



# Status Report

## Pharmaceutical Industry R&D for Diseases of the Developing World

This document lists research-based pharmaceutical company<sup>(1)</sup> projects<sup>(2)</sup> to develop new medicines and vaccines for the ten diseases of the developing world (DDW) prioritized by the WHO/UNICEF/UNDP/World Bank Special Program for Research & Training in Tropical Diseases (TDR):

- Priority 1: African trypanosomiasis, Dengue & Leishmaniasis,
- Priority 2: Malaria, Schistosomiasis & Tuberculosis,
- Priority 3: Chagas Disease, Leprosy, Lymphatic Filariasis & Onchocerciasis.

Data on research projects underway for these diseases published in 2005 by the Pharmaceutical R&D Policy Project<sup>(3)</sup> under Dr. Mary Moran and subsequently by the IFPMA show the evolution and status of industry R&D for DDW.

### Industry DDW R&D – Evolution, 2005-2007

	2005	2006	2007
<b>Medicines</b>	32	43	50
<b>Vaccines</b>	(not counted)	6	8

### Industry DDW R&D – Status Overview as of 30 October 2007

Diseases	Ongoing: Medicines	Ongoing: Vaccines	Approvals since 2005	Stopped since 2005
<b>Tuberculosis</b>	20	2	-	1
<b>Malaria</b>	24	4	-	4
<b>Other TDR Diseases</b>	6	2	1	1
<b>Totals</b>	<b>50</b>	<b>8</b>	<b>1</b>	<b>6</b>

Slightly more than half of these R&D programs are being undertaken by companies working with Product Development Partnerships<sup>(4)</sup>, while the rest are by companies on their own. The industry's efforts to help improve global health are supported by four company R&D centers which are dedicated solely to research and development for diseases of the developing world.

### Industry Dedicated DDW R&D Centers

Company	Center	Location	Disease(s)	Started
AstraZeneca	Bangalore Research Institute	Bangalore, India	Tuberculosis	2003
Eli Lilly	TB Drug Discovery Partnership	Seattle, USA	Tuberculosis	2007
GlaxoSmithKline	DDW Drug Discovery Center	Tres Cantos, Spain	Malaria Tuberculosis	2002
Novartis	Novartis Institute for Tropical Diseases	Singapore	Dengue Fever Malaria Tuberculosis	2002

This document does not cover R&D for HIV/AIDS, which is a health issue in both developed and developing countries, but it should be noted pharmaceutical companies have developed 22 antiretroviral (ARV) medicines, of which 11 are available in pediatric formulations and, in 2006, were developing a further 35 new ARVs, at least 6 additional pediatric formulations for ARVs and 19 HIV vaccines.<sup>(5)</sup>

## 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. TB is linked to HIV/AIDS, so compatibility of therapies is an issue.

**Access & Capacity Building:** Programs by AstraZeneca, Eli Lilly, GlaxoSmithKline & Novartis.

**Products approved since 2005:** None to date.

**Projects stopped since 2005:** Methyl erythritol pathway inhibitors (AstraZeneca).

**Notes:** Lupin of India has licensed Gatifloxacin from Kyorin Pharmaceutical of Japan for tuberculosis.

Company	Partners	Project	Phase
AstraZeneca	<i>company</i>	DNA synthesis / repair inhibitors	Lead identification
AstraZeneca	TB A	Screening, target identification (multiple)	Lead identification
Bayer HealthCare	TB A	Moxifloxacin	Phase II
GlaxoSmithKline	TB A	Mycobacterial Gyrase Inhibitors / MGI	Lead optimization
GlaxoSmithKline	TB A	Pleuromutilins	Lead optimization
GlaxoSmithKline	TB A, Tex	InhA Inhibitors	Lead identification
GlaxoSmithKline	TB A, Tex	Malate Synthase Inhibitors	Lead identification
GlaxoSmithKline	TB A	Antimicrobial Screening program	Lead identification
J&J (Tibotec)	<i>company</i>	Diarylquinolines / DARQ (TMC207)	Phase II
Lupin	TDR	Gatifloxacin	Phase III
Lupin	<i>company</i>	3 compounds	Preclinical
Novartis	TB A	Nitroimidazole PA-824	Phase I
Novartis	TB A	PA 824 backup compounds	Lead optimization
Novartis	<i>company</i>	Peptide deformylase / PDF	Phase I
Otsuka	<i>company</i>	Nitroimidazole (OPC-67683)	Phase II
Otsuka	<i>company</i>	Nitroimidazole backup compound	Preclinical
Pfizer	<i>company</i>	PNU-100480	Preclinical
sanofi-aventis	<i>company</i>	Improving existing treatments	Phase IIIb/IV
sanofi-aventis	<i>company</i>	Antimycobacterial screening program	Discovery
sanofi-aventis	<i>company</i>	Target selection and screenings (3 in progress)	Discovery
<b>Vaccines</b>			
Crucell	Aeras, SATVI	Aeras-402 vaccine (AdVac®)	Phase I
GlaxoSmithKline	Aeras	Vaccine (M72/AS01)	Phase II

## 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 resistance: Artemether-lumefantrine or Artesunate + Amodiaquine / Mefloquine / Sulfadoxine-pyrimethamine.

**Access & Capacity Building:** Programs by GlaxoSmithKline, Novartis, Pfizer & sanofi-aventis.

**Products approved since 2005:** Artesunate-Amodiaquine FDC (sanofi-aventis, DNDi) in Morocco.

**Projects stopped since 2005:** Artemifone (Bayer HealthCare/MMV), peptide deformylase inhibitor (GlaxoSmithKline/MMV), protein franesyltransferase inhibitors (Bristol-Myers Squibb/MMV) and 4(1H)-pyridone derivate (GlaxoSmithKline/MMV).

**Notes:** Roche has handed OZ277 to Ranbaxy for further development.

Company	Partners	Project	Phase
GlaxoSmithKline	MMV, TDR, Liv	Dacart™ (chloroproguanil-dapsone-artesunate)	Pre-registration
GlaxoSmithKline	MMV, WRAIR	Tafenoquine (radical cure of P vivax)	Phase II
GlaxoSmithKline	Liv	n-tert butyl Isoquine (GSK 369796)	Preclinical
GlaxoSmithKline	MMV	4(1H) pyridones Lead (GSK 932121)	Preclinical
GlaxoSmithKline	MMV	4(1H) pyridones back-ups	Lead optimization
GlaxoSmithKline	MMV, UCSF	Falcipain Inhibitors (Cysteine Protease)	Lead optimization
GlaxoSmithKline	MMV, Tex, Col	Fatty Acid Biosynthesis / FabI	Discovery
GlaxoSmithKline	MMV	Antimalarial screening program	Discovery
GlaxoSmithKline	WRAIR	Novel Macrolide	Discovery
Novartis	MMV	Pediatric Coartem®	Registration
Novartis	Wellcome, MMV	Mini-portfolio	Discovery
Pfizer	company	Azithromycin & Chloroquine	Phase III
Ranbaxy	company	Synthetic Peroxide (OZ277/RBx11160)	Phase II
sanofi-aventis	DNDi	Artesunate-Amodiaquine FDC	Registration
sanofi-aventis	company	Intrarectal Quinine	Phase III
sanofi-aventis	company	Thiazolium (SAR97276A)	Phase I
sanofi-aventis	CNRS	Thiazolium back-up	Discovery
sanofi-aventis	company	Ferroquine (SSR97193)	Phase II
sanofi-aventis	company	Trioxaquine (SAR116242/PA1103)	Preclinical
sanofi-aventis + Palumed	company	Trioxaquine back-up	Discovery
sanofi-aventis	company	Target selection and screenings	Discovery
Sigma-Tau + Holley	MMV, Oxon	Eurartesim® (Dihydroartemisinin & Piperaquine)	Phase III
Sigma-Tau	WRAIR, MMV, EDCTP	Intravenous Artesunate (in children)	Phase III
Shin Poong	MMV, Iowa	pyronaridine artesunate / Pyramax®	Phase III
<b>Vaccines</b>			
Amgen	MVI	MSP1-42 and AMA-1 vaccine	Phase I
Crucell	NIAID	AdVac®-based malaria vaccine	Phase I
GlaxoSmithKline	MVI	RTS,S/AS01E vaccine	Phase IIb
sanofi-aventis	Inst. Pasteur	P.falciparum vaccine	Preclinical

## 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).

**Access / Capacity Building:** Programs by Bayer HealthCare & sanofi-aventis.

**Products approved since 2005:** None to date.

**Projects stopped since 2005:** None to date.

Company	Partners	Project	Phase
sanofi-aventis & Bayer HealthCare	TDR, DNDi	Oral Nifurtimox & Eflornithine	Phase III

## 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).

**Access / Capacity Building:** Programs by Gilead & sanofi-aventis.

**Products approved since 2005:** Miltefosine / Impavido® (Zentaris, TDR).

**Projects stopped since 2005:** None to date.

Company	Partners	Project	Phase
GlaxoSmithKline	<i>company</i>	Sitamaquine (WR6026)	Phase IIb

## 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.

**Access / Capacity Building:** Program by Bayer HealthCare (prevention oriented).

**Products approved since 2005:** None to date.

**Projects stopped since 2005:** None to date.

Company	Partners	Project	Phase
Novartis	<i>company</i>	NS3 helicase	Discovery
Novartis	<i>company</i>	NS3 polymerase	Discovery
Novartis	<i>company</i>	NS3 protease	Discovery
<b>Vaccines</b>			
GlaxoSmithKline	WRAIR, PDVI	Tetavalent live attenuated vaccine	Phase II
sanofi-aventis	PDVI	Vaccine	Phase II

## **Onchocerciasis (River blindness)**

**Disease impact:** Negligible 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.

**Access / Capacity Building:** Program by Merck & Co.

**Products approved since 2005:** None to date.

**Projects stopped since 2005:** None to date.

Company	Partners	Project	Phase
Wyeth	TDR	Moxidectin	Phase II

## **Other Tropical Diseases**

### **Shistosomiasis**

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

**Available therapies:** Praziquantel allows safe & effective treatment.

**Access / Capacity Building:** Program by Merck KGaA.

**Products approved since 2005:** None to date.

**Projects stopped since 2005:** Oxominiquine & Praziquantel (Pfizer, TDR).

### **American Trypanosomiasis (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).

**Access / Capacity Building:** Programs by Bayer HealthCare & sanofi-aventis.

**Products approved since 2005:** None to date.

**Projects stopped since 2005:** None to date.

**Note:** Schering-Plough discussing studying Noxafil in Chagas with various stakeholders, including WHO.

### **Leprosy**

**Disease impact:** Negligible direct mortality, extensive long-term morbidity, ~500,000 new cases in 2003; ~220,000 in 2005.

**Available therapies:** Dapsone, Rifampicin & Clofazimine allow safe & effective treatment.

**Access / Capacity Building:** Program by Novartis.

**Products approved since 2005:** None to date.

**Projects stopped since 2005:** None to date.

### **Lymphatic Filariasis**

**Disease impact:** Negligible direct mortality, extensive long-term morbidity, ~119 million infected.

**Available therapies:** Diethylcarbamazine or Ivermectin & Albendazole allow safe, effective treatment.

**Access / Capacity Building:** programs by GlaxoSmithKline and Merck & Co..

**Products approved since 2005:** None to date.

**Projects stopped since 2005:** None to date.

## Notes

- (1) Companies which are direct members of the IFPMA or members of an IFPMA member association.
- (2) A project is 1) a compound in development for a disease target, or 2) a program to screen compounds against a disease. Data is from responses to IFPMA queries and open sources.
- (3) *The New Landscape of Neglected Disease Drug Development*, Dr. Mary Moran, the Pharmaceutical R&D Policy Project, published in 2005 by the LSE and the Wellcome Trust.
- (4) The DDW PDP partners referred to in this document are:

<b>Aeras Global TB Vaccine Foundation (Aeras)</b>	<b>National Institute of Allergy &amp; Infectious Diseases, USA (NIAID)</b>
<b>Centre national de la recherche scientifique, France (CNRS)</b>	<b>Oxford University, UK (Oxon)</b>
<b>Columbia University, USA (Col)</b>	<b>Pediatric Dengue Vaccine Initiative (PDVI)</b>
<b>Drugs for Neglected Diseases initiative (DNDi)</b>	<b>South African TB Vaccine Initiative (SATVI)</b>
<b>European &amp; Developing Countries Clinical Trials Partnership (EDCTP)</b>	<b>Texas A&amp;M University; USA (Tex)</b>
<b>Global Alliance for TB Drug Development (TB A)</b>	<b>University of Iowa; USA (Iowa)</b>
<b>Institut Pasteur (Inst. Pasteur)</b>	<b>W. Reed Army Institute of Research, USA (WRAIR)</b>
<b>Liverpool University; UK (Liv)</b>	<b>Wellcome Trust, UK (Wellcome)</b>
<b>Medicines for Malaria Venture (MMV)</b>	<b>WHO/UNICEF/UNDP/World Bank Special Program for Research &amp; Training in Tropical Diseases (TDR)</b>
<b>Malaria Vaccine Initiative (MVI)</b>	

- (5) PhRMA, USA. See "Medicines in Development", under "Innovation" at [www.pharma.org](http://www.pharma.org).

## Accessing Details of Ongoing Clinical Trials & Reports of Completed Trials

IFPMA Member Companies are committed to post appropriate details of ongoing hypothesis-confirming clinical trials, plus summary results of completed trials, on publicly accessible clinical trial sites. To facilitate access to this information, the IFPMA has created a specialized search engine, the IFPMA Clinical Trials Portal ([www.ifpma.org/clinicaltrials](http://www.ifpma.org/clinicaltrials)), offering a single, easy-to-use point of access to on-line registry information available around the world, including Phase II and III trials for DDW candidate DDW medicines, as well as Phase IV trials of approved medicines.

## About the IFPMA

The International Federation of Pharmaceutical Manufacturers & Associations is the global non-profit NGO representing the research-based pharmaceutical, biotech and vaccine sectors. Its members comprise 25 leading international companies and 46 national and regional industry associations covering 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](http://www.ifpma.org/clinicaltrials)), the IFPMA's Ethical Promotion online resource ([www.ifpma.org/EthicalPromotion/](http://www.ifpma.org/EthicalPromotion/)) and its Health Partnerships information ([www.ifpma.org](http://www.ifpma.org) – Developing World) 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 Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

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