
INDUSTRY PROPOSALS TO INCREASE RESEARCH & DEVELOPMENT FOR "NEGLECTED DISEASES"

BACKGROUND: NEGLECTED DISEASES

In accordance with resolution WHA56.27 of the World Health Assembly of May 2003, the WHO Commission on IP rights, Innovation and Public Health (the "Commission") is *"to collect data and proposals from the different actors involved and produce an analysis of intellectual property rights, innovation, and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries ..."*

During a meeting held at PAHO offices in Washington DC in October 2004, members of the Biomedical Industry Advisory Group ("BIAG") presented to the Commission the conclusions of a paper on the lessons learned so far in the fight against neglected diseases and some of the critical gaps remaining in the R&D process ("Research and Development for Neglected Diseases", 2004). This paper was in line with Commission's preliminary work of "collecting the data", as prescribed by the WHA resolution above. During that meeting, the Commissioners asked that the industry provide the CIPIH with its views on proposals relevant and useful to that industry, stimulating new research into these diseases. Industry has reviewed a number of mechanisms and the present paper reflects a consensus achieved by the IFPMA Council. We believe that the initiatives described below, if implemented, would significantly improve the environment for research and development ("R&D") for neglected diseases.

In the field of neglected diseases, the Commission is looking for solutions about how we can build a system that ensures the sustainability of a long-term research effort for diseases that (1) are insufficiently understood by basic science researchers; (2) often receive a low research priority by the public and private sectors as they have a relatively low occurrence in the burden of global disease; (3) become frequently drug resistant in poverty situations; and (4) affect very poor populations (located in poor countries with higher health-related priorities such as clean water, immunization, and better living standards). The problem is compounded by the fact that even existing, inexpensive, and safe therapies that could save millions do not yet get utilized (see articles #1 and 2 in this submission).

Fortunately, most diseases that affect low-income countries can be treated or prevented with existing agents, such as medicines from the WHO's Essential Drugs List. Unfortunately, one of the biggest remaining challenges is getting the interventions to the people who need them. Such a situation has led Dr Asamoah-Baah, WHO Assistant Director General to talk about "neglected populations"³ rather than just neglected diseases.

GOVERNMENTS ARE KEY TO SETTING PUBLIC HEALTH PRIORITIES

Furthermore, a series of targeted policies cannot be underestimated. Political leadership sets the public health agenda, which has a great impact in focusing efforts in a particular direction...or in redirecting such efforts in a different direction.

Millions of people in the world are unable to lead a healthy, productive life because of diseases such as lymphatic filariasis (elephantiasis), schistosomiasis, intestinal parasites, leprosy, sleeping sickness (African Trypanosomiasis) and others. Affected populations live in resource-poor communities, without political influence, and often in remote areas, conflict zones or urban slums where there is little or no access to health care.

In an international workshop organized by WHO and other partners in December 2003, the key issues surrounding neglected diseases were described as follows:

"Although medically diverse, neglected diseases share features that allow them to persist in conditions of poverty, where they cluster and frequently overlap. Unsafe water and poor sanitation sustain transmission cycles and favour the proliferation of vectors. Lack of access to health services, low levels of literacy, inadequate nutrition and poor personal hygiene all help to increase vulnerability to infection and work against prevention. Where curative interventions exist, they generally fail to reach populations early enough to prevent permanent impairments. Conditions of poverty also work to exclude affected populations from the social systems set up to safeguard health as a fundamental human right." (WHO Report "Intensified Control of Neglected Diseases" Dec. 2003)

Examples of successful interventions exist for several tropical diseases (onchocerciasis, leprosy, trachoma, etc.), where public health authorities, local communities and pharmaceutical companies have implemented effective disease control programs, which may lead to elimination of diseases previously regarded as neglected. (See Tables 1 and 2 attached)

However, safer and easier to administer medicines are needed for a limited number of "most neglected" diseases, such as Chagas Disease, leishmaniasis, and African Trypanosomiasis. Nevertheless, in addition to such a limited list of priority research areas, the on-going risk of resistance to existing drugs also requires policies aimed at supporting sustainable R&D for all tropical diseases. New medicines need to overcome the shortcomings of existing therapies, but also they should be inexpensive to avoid burdening overstretched healthcare budgets. Fortunately, the R&D process allows for a succession of incremental innovative steps for better and more cost effective products to emerge—if the signals are present to encourage the development of such new products. It is often difficult for companies to undertake extensive, risky and expensive R&D efforts for new medicines when currently available and effective medicines at low cost are available, but not utilized due to a variety of problems as outlined in articles #1 and 2 in this submission.

PUSH & PULL PROGRAMS TO INCREASE R&D FOR DISEASES OF DEVELOPING COUNTRIES

The literature on research incentives distinguishes between push and pull mechanisms. Push mechanisms promote research *inputs* through means such as research grants, tax credits for R&D expenditures, and government expenditure for basic research. Pull mechanisms promote research *outputs*, by increasing the rewards for developing and marketing new products, for example, by guaranteeing that a given product will be purchased, usually for a certain amount and volume per year.

The economics of the private sector are such that the return on R&D efforts reflects the opportunity costs involved in drug development, and also reflects a risk-reward business model. Any scheme designed only to reduce the costs of R&D may not by itself make a significant difference in strategic R&D decisions. For example how do we ensure that once a product is developed, it will be delivered (produced and distributed) to neglected populations on a sustained basis? A more meaningful incentive would need to address the demand side and target a larger scale. It may be that the incentives could vary according to the type of research undertaken as this can affect the costs and risks. For example:

- Development of a new formulation of a known product: Potentially useful for resource poor countries where climactic and infrastructure problems require special formulations; the risk and cost will be comparatively modest as it is likely that relevant information on the safety and efficacy of the product is known.
- Development of a new indication for a known product: the risk and cost will be higher as although relevant information about the safety profile is likely to be known, the efficacy and safety profile in the target population for the required dosage may not be known, which would increase the risk.
- Development of a new compound showing preclinical activity: cost and risk will be high as nothing will be known about the clinical safety and efficacy.
- Discovery and development of a new compound: cost and risk will be highest as molecular targets will need to be identified and validated, compounds screened against the targets, compounds discovered, the compound(s) formulated and scaled for clinical supplies, and preclinical safety determined, and this all prior to clinical development.

CHOOSING DIFFERENT MECHANISMS TO ENCOURAGE R&D INTO NEGLECTED DISEASES

Choosing among a number of different possible measures to encourage R&D into neglected diseases requires an assessment of a number of different factors, including: (1) Probability of success (feasibility, complexity, flexibility, use of a proven system, sustainability); (2) Attractiveness to innovative companies (lowering risk, reducing costs, guaranteeing access); (3) Size of the potential impact (encouraging new R&D; speeding up existing R&D; accelerating access to patients); and (4) Political acceptability (perceived equity; cost/benefit; transparency; potential private interest opposition). This paper cannot possibly assess these factors thoroughly. Rather, the rest of the paper discusses those actions that industry believes could help address gaps currently in the global system.

PRODUCT DEVELOPMENT PUBLIC PRIVATE PARTNERSHIPS (PPPS)

It is widely understood that neither the public nor the private sector alone can eliminate health research inequities. In recent years, public-private partnerships (PPPs) have been all the rage as a complementary way to develop research portfolios in areas of crucial needs for developing countries (such as HIV/AIDS, malaria, TB, neglected diseases, etc.). Product development PPPs are stand alone organizations governed by both public and private sector stakeholders. Their core objective is to attract public and private funding to finance applied research with private sector partners in neglected areas. Funding comes from both public and private sources, primarily from philanthropic foundations and some donor governmental agencies. Donors contribute to the functioning of the structure and for the purchase of outside services. Pharmaceutical companies make in-kind contributions through transfer of know-how and expertise, actively participate in the R&D activity, or play a key advisory role. Examples of product development PPPs include the Global Alliance for TB (GATB) and the Medicines for Malaria Venture (MMV). In favor of product-development PPPs is the fact that they can help create highly focused expertise in fields left unattended by for-profit companies. Their not-for-profit and philanthropic nature also helps lower R&D costs by leveraging in-kind donation, or below market price, of labor and resources. As a testimony to their success, product-development PPPs now have a significantly growing portfolio against tropical diseases. They do increasingly face costly final clinical development, and thus their long-term viability needs to be addressed more securely, so that they can actually serve as a sustainable supplement to the pharmaceutical industry's sole R&D facility. Industry supports PPPs for neglected diseases because they link up most relevant skills and capacities of different players and there is a clear division of labor between public and private sectors. Governments might consider fiscal incentives to encourage a larger number of companies to collaborate with these PPPs. Examples are discussed more extensively in article #2 in this submission.

ADVANCED PURCHASING COMMITMENTS (APC)

Patients affected by tropical diseases in developing countries do not benefit from a sustainable financing mechanism for their health needs and are often too poor to purchase innovative drugs. This lack of financing then discourages certain strategic choices for R&D priorities. Advance purchasing commitments are an attempt to correct this lack of market by creating from the ground up such a promise that new medicines will be purchased, and that R&D efforts in the area of tropical diseases are worthwhile. In order to replace a nonexistent market for a number of tropical diseases, an APC is a contract entered between a potential purchaser (public or private donor) and a research-based company whereby the potential purchaser promises the company a set price and volume for a fully developed product that meets pre-specified eligibility criteria. The set price and volume provides the necessary reward for the R&D efforts in lieu of a real market. Actual payments only start if a new drug or vaccine is fully developed. An APC provides a valid alternative incentive to fund R&D in diseases that lack a viable market, especially in areas where most needs can be met through adaptive research. It is flexible enough to be implemented without legislative or regulatory change (any public or private donor could enter into such a contract now). The set price and volume also need to be sufficient to cover costs. This approach could replace nonexistent markets for tropical diseases, but its long-term sustainability is highly dependent upon the will of donors to commit on a long-term basis.

GLOBAL FUND FOR TROPICAL DISEASES

Financing healthcare for tropical diseases has been neglected and a similar approach in the form of a Global Fund for Tropical Diseases should be considered to ensure that necessary funds are available to countries and communities to purchase new (and existing) drugs for neglected diseases. Launched in 2002, the Global Fund against AIDS, TB and Malaria is a demand-driven financing model where country-level grant applications are developed and submitted by a consortium of public and private sector NGOs. Also, the Global Alliance for Vaccines and Immunization (GAVI) has made a major progression towards making vaccines more available to patients in poor countries. It has also allowed companies developing new vaccines to consider the patient populations in developing countries in their R&D programs. A new Global Fund for Tropical Diseases would help replace nonexistent markets for tropical diseases and thus directly increase access to drugs. Its impact on redirecting R&D priorities would depend upon a demonstration of its sustainability and ability to attract funds on a long-term basis.

TROPICAL DISEASES DRUG ACT

Similar in spirit to the US, EU or other national “Orphan Drug Acts”, a Tropical Diseases Drug Act there could be a legislative package intended to provide a favorable framework of incentives to increase R&D for drugs targeting diseases of the developing world. Such a package would include both research incentives (R&D tax credits, research grants, lower regulatory fees, fast-track approval) and market incentives (e.g., advanced purchasing commitments). By providing a series of “push/pull” mechanisms, a Tropical Diseases Drug Act represents a comprehensive and potentially stand-alone measure. A Tropical Diseases Drug Act would send a very strong political message to the R&D community about developed countries commitment to fight diseases of the developing world. Smaller companies in particular might be encouraged to conduct early research projects. However, it differs from the existing Orphan Drug Acts in a major way in terms of potential impact: whereas in developed countries, markets exist for orphan drugs, the success of such a new framework for neglected populations requires an accompanying purchasing mechanism so that R&D efforts are met with an ability to pay for the new products developed under a new Tropical Disease Drug Act. This is due to the lack of any purchasing capability for most countries with endemic tropical diseases.

TABLE 1. EXAMPLES OF DISEASES FOR WHICH EFFECTIVE MEDICINES EXIST

Disease	Current Disease Status	Existing Treatment
Childhood diseases	1.12 million children die each year	Effective, low cost vaccines exist for all of major childhood diseases, including pertussis, polio, diphtheria, measles, and tetanus
Diarrhoeal diseases	1.8 million deaths result from diarrhoea each year	Oral rehydration therapy (ORT), once considered the most important medical advance in this century ⁱ , can prevent about 90% of child deaths from diarrhoeal dehydration at the cost of 10 cents per treatment ⁱⁱ .
Malaria	1.3 million deaths result from malaria each year	Effective prevention and treatment tools exist, which if applied properly, could lead to elimination of malaria. ^{iii, iv, v}
Schistosomiasis	200 million people are affected globally, of which 85 percent in Africa	Schistosomiasis can be treated with praziquantel at the cost of 30 cents per child, per year, including delivery costs.
Vitamin A deficiency	140 million children at risk of blindness 500,000 children blinded each year and half of them die within a year ^{vi}	Vitamin A is low cost and can be easily administered as a food supplement. ^{vii}

TABLE 2. EXAMPLES OF ONGOING DISEASES CONTROL PROGRAMS

Disease/Program	Pharmaceutical Industry's Contributions ^{viii}	Achievements
<i>Onchocerciasis</i> Mectizan Donation Program	Merck donates Mectizan® to all who need it and as long as necessary. To date, the company has donated over one billion tablets, with more than 300 million cumulative treatments distributed.	Over 25 years, the Onchocerciasis Control Program has protected approximately 11 million children against onchocerciasis – and around 1 million people have been saved from blindness. Some 250,000 km ² of previously infested areas has been resettled and is now being cultivated ^{ix} .
<i>Leprosy</i> Global Alliance to Eliminate Leprosy	Novartis donates \$35 million in multi-drug treatment for leprosy, and works with WHO and other partners to improve delivery and care.	Over 13 million people have been cured of leprosy and the prevalence rate has dropped by over 90 percent since 1985, and the number of countries considered endemic has been reduced from 122 to 15.
<i>Lymphatic Filariasis</i> Global Alliance to Eliminate Lymphatic Filariasis	GlaxoSmithKline donates albendazole, and Merck donates Mectizan®. To date 250 million treatments of albendazole and 20 million treatments of Mectizan® have been donated.	By the end of 2003 almost 80 million people in 37 countries had received treatment for lymphatic filariasis. This is a marked increase compared to the year 2000 when only 3 million people at risk were covered ^x .
<i>Guinea Worm</i> Guinea Worm Eradication Program	Johnson&Johnson has donated enough medical supplies such as Tylenol®, forceps and gauze, to treat more than 3,000 villages in the endemic countries.	The number of people suffering from guinea worm has dropped from 10-15 million at the start of the 1980s to 32,000 in 2003. Globally, over 150 countries and territories have been certified free of parasite transmission.
<i>Blinding Trachoma</i> International Trachoma Initiative	Pfizer has donated more than \$130 million in product donations (Zithromax®) and health educational grants.	Over 5 million people have been rid of active trachoma infection through antibiotic treatment and more than 70,000 cases of blindness have been prevented through surgeries ^x .
<i>African trypanosomiasis</i> WHO Program to Eliminate Sleeping Sickness	Aventis has supplied some 1.2 million drug ampoules of three medicines used in treatment, as well as financially supported the work of mobile medical teams and research activities of WHO on a new formulation of a drug for African trypanosomiasis.	During the past three years, more than 60,000 people have benefited from this initiative, receiving medical counsel, screening and treatment.

REFERENCES

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