national cooperation. This is targeted towards the successful adoption and practical implementation of new legislative instruments to increase access to generic versions of new essential medicines by countries without manufacturing capacity

The distinctly academic tone to ATPs intentions has to be contrasted with the intentions behind the formation of WIPO Re:Search which may have upstaged the purposes of the EU project considerably. There is some commonality between the partners in the ATP and WIPO Re:Search.

Some of the policies adopted by the US and Europe in the field of rare diseases and orphan drugs (those that are not feasible economically under the blockbuster model and are of less interest to the pharmaceutical industry because the market too small), may be extrapolated to the Developing Countries. However, in 1983 the US Federal Government enacted new legislation that would allow the development of drugs for rare diseases. The *Orphan Drug Act (ODA)* provided a number of development incentives (Guarino 2009) including a:

(i) Tax credit of 50% of the cost of conducting human clinical trials

(ii) Seven-year market exclusivity to sponsors or companies of approved orphan products

(iii) Federal research grants for clinical testing of new therapies

Through the Office for Orphan Products Development (OOPD), the FDA encourages clinical development of products for the treatment of rare diseases by:

(i) Providing assistance for sponsors of drugs for rare diseases

(ii) Encouraging sponsors to carry out open protocols

(iii) Allowing patients to be added to ongoing studies to facilitate the availability of promising drugs to extremely ill patients as early as possible in the drug development programme

Companies developing orphan products are also exempt from the user drug application fees charged by the FDA and can also be eligible for a fast track review of their application. Once again the intervention created by WIPO Re:Search has to be worked out in the practical world.

Summary

Some first steps in learning about orphan and rare diseases and who is involved in developing ways to ameliorate the complex situation they pose, is all that we have attempted here: an Appendix 3 summarises the current situation, which is changing rapidly as significant resources are becoming available from various organizations, some philanthropic, others corporate and yet more NGOs including academia globally.

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Appendix 1 Brief descriptions of some orphan diseases

Bruli ulcer (Mycobacterium ulcerans infection)

Buruli ulcer, a disease caused by infection with Mycobacterium ulcerans, is one of the most neglected but treatable tropical diseases. The causative organism is from the family of bacteria which causes tuberculosis and leprosy but Buruli ulcer has received less attention than these diseases. Infection leads to extensive destruction of skin and soft tissue with the formation of large ulcers usually on the legs or arms. Patients who are not treated early often suffer long-term functional disability such as restriction of joint movement as well as the obvious cosmetic problem. Early diagnosis and treatment are vital in preventing such disabilities. (WHO Fact sheet N°199 Revised March 2007)

Chagas disease (American trypanosomiasis)

Chagas disease is a potentially life-threatening illness caused by the protozoan parasite, Trypanosoma cruzi (T. cruzi). It is found mainly in Latin America, where it is mostly transmitted to humans by the faeces of triatomine bugs, known as 'kissing bugs', among other names, depending on the geographical area. An estimated 10 million people are infected with Trypanosoma cruzi worldwide. Chagas disease was once entirely confined to the Region of the Americas but it has now spread to other continents. Chagas disease is curable if treatment is initiated soon after infection. Up to 30% of chronically infected people develop cardiac alterations and up to 10% develop digestive, neurological or mixed alterations, for which specific treatment may become necessary. Vector control is the most useful method to prevent Chagas disease in Latin America. Blood screening is vital to prevent infection through transfusion and organ transplantation (WHO Fact sheet N°340 June 2010)

Cysticercosis

Cysticercosis is an infection by a parasite called Taenia solium (T. solium), a pork tapeworm, that creates cysts in different areas in the body. Cysticercosis is caused by swallowing eggs from T. solium, which are found in contaminated food. Autoinfection is when a person is already infected with adult T. solium, then swallows eggs following improper hand washing after a bowel movement. Risk factors include eating pork, fruits, and vegetables contaminated with T. solium as a result of unhealthy cooking preparation. The disease can also be spread by contact with infected people or fecal matter (NCBI)

Dengue/dengue haemorrhagic fever

Dengue is caused by any one of four related viruses transmitted by mosquitoes. There are not yet any vaccines to prevent infection with dengue virus (DENV) and the most effective protective measures are those that avoid mosquito bites. When infected, early recognition and prompt supportive treatment can substantially lower the risk of developing severe disease. Dengue has emerged as a worldwide problem only since the 1950s. Although dengue rarely occurs in the continental United States, it is endemic in Puerto Rico, and in many popular tourist destinations in Latin America and Southeast Asia; periodic outbreaks occur in Samoa and Guam (CDC)

Dracunculiasis (guinea-worm disease)

Dracunculiasis is infection with Dracunculus medinensis, a nematode worm. It is caused by drinking water containing water fleas (Cyclops species) that have ingested Dracunculus larvae. In the human body, the larvae are released and migrate through the intestinal wall into body tissues, where they develop into adult worms. The female worms move through the person’s subcutaneous tissue, causing intense pain, and eventually emerge through the skin, usually at the feet, producing oedema, a blister and eventually an ulcer, accompanied by fever, nausea, and vomiting. If they come into contact with water as they are emerging, the female worms discharge their larvae, setting in motion a new life cycle. There are no drugs available for the treatment of this disease. However, it can be prevented by protecting water sources and filtering potentially contaminated water (WHO)

Ebola haemorrhagic fever

Ebola haemorrhagic fever (EHF) is a viral haemorrhagic fever and one of the most virulent viral diseases known to humankind. The Ebola virus was first identified in the western equatorial province of Sudan and in a nearby region of Zaire (now Democratic Republic of the Congo) in 1976 after significant epidemics in Nzara, southern Sudan and Yambuku, northern Zaire. There are five distinct species of the Ebola virus: Bundibugyo, Côte d’Ivoire, Reston, Sudan and Zaire. Bundibugyo, Sudan and Zaire species have been associated with large outbreaks of Ebola haemorrhagic fever (EHF) in Africa causing death in 25-90% of all clinically ill cases, while Côte d’Ivoire and Res-
The Ebola virus is transmitted by direct contact with the blood, body fluids and tissues of infected persons. Transmission of the Ebola virus has also occurred by handling sick or dead infected wild animals (chimpanzees, gorillas, monkeys, forest antelope, fruit bats). The predominant treatment is general supportive therapy (WHO).

**Echinococcosis**

Echinococcosis is a parasitic disease caused by an infection from tiny tapeworms of the genus *Echinococcus*. Echinococcosis is classified as either Cystic echinococcosis or Alveolar echinococcosis.

**Cystic echinococcosis (CE)**, also known as hydatid disease, is caused by an infection with *Echinococcus granulosus*, an ~2-7 millimeter long tapeworm found most commonly in dogs (definitive host), in addition to sheep, cattle, goats, and pigs (intermediate hosts). Although most infections in humans are asymptomatic, CE causes harmful, slowly enlarging cysts in the liver, lungs, and other organs that often grow unnoticed and neglected for years.

**Alveolar echinococcosis (AE)** disease is caused by an infection with the larval stage of *Echinococcus multilocularis*, an ~1-4 millimeter long tapeworm found in foxes, coyotes, and dogs (definitive hosts). Although cases of AE in animals in endemic areas are relatively common, human cases are rare. AE poses a much greater threat to people than CE, causing parasitic tumors to form in the liver, lungs, brain, and other organs. If left untreated, AE can be fatal (CDC).

**Endemic treponematoses (Yaws)**

Yaws is a chronic infection that affects mainly the skin, bone and cartilage. The causative organism is a bacterium called *Treponema pertenue*, a subspecies of *Treponema pallidum* that causes venereal syphilis. However, yaws is a non-venereal infection. The disease occurs mainly in poor communities in warm, humid tropical areas of Africa, Asia and Latin America. Almost 75% of people affected are children under 15 years, although peak incidence occurs in children between the ages 6-10. Endemic treponematoses are a group of chronic bacterial infections caused by treponemes, which include yaws (also known as framboesia, pian), endemic syphilis (bejel) and pinta. All these infections often present as skin lesions and the most common of these is yaws (WHO).

Over 100 species of foodborne trematodes are known to cause infections – trematodiasis – in humans. Clonorchiasis, opisthorchiasis, fascioliasis and paragonimiasis are the infections that pose the most significant public health and economic burden. Clonorchiasis and opisthorchiasis are confined to Asia, while paragonimiasis can be found in Africa, Asia and Latin America. Fascioliasis is a global disease, affecting a significant number of countries throughout the world. At community level, transmission of these four infections is usually focal and it is not uncommon for a given disease to affect one particular village and not a neighbouring one. On a broader geographical scale, the distribution pattern of FBT infections is more diverse. For example, transmission of paragonimiasis is usually limited to a group of districts and the disease can still be described as focal. Clonorchiasis, opisthorchiasis and fascioliasis, on the other hand, tend to be more diffuse and to affect larger geographical areas (WHO).

**Hendra virus**

Hendra virus (HeV) is a rare, emerging zoonotic virus (a virus transmitted to humans from animals), that can cause respiratory and neurological disease and death in people. It can also cause severe disease and death in horses, resulting in considerable economic losses for horse breeders. Initially named Equine Morbillivirus, Hendra virus is a member of the genus *Henipavirus*, a new class of virus in the *Paramyxoviridae* family. It is closely related to Nipah virus. Although Hendra virus has caused only a few outbreaks, its potential for further spread and ability to cause disease and death in people have made it a public health concern. The concern has heightened in the most recent outbreaks, as the horses’ symptoms have shifted to become largely neurological instead of respiratory. This suggests the possibility of genetic diversity in the strain, and potentially a more infective virus (WHO Fact sheet N°329 July 2009).

**Key facts**

- Hendra virus can cause fatal respiratory and neurological diseases
- Hendra virus can be transmitted to people from horses
- Hendra virus can cause severe disease and death in horses
- There is no treatment or vaccine available for either people or horses
Fruit bats of the Pteropodidae family are the natural hosts of Hendra virus. 

**Human African trypanosomiasis**

Human African trypanosomiasis, also known as sleeping sickness, is a parasitic disease transmitted by the bite of the 'Glossina' insect, commonly known as the tsetse fly. The disease affects mostly poor populations living in remote rural areas of Africa. Untreated, it is usually fatal. Travelers also risk becoming infected if they venture through regions where the insect is common. Generally, the disease is not found in urban areas, although some cases have been reported in suburban areas of Kinshasa, capital of the Democratic Republic of Congo and Luanda, the capital city of Angola (WHO).

**Leishmaniasis**

Leishmaniasis is caused by parasitic protozoa of the genus *Leishmania*. Humans are infected via the bite of phlebotomine sandflies, which breed in forest areas, caves, or the burrows of small rodents. There are four main types of the disease:

- **In cutaneous forms**, skin ulcers usually form on exposed areas, such as the face, arms and legs. These usually heal within a few months, leaving scars.

- **Diffuse cutaneous leishmaniasis** produces disseminated and chronic skin lesions resembling those of lepromatous leprosy. It is difficult to treat.

- **In mucocutaneous forms**, the lesions can partially or totally destroy the mucous membranes of the nose, mouth and throat cavities and surrounding tissues.

- **Visceral leishmaniasis**, also known as kala azar, is characterized by high fever, substantial weight loss, swelling of the spleen and liver, and anaemia. If left untreated, the disease can have a fatality rate as high as 100% within two years (WHO).

**Leprosy**

Leprosy is caused by a slow-growing bacillus, *Mycobacterium leprae*. It is transmitted via droplets from the nose and mouth of untreated patients with severe disease, but is not highly infectious. If left untreated, the disease can cause nerve damage, leading to muscle weakness and atrophy, and permanent disabilities. Leprosy can be easily treated with a 6–12-month course of multidrug therapy. The treatment is highly effective, and has few side-effects and low relapse rates; there is no known drug resistance (WHO).

**Lymphatic filariasis**

Lymphatic filariasis, commonly known as elephantiasis, is a neglected tropical disease. Infection occurs when filarial parasites are transmitted to humans through mosquitoes. When a mosquito with infective stage larvae bites a person, the parasites are deposited on the person's skin from where they enter the body. The larvae then migrate to the lymphatic vessels where they develop into adult worms forming 'nests' in the human lymphatic system. Infection is usually acquired in childhood, but the painful and profoundly disfiguring visible manifestations of the disease occur later in life. Whereas acute episodes of the disease cause temporary disability, lymphatic filariasis leads to permanent disability.

- More than 1.3 billion people in 81 countries worldwide are threatened by lymphatic filariasis, commonly known as elephantiasis.

- Over 120 million people are currently infected, with about 40 million disfigured and incapacitated by the disease.

- Lymphatic filariasis can result in an altered lymphatic system and the abnormal enlargement of body parts, causing pain and severe disability.

- Acute episodes of local inflammation involving the skin, lymph nodes and lymphatic vessels often accompany chronic lymphoedema (WHO).

**Malaria**

Malaria is caused by a parasite called Plasmodium, which is transmitted via the bites of infected mosquitoes. In the human body, the parasites multiply in the liver, and then infect red blood cells. Symptoms of malaria include fever, headache, and vomiting, and usually appear between 10 and 15 days after the mosquito bite. If not treated, malaria can quickly become life-threatening by disrupting the blood supply to vital organs. In many parts of the world, the parasites have developed resistance to a number of malaria medicines. Key interventions to control malaria include: prompt and effective treatment with artemisinin-based combination therapies; use of insecticidal nets by people at risk; and indoor
residual spraying with insecticide to control the vector mosquitoes (WHO)

**Nipah virus**

Nipah virus (NiV) is an emerging zoonotic virus (a virus transmitted to humans from animals). In infected people, Nipah virus causes severe illness characterized by inflammation of the brain (encephalitis) or respiratory diseases. It can also cause severe disease in animals such as pigs, resulting in significant economic losses for farmers. Nipah virus is closely related to Hendra virus. Both are members of the genus Henipavirus, a new class of virus in the Paramyxoviridae family. Although Nipah virus has caused only a few outbreaks, it infects a wide range of animals and causes severe disease and death in people, making it a public health concern (Fact sheet N°262 Revised July 2009)

**Key Facts**

- Nipah virus causes severe illness characterized by inflammation of the brain (encephalitis) or respiratory diseases.
- Nipah virus can be transmitted to humans from animals, and can also be transmitted directly from human-to-human; in Bangladesh, half of reported cases between 2001 and 2008 were due to human-to-human transmission.
- Nipah virus can cause severe disease in domestic animals such as pigs.
- There is no treatment or vaccine available for either people or animals.
- Fruit bats of the Pteropodidae family are the natural host of Nipah virus.

**Onchocerciasis**

Onchocerciasis is a parasitic disease caused by the filarial worm *Onchocerca volvulus*. It is transmitted through the bites of infected blackflies of *Simulium* species, which carry immature larval forms of the parasite from human to human. In the human body, the larvae form nodules in the subcutaneous tissue, where they mature to adult worms. After mating, the female adult worm can release up to 1000 microfilariae a day. These move through the body, and when they die they cause a variety of conditions, including blindness, skin rashes, lesions, intense itching and skin depigmentation. In a number of countries, onchocerciasis has been controlled through spraying of blackfly breeding sites with insecticide. In addition, a drug is available that kills the microfilariae, alleviating symptoms and reducing transmission. An international control effort aims to bring annual treatment with this drug to all populations at risk by the year 2010. When that is achieved, onchocerciasis may cease to be a public health problem (WHO)

**Podoconiosis**

Podoconiosis is a type of tropical lymphoedema clinically distinguished from lymphatic filariasis (LF) through being ascending and commonly bilateral but asymmetric. Evidence suggests that podoconiosis is the result of a genetically determined abnormal inflammatory reaction to mineral particles in irritant red clay soils derived from volcanic deposits. Podoconiosis is found in highland areas of tropical Africa, Central America and north-west India

**Rabies**

Rabies is a preventable viral disease of mammals most often transmitted through the bite of a rabid animal. The vast majority of rabies cases reported to the Centers for Disease Control and Prevention (CDC) each year occur in wild animals like raccoons, skunks, bats, and foxes. The rabies virus infects the central nervous system, ultimately causing disease in the brain and death. The early symptoms of rabies in people are similar to that of many other illnesses, including fever, headache, and general weakness or discomfort. As the disease progresses, more specific symptoms appear and may include insomnia, anxiety, confusion, slight or partial paralysis, excitement, hallucinations, agitation, hypersalivation (increase in saliva), difficulty swallowing, and hydrophobia (fear of water). Death usually occurs within days of the onset of these symptoms (CDC)

**Schistosomiasis**

Schistosomiasis, or bilharzia, is a parasitic disease caused by trematode flatworms of the genus *Schistosoma*. Larval forms of the parasites, which are released by freshwater snails, penetrate the skin of people in the water. In the body, the larvae develop into adult schistosomes, which live in the blood vessels. The females release eggs, some of which are passed out of the body in the urine or faeces. Others are trapped in body tissues, causing an immune reaction. In urinary schistosomiasis, there is progressive damage to the bladder, ureters and kidneys. In intestinal schistosomiasis, there is progressive enlargement of the liver and spleen, intestinal damage, and
hypertension of the abdominal blood vessels. Control of schistosomiasis is based on drug treatment, snail control, improved sanitation and health education (WHO)

**Snakebite**

Envenoming resulting from snake bites is a particularly important public health problem in rural areas of tropical and subtropical countries situated in Africa, Asia, Oceania and Latin America. A recent study estimates that at least 421,000 envenomings and 20,000 deaths occur worldwide from snakebite each year, but warns that these figures may be as high as 1,841,000 envenomings and 94,000 deaths. The highest burden of snakebites is in South Asia, Southeast Asia, and sub-Saharan Africa. Snake bite is primarily a problem of the poorer rural populations in these regions and affects mainly those involved in subsistence farming activities. Poor access to health services in these settings and, in some instances, a scarcity of antivenom, often leads to poor outcomes and considerable morbidity and mortality. Many victims fail to reach hospital in time or seek medical care after a considerable delay because they first seek treatment from traditional healers. Some even die before reaching hospital. Hospital statistics on snakebites therefore underestimate the true burden. In addition to mortality, some snakebite victims survive with permanent physical sequelae due to local tissue necrosis and, sometimes psychological sequelae. Because most victims are young, the economic impact of snakebite can be considerable (WHO)

**Soil transmitted helminthiasis**

Soil-transmitted helminths common known as intestinal worms, are the most common infections worldwide affecting the most deprived communities. The causal agent of soil-transmitted helminthiasis is any of the following worms: *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms. Recent estimates suggest that *A. lumbricoides* infects over 1 billion people, *T. trichiura* 795 million, and hookworms (*Ancylostoma duodenale* and *Necator americanus*) 740 million. The greatest numbers of soil-transmitted helminth infections occur in sub-Saharan Africa, the Americas, China and east Asia. Infection is caused by ingestion of eggs from contaminated soil (*A. lumbricoides* and *T. trichiura*) or by active penetration of the skin by larvae in the soil (hookworms). Soil-transmitted helminths produce a wide range of symptoms including intestinal manifestations (diarrhoea, abdominal pain), general malaise and weakness, that may affect working and learning capacities and impair physical growth. Hookworms cause chronic intestinal blood loss that results in anaemia

**Trachoma**

Trachoma is the result of infection of the eye with *Chlamydia trachomatis*. Infection spreads from person to person, and is frequently passed from child to child and from child to mother, especially where there are shortages of water, numerous flies, and crowded living conditions. Infection often begins during infancy or childhood and can become chronic. If left untreated, the infection eventually causes the eyelid to turn inwards, which in turn causes the eyelashes to rub on the eyeball, resulting in intense pain and scarring of the front of the eye. This ultimately leads to irreversible blindness, typically between 30 and 40 years of age (WHO)

**Tuberculosis**

Tuberculosis (TB) is a contagious disease. Like the common cold, it spreads through the air. Only people who are sick with TB in their lungs are infectious. When infectious people cough, sneeze, talk or spit, they propel TB germs, known as bacilli, into the air. A person needs only to inhale a small number of these to be infected. Left untreated, each person with active TB disease will infect on average between 10 and 15 people every year. But people infected with TB bacilli will not necessarily become sick with the disease. The immune system "walls off" the TB bacilli which, protected by a thick waxy coat, can lie dormant for years. When someone’s immune system is weakened, the chances of becoming sick are greater.

- Overall, one-third of the world’s population is currently infected with the TB bacillus.
- 5-10% of people who are infected with TB bacilli (but who are not infected with HIV) become sick or infectious at some time during their life. People with HIV and TB infection are much more likely to develop TB (WHO)
Appendix 2 Principles of self-assessment of expertise

Expertise is both sought after and denigrated simultaneously: it is a deeply personal matter much influenced by the interactions (often called the 'personal chemistry') between the people involved in understanding (or trying to) complex, dynamic situations. In 1982 Lipinski & Loveridge described five vignettes of levels of expertise that enabled 'Self-assessment' of one's own expertise in a particular topic or field. In itself, this was a further development of a process used in a survey of expert opinion relating to 'Climate Change to the year 2000', sponsored by the National Defense University and reported on in February 1978. The criteria set out here were used in a further modified form in the United Kingdom's Technology Foresight Programme that ran from 1994-95.

Self-evaluation criteria: guidance to self-ranking of expertise

1 You are unfamiliar with the subject matter if the mention of it encounters a veritable blank in your memory or if you have heard of the subject, yet are unable to say anything meaningful about it

2 You are casually acquainted with the subject matter if you at least know what the issue is about, have read something on the subject, and/or have heard a debate about it on either a major television or radio network or an educational channel

3 You are familiar with the subject matter if you know most of the arguments advanced for and against some of the controversial issues surrounding this subject, have read a substantial amount about it, and have formed some opinion about it. However, if someone tried to pin you down you would soon have to admit that your knowledge is inadequate to do so

4 You are quite familiar with the subject matter either if you were an expert some time ago but feel somewhat rusty now because other assignments have intervened (even though, because of the previous interest, you have kept reasonably abreast of current developments in the field); if you are in the process of becoming an expert but still have some way to go; or if your concern is with integrating detailed developments in the area, thus trading breadth of understanding for depth of specialization.

5 You should consider yourself an expert if you belong to that small community of people who currently study, work on, and dedicate themselves to, the subject matter. Typically, you know who else works in this area; you know the literature of your country and probably the foreign literature; you attend conferences and seminars on the subject, sometimes reading a paper and sometimes chairing the sessions; you are most likely to have written up and/or published the results of your work. Other experts in this field may disagree with your views but invariably respect your judgment; comments such as 'this is an excellent person on this subject' would be typical when inquiring about you.

Decimalization of Self-assessments (e.g. 3.1 or 4.8) is permitted.
# Appendix 3 Corporations and how they are involved in orphan disease

<table>
<thead>
<tr>
<th>Corporation</th>
<th>Programme</th>
<th>Objectives</th>
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<tbody>
<tr>
<td>MSD (Merck Sharp &amp; Dohme)</td>
<td>African Programme for Onchocerciasis Control (APOC)</td>
<td>MSD committed in 1995 to donating Mectizan® (ivermectin, MSD), a drug for controlling onchocerciasis or “river blindness” in Africa. APOC is extended until 2015 and intends to treat over 90 million people annually in 19 countries</td>
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<tr>
<td>MSD - GSK</td>
<td>Global Programme to Eliminate Lymphatic Filariasis (Elephantiasis)</td>
<td>MSD expanded the mandate of the APOC program to include lymphatic filariasis elimination through the co-administration of mectizan and albendazole, donated by GSK, in African countries and Yemen. GSK has also reaffirmed its commitment to supply all the albendazole needed to eliminate lymphatic filariasis worldwide by 2020. GSK currently donates 600 million tablets of albendazole each year to WHO.</td>
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<tr>
<td>Pfizer</td>
<td>International Trachoma Initiative (ITI)</td>
<td>Since 1998, Pfizer collaborates with ITI to distribute Zithromax® (azithromycin), with the aim of eliminating Trachoma by 2020. Up to date, Pfizer has donated 225 million Zithromax® in 19 countries and is expecting to expand up to 42 countries.</td>
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<tr>
<td>Johnson &amp; Johnson’s</td>
<td>Children Without Worms (CWW) Initiative</td>
<td>CWW initiative donates mebendazole to prevent intestinal worms. This initiative enables treating 25 million children a year. Besides, drug donation, J&amp;J also contributes with national and international initiatives to control intestinal worms.</td>
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<tr>
<td>Sanofi-Aventis</td>
<td>WHO Programme to Eliminate Sleeping Sickness</td>
<td>Sanofi-Aventis and the non-profit Drugs for Neglected Diseases initiative (DNDi) announced in 2009 the sign of an agreement for the development, manufacturing and distribution of fexinidazole, a promising new drug for the treatment of human African trypanosomiasis, also known as sleeping sickness, a fatal disease that threatens 60 million people in Sub-Saharan Africa.</td>
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<tr>
<td>Novartis</td>
<td>Leprosy Drug Donation</td>
<td>Since 2000, Novartis provides multi-drug therapy free of charge to all leprosy patients. To date, Novartis has donated more than 48 million blister packs to cure over 5 million leprosy patients worldwide.</td>
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<tr>
<td>GSK</td>
<td>Africa Malaria Partnership Programme</td>
<td>GSK contributes to the African Malaria Partnership Programme (AMP) through research into medicines and vaccines and a preferential pricing system for anti-malarials in Sub-Saharan Africa.</td>
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<tr>
<td>Bayer</td>
<td><strong>Chagas Disease Treatment</strong></td>
<td>Bayer committed to give WHO nifurtimox (a drug to fight against Chagas disease) for distribution across countries. It is estimated that this provision helps 30,000 patients over five years.</td>
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<tr>
<td>Bayer</td>
<td><strong>Tuberculosis treatment</strong></td>
<td>In 2005, Bayer in conjunction with TB Alliance, launched an historic clinical trial program to test whether Bayer’s moxifloxacin could be used to significantly shorten the time it takes to cure TB. If successful, this program could result in the first new drug approved for tuberculosis in over forty years.</td>
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Appendix 4 Metaphors for forms of Ignorance

For centuries humanity has focused its attention on knowledge: how much we think we know is celebrated and prized by all manner of people and organizations from business through to academia. It is only when things do not accord to received ideas (or paradigms), and they frequently do, that we begin to query just how much we do know. Ignorance is an awkward concept but one that we broach here as it is particularly relevant to NTDs. Quoting from Wikipedia 'Ignorance (or witlessness) is a state of being uninformed (lack of knowledge).[1] The word ignorant is an adjective describing a person in the state of being unaware and is often used as an insult. Ignoramus is commonly used in the US, the UK, and Ireland as a name of someone who is willfully ignorant'.

Ignorance can be distinguished from stupidity, although both can lead to "unwise" acts.

Writer Thomas Pynchon described the scope and structure of one's ignorance as: '.. not just a blank space on a person's mental map. It has contours and coherence, and for all I know rules of operation as well. So as a corollary to [the advice of] writing about what we know, maybe we should add getting familiar with our ignorance, and the possibilities therein for writing a good story.'[2]

Whether it was ideas of this kind that led Donald Rumsfeld to enunciate a brief taxonomy of ignorance in a well known press conference in 2002, it is hard to tell, while Roberts & Armitage (2008) have developed ideas relating to 'The ignorance economy'. A further complication is the ever present 'selective' state of unawareness. All of these are embodied in Rumsfeld's taxonomy which characterizes ignorance in the following three ways: known unknowns, unknown knowns and unknown unknowns. These three sources of ignorance are perched rather precariously on top of what is known (or knowledge), which is often a good deal less certain than is recognized a matter reflected in Einstein's comment that 'You believe in a God who plays dice, and I in a complete new order'. However, Stewart maintains that 'What is important is not whether God plays dice - but how' (Stewart 1989) Charles Darwin observed, 'ignorance more frequently begets confidence than does knowledge'.

References
Einstein, A. In a letter to Max Born