International Federation of Pharmaceutical Manufacturers & Associations
Fédération Internationale de l'Industrie du Médicament
Federación Internacional de la Industria del Medicamento

Backgrounder

R&D into Neglected Diseases by the Innovative Pharmaceutical Industry

Neglected diseases, primarily affecting developing countries, are so-called because it was believed that the poverty of the countries affected limits the commercial prospects of any medicine for these indications and so discourages research and development into these conditions by profit-oriented pharmaceutical companies.

This view was supported by a 1999 publication[1] which reported that only 13 new medicines for "neglected diseases" were developed in the period 1975-1997. However, *The New Landscape of Neglected Disease Drug Development*[2] by Dr. Mary Moran et al in late 2005 reported 63 neglected disease R&D projects underway in 2004 in the 10 diseases targeted by the WHO's TDR tropical disease research organization. Of these, 16 involved multinational pharmaceutical companies (all IFPMA members) working in public-private partnerships and 16 more were being undertaken by such companies on their own, with two medicines were reported as submitted for registration.

Moran assessed that the public-private partnership approach was helping to bring company resources to bear on neglected diseases. One factor in this is intellectual property for neglected disease applications, where she commented that "large companies are often willing to provide such IP for not-for-profit use and to work collaboratively on its development". She also noted that companies might be motivated by a sense of corporate social responsibility and by a desire to establish a presence in emerging markets.

Today, we see that there are at least 21 neglected disease R&D projects underway involving multinational companies in public private partnerships (plus two more by Indian companies which are not multinationals but are in IFPMA's Indian member association OPPI), while 20 more being undertaken by companies alone. There are currently four projects with candidate medicines submitted for registration. In addition, IFPMA companies are working in partnerships to develop 7 vaccines in three different TDR disease areas.

Private Partnerships mentioned in this document include the Aeras Global TB Vaccine Foundation (Aer), the Drugs for Neglected Diseases initiative (DNDi), the Medicines for Malaria Venture (MMV), the Malaria Vaccine Initiative (MVI), Pediatric Dengue Vaccine Initiative (PDVI), the TB Alliance: Global Alliance for TB Drug Development (TB A) and the WHO / UNICEF / UNDP / World Bank Special Program for Research & Training in Tropical Diseases (TDR). The US National institute of Allergy and Infectious Diseases (NIAID) is also active in neglected disease research. "M" in the right hand column denotes projects recorded by Moran.

Tuberculosis

Disease impact: Estimated 2 million deaths per year, 90% in developing countries. Some 2 billion infected.

Available therapies: WHO recommends Directly Observed Treatment, Short-Course to ensure patients adhere to long treatment with anti-TB cocktail (options include Isoniazid, Rifampicin, Pyrazinamide, Streptomycin and Ethambutol), but this places a heavy burden on health care resources. Length of treatment encourages non-adherence which facilitates development of resistance and now multi-drug resistance, which is increasingly difficult to treat. TB is linked to HIV/AIDS, so compatibility of therapies is an issue.

TDR R&D priority: 2 (development and testing of new disease control tools and strategies)

Industry R&D:

AstraZeneca	none	DNA synthesis inhibitors	Lead ident.	M
AstraZeneca	none	Methyl Erythritol Pathway inhibitors	Lead ident.	M
AstraZeneca	none	Screening & Target Identification	Lead optimiz.	M
Bayer HealthCare	TB A	Moxifloxacin	Phase II	-
Lupin	TDR	Gatifloxacin	Phase III	M
GlaxoSmithKline	TB A	Bacterial Topoisomerase	Lead ident.	M
GlaxoSmithKline	TB A	Pleuromutilins	Lead optimiz.	M
GlaxoSmithKline	TB A	InhA Inhibitors	Lead identif.	M
GlaxoSmithKline	TB A	Focused screening (2 target areas)	Discovery	M
Johnson & Johnson	none	TMC207 Diarylquinolines (DARQ)	Phase I	-

Industry R&D (cont.):

Novartis	TB A	Nitroimidazole PA-824	Phase I	-
Novartis	TB A	PA 824 backup compounds	lead optimiz.	M
Novartis	none	PDF inhibitors	Phase I	M
Otsuka	none	Nitroimidazole OPC-67683	Phase II	-
Otsuka	none	Nitroimidazole backup compound	Precinical	-
Pfizer	none	U 100480	Preclinical	M
sanofi-aventis	none	Improving existing treatments	Preclinical	-
Crucell	Aer	Aeras-402 vaccine	Phase I	-
GlaxoSmithKline	Aer	Vaccine (Mtb72F/AS02A)	Phase I	-

TB A is talking to AstraZeneca about a screening program and to Otsuka. Lupin (an IFPMA member via OPPI, India) licensed Gatifloxacin from Kyorin Pharmaceutical (an IFPMA member via JPMA, Japan). Biotech companies like Sequella also working on TB therapies.

Malaria

Disease impact: Estimated 1 million deaths per year, 90% in sub-Saharan Africa, mostly children under five years. Annually, 300-500 million people contract malaria.

Available therapies: WHO recommends combinations to slow continually evolving treatment resistance: Artemether-lumefantrine or Artesunate + Amodiaquine / Mefloquine / Sulfadoxine-pyrimethamine. GlaxoSmithKline, Novartis and sanofi-aventis run access programs with various partners, including WHO.

TDR R&D priority: 2 (development and testing of new disease control tools and strategies)

Industry R&D:

Bayer HealthCare	MMV	Artemisone	Phase III	M
GlaxoSmithKline	MMV	Chloroproguanil-Dapsone-Artesunate	Registration	M
GlaxoSmithKline	MMV	4(1H) pyridones	Preclinical	M
GlaxoSmithKline	MMV	4(1H) pyridones back-ups	Lead optimiz.	M
GlaxoSmithKline	MMV	Isoquine	Phase I	M
GlaxoSmithKline	MMV	FAB 1	Discovery	M
GlaxoSmithKline	MMV	Falcipain	Lead ident.	M
GlaxoSmithKline	none	Etaquine	Phase III	-
Novartis	MMV	Pediatric Coartem	Registration	M
Pfizer	none	Zithromycin & Chloroloquine	Phase III	M
Ranbaxy	MMV	Synthetic Peroxide (OS277)	Phase I	M
sanofi-aventis	DNDi	Artesunate-Amodiaquine FDC	Registration	M
sanofi-aventis	none	Thiazolium	Lead optimiz.	M
sanofi-aventis	none	Choline uptake inhibitors	Lead optimiz.	M
sanofi-aventis	none	Ferroquine (SSR 97193)	Phase I	M
sanofi-aventis	none	Trioxaquine	Lead optimiz.	M
sanofi-aventis	none	Intrarectal Quinine	Phase III	M
Sigma-Tau (et al)	MMV	Artekin (DHA Piperaquine)	Registration	M
Crucell	NIAID	AdVac vaccine	Phase I	-
GlaxoSmithKline	MVI	Vaccine (RTS,S/AS02A)	Phase III	-

The GlaxoSmithKline / MMV Peptide deformylase project listed by Moran has been stopped work on. Roche has handed OS277 to Ranbaxy (IFPMA member via OPPI, India). MMV is negotiating new partnership projects with Novartis and GlaxoSmithKline has further early stage projects, beyond those listed above.

African trypanosomiasis (Sleeping Sickness)

Disease impact: Estimated 250-300,000 deaths per year. 300-500,000 currently infected.

Available therapies: All intravenous. Suramin (1920, serious adverse effects), Melarsoprol (1932, used for late-stage disease, adverse effects), Pentamidine (1941, ineffective against late-stage disease, resistance), Eflornithine (1991, effective for late-stage disease, less adverse effects than melarsoprol).

TDR R&D priority: 1 (acquisition of new knowledge, design of new disease control tools and systems)

Industry R&D:

Bayer HealthCare, sanofi-aventis	TDR, DNDi	Oral Nifurtimox & Eflornithine	Phase III	M

Shistosomiasis

Disease impact: Estimated 150,000 deaths per year. Some 200 million infected, 85% in sub-Saharan Africa.

Available therapies: Praziquantel allows safe & effective treatment. Cheap, but so far only used on a large scale in China.

TDR R&D priority: 2 (development and testing of new disease control tools and strategies)

Industry R&D:

Pfizer	TDR	oxominiquine + prazinquantel	early	-

Leishmaniasis (Kala Azar)

Disease impact: Estimated 80,000 deaths per year, but totals will surge in epidemics, as in Sudan in the early 1990s. Approximately 12 million infected, with 1.5-2 million new cases per year.

Available therapies: pentavalent antimony (intravenous, adverse effects, effectiveness questioned), AmBisome® (highly effective, but expensive ≥USD1,500 / person, only registered in India, manufacturer Astellas talking to DNDi about trials elsewhere with view to obtaining wider registration).

TDR R&D priority: 1 (acquisition of new knowledge, design of new disease control tools and systems)

Industry R&D:

Zentaris	TDR	Miltefosin	Phase IV	-
GlaxoSmithKline	none	Sitamaquine (WR6026)	Phase III	M

Amercian trypanosomiasi (Chagas Disease)

Disease impact: Estimated 45-50,000 deaths per year. Approximately 18 million infected.

Available therapies: Nifurtimox and Benznidazole (for acute early, indeterminate and congenital cases, much less effective against chronic stage, which can be fatal). Bayer HealthCare and WHO run an access program.

TDR R&D priority: 3 (improvement and wider dissemination of existing tools and strategies, risk avoidance)

Industry R&D:

Schering-Plough is discussing studying Noxafil in Chagas with various stakeholders, including the WHO.

Dengue / Dengue Hemorrhagic Fever

Disease impact: Estimated 24,000 deaths per year (probably an underestimate; deaths could be as much as 1% of all infections). 50-100 million infections per year, of which 250-500,000 are the potentially fatal hemorrhagic form.

Available therapies: None

TDR R&D priority: 1 (acquisition of new knowledge, design of new disease control tools and systems)

Industry R&D:

Novartis	none	NS3 helcase	Discovery	M
Novartis	none	NS3 polymerase	Discovery	M
Novartis	none	NS3 protease	Discovery	M
GlaxoSmithKline	PDVI	Vaccine	Phase II	-
sanofi-aventis	PDVI	Vaccine	Phase II	-

Leprosy

Disease impact: Neglible directly attributable mortality, but extensive long-term morbidity. Around 500,000 new cases in 2003; 220,000 new cases in 2005.

Available therapies: Dapsone, Rifampicin & Clofazimine allow safe & effective treatment. Novartis works with WHO to provide an access program, aiming to reach all leprosy sufferers.

TDR R&D priority: 3 (improvement and wider dissemination of existing tools and strategies, risk avoidance)

Industry R&D:

Lymphatic Filiarisis (Elephantiasis)

Disease impact: Neglible directly attributable mortality, but extensive long-term morbidity. Estimated 119 million infected.

Available therapies: Diethylcarbamazine or Ivermectin and Albendazole allow safe & effective treatment. GlaxoSmithKline and Merck & Co. run a joint access program.

TDR R&D priority: 3 (improvement and wider dissemination of existing tools and strategies, risk avoidance)

Industry R&D:

Onchocerciasis (River Blindness)

Disease impact: Neglible directly attributable mortality, but extensive long-term morbidity. 16-18 million infected, 99% of whom in sub-Saharan Africa.

Available therapies: Ivermectin allows safe & effective treatment. Merck & Co. runs an access program.

TDR R&D priority: 3 (improvement and wider dissemination of existing tools and strategies, risk avoidance)

Industry R&D:

Wyeth	TDR	Moxidectin	Phase II	M

Accessing details of ongoing clinical trials

In 2005, IFPMA Member Companies agreed a joint industry position whereby they will post appropriate details of ongoing hypothesis-confirming clinical trials on publicly accessible clinical trial registries. To help locate clinical trial, the IFPMA has created a specialized search engine, the IFPMA Clinical Trials Portal (www.ifpma.org/clinicaltrials), offering a single, easy-to-use point of access to on-line registry information available around the world, including many of the Phase II, III and IV trials listed above.

Sources:

[1] Pecoul B, Chirac P, Trouiller P, Pinel J (1999). *Access to essential drugs in poor countries: a lost battle?* JAM. 281: 361-67.

[2] *The New Landscape of Neglected Disease Drug Development* Dr. Mary Moran, the Pharmaceutical R&D Policy Project, published by the London School of Economics and Political Science and the Wellcome Trust. Dr. Moran and her team are now working with the George Institute for International Health in Australia.

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About the IFPMA:

The International Federation of Pharmaceutical Manufacturers & Associations is the global non-profit NGO directly representing twenty-six research-based pharmaceutical, biotech and vaccine companies and sixty national industry associations in developed and developing countries. The industry's R&D pipeline contains hundreds of new medicines and vaccines being developed to address global disease threats, including cancer, heart disease, HIV/AIDS and malaria. The IFPMA Clinical Trials Portal (www.ifpma.org/clinicaltrials) and the IFPMA Health Partnerships Survey help make the industry's activities more transparent. The IFPMA strengthens patient safety by improving risk assessment of medicines and combating their counterfeiting. It also provides the secretariat for the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

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