

# Status Report

## Pharmaceutical Industry R&D for Diseases of the Developing World - 2008

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 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, 2005-2008

	2005	2006	2007	2008
<b>Medicines</b>	32	43	50	58
<b>Vaccines</b>	(not counted)	6	8	9

### Industry DDW R&D – Status Overview as of November 2008

Diseases	Ongoing: Medicines	Ongoing: Vaccines	Approvals since 2005	Stopped since 2005
<b>Tuberculosis</b>	21	3	0	5
<b>Malaria</b>	28	4	1	7
<b>Other TDR Diseases</b>	9	2	2	2
<b>Totals</b>	<b>58</b>	<b>9</b>	<b>3</b>	<b>14</b>

49 of these R&D programs are by companies working with Product Development Partnerships<sup>(4)</sup>, while 18 are by companies on their own. The industry's efforts are supported by five company-owned R&D centers which are dedicated solely to DDW R&D.

### Industry Dedicated DDW R&D Centers

Company	Center	Location	Disease(s)	Since
AstraZeneca	Bangalore Research Institute	Bangalore, India	Tuberculosis	2003
Eli Lilly and Company	Lilly TB Drug Discovery Initiative (not-for-profit) in the Infectious Disease Research Institute	Seattle, USA	Tuberculosis	2007
GlaxoSmithKline	DDW Drug Discovery Center	Tres Cantos, Spain	Malaria Tuberculosis Kinetoplastids	2002
Novartis	Novartis Institute for Tropical Diseases	Singapore	Dengue Fever Malaria Tuberculosis	2002
Novartis	Novartis Vaccines Institute for Global Health (NVGH)	Siena, Italy	Diarrheal diseases Salmonella	2008

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 so far developed 22 antiretroviral (ARV) medicines, of which 11 are available in pediatric formulations and, in 2007, were developing a further 46 new ARVs, at least 7 additional pediatric formulations for ARVs and 20 HIV vaccines<sup>(5)</sup>.

\* Supported by Merck & Co., Inc. through access to compounds for screening.

## Tuberculosis

**Disease impact:** Estimated 1.7 million deaths per year, 90% in developing countries. Some 2 billion infected.

**Available therapies:** WHO recommends Directly Observed Treatment, Short-Course (DOTS) 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 closely linked to HIV/AIDS, but incompatibility of ARVs and TB therapies is an issue.

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

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

**Projects stopped since 2005:** Methyl erythritol pathway inhibitors (AstraZeneca); Isocitrate lyase inhibitors (GSK/TB A); Peptide deformylase inhibitors (GSK/TB A), Peptide deformylase, PDF (Novartis, 2007) and nitroimidazole backup compounds (Novartis, 2008).

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

Company	Partners	Project	Phase
AstraZeneca	company	DNA synthesis / repair inhibitors	Lead identification
AstraZeneca	company	Screening, target identification (multiple)	Lead identification
Eli Lilly & Co.*	NIH	CPZEN-45	Preclinical
Eli Lilly & Co.*	NIH	Screening program	Discovery
Bayer HealthCare	TB A, CDC, JHU, BMRC, UCL	Moxifloxacin	Phase III
GlaxoSmithKline	TB A	Mycobacterial Gyrase Inhibitors / MGI	Lead optimization
GlaxoSmithKline	TB A	Pleuromutilins	Lead optimization
GlaxoSmithKline	TB A	InhA Inhibitors	Lead identification
GlaxoSmithKline	TB A, Tex	Malate Synthase Inhibitors	Lead identification
GlaxoSmithKline	TB A	Antimicrobial Screening program	Lead identification
J&J (Tibotec)	company	Diarylquinolines / DARQ (TMC207)	Phase II
Lupin	TDR	Gatifloxacin	Phase III
Lupin	company	3 compounds	Preclinical
Novartis	TB A	Nitroimidazole PA-824	Phase II
Novartis	GC11	Mini-portfolio	Discovery
Otsuka	company	Nitroimidazole (OPC-67683)	Phase II
Otsuka	company	Nitroimidazole backup compound	Preclinical
Pfizer	company	PNU-100480	Preclinical
sanofi-aventis	company	Improving existing treatments	Phase IIIb / IV
sanofi-aventis	company	Antimycobacterial screening program	Discovery
sanofi-aventis	company	Target selection and screenings (3 in progress)	Discovery
<b>Vaccines</b>			
Crucell	Aeras, SATVI	Aeras-402 vaccine (AdVac®)	Phase I / II
GlaxoSmithKline	Aeras	Vaccine (GSK M72)	Phase II
sanofi-aventis	SSI, Aeras, Intercell	Vaccine HyVac4 IC31 (AERAS-404)]	Phase I

\* Supported in part by Merck & Co., through access to compounds for screening.

## 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 and sub-Saharan countries (2007), WHO prequalified (2008).

**Projects stopped since 2005:** Artemifone (Bayer HealthCare/MMV), peptide deformylase inhibitor (GlaxoSmithKline/MMV), protein fransyltransferase inhibitors (Bristol-Myers Squibb/MMV), intrarectal quinine (sanofi-aventis), 4(1H)-pyridone derivate (GlaxoSmithKline/MMV), Fatty Acid Biosynthesis/Fab I (GSK/MMV) and Dacart™ (chloroproguanil-dapsone-artesunate) (GSK/MMV).

**Notes:** In 2003 Roche has handed OZ277 (RBx 11160) to Ranbaxy for further development.

Company	Partners	Project	Phase
Eisai	<i>company</i>	Compound screenings	Discovery
Eisai	<i>academia</i>	Compound screenings	Discovery
Genzyme	MMV, ATI, Harvard	Mini-portfolio	Discovery
GlaxoSmithKline	MMV, WRAIR	Tafenoquine (radical cure of P vivax)	Phase I / II
GlaxoSmithKline	Liv, MMV	n- <i>tert</i> butyl Isoquine (GSK 369796)	Phase I
GlaxoSmithKline	MMV	4(1H) pyridones Lead (GSK 932121)	Preclinical
GlaxoSmithKline	MMV	Pyridone Back-up	Lead Optimization
GlaxoSmithKline	MMV	DHODH inhibitors	Discovery
GlaxoSmithKline	MMV, UCSF	Falcpain Inhibitors (Cysteine Protease)	Discovery
GlaxoSmithKline	MMV	Antimalarial screening program	Discovery
GlaxoSmithKline	MMV	Novel Macrolide	Discovery
Holley Pharm	MMV	Duo Cotecxin® (Dihydroartemisinin & Piperaquine)	Registration
Merck KGaA	TDR	Target screening and hit optimization	Discovery
Novartis	MMV	Pediatric Coartem®	Registration
Novartis	Wellcome, MMV	Mini-portfolio	Discovery
Pfizer	MMV	Azithromycin & Chloroquine	Phase III
Ranbaxy	<i>company</i>	Arterolane (RBx 11160) & Piperaquine	Phase II
sanofi-aventis	iOWH	Semi-synthetic artemisinin	Discovery
sanofi-aventis	DNDi	Artesunate-Amodiaquine FDC	Registration
sanofi-aventis	<i>company</i>	Bis-thiazolium (SAR97276A/T3)	Phase II
sanofi-aventis	CNRS	Thiazolium back-up	Discovery
sanofi-aventis	<i>company</i>	Ferroquine (SSR97193)	Phase II
sanofi-aventis	<i>company</i>	Trioxaquine (SAR116242/PA1103)	Preclinical
sanofi-aventis	Palumed	Trioxaquine back-up	Discovery
sanofi-aventis	<i>company</i>	Target selection and screenings	Discovery
Sigma-Tau	MMV	Eurartesim® (Dihydroartemisinin & Piperaquine)	Registration
Sigma-Tau	WRAIR, MMV, EDCTP	Intravenous Artesunate (in children)	Phase III
Shin Poong	MMV, Iowa	pyronaridine artesunate / Pyramax®	Phase III

Vaccines			
Amgen	<i>company</i>	MSP1-42 and AMA-1 vaccine	Phase I
Crucell	MVI	AdVac®-based malaria vaccine	Preclinical
GlaxoSmithKline	MVI	RTS,S/AS01E vaccine	Phase IIb
sanofi-aventis	Inst. Pasteur	P. falciparum vaccine	Preclinical

### African Trypanosomiasis (Sleeping Sickness)

**Disease impact:** Estimated 50-70,000 cases infected per year, but totals have surged in previous epidemics. 48,000 deaths per year (last estimate per 2004 World Health Report – those not treated effectively will die).

**Available therapies:** All intravenous or intramuscular. Suramin (1920, serious adverse effects), Melarsoprol (1932, used for late-stage disease, serious 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
GlaxoSmithKline	DNDi	Exploratory e-transport & cysteine protease inhib	Discovery
Merck KGaA	TDR	Target screening and hit optimization	Discovery
sanofi-aventis & Bayer HealthCare	TDR, DNDi, Epicentre, MSF, STI, WHO	Nifurtimox oral & Eflornithine IV in combination	Registration

### Leishmaniasis

**Disease impact:** Approximately 12 million infected (500,000 cases of visceral leishmaniasis – VL or Kala-Azar; 1.5 million cases of cutaneous leishmaniasis). Estimated 51,000 deaths per year (per WHO 2007 report on HIV/Leishmaniasis co-infection), but totals will surge in epidemics, as in Sudan in early 1990s.

**Available therapies:** Pentavalent antimony (intravenous, adverse effects, resistance), 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 - sold to Paladin Labs in 2008 - TDR), Paromomycin IM (iOWH).

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

Company	Partners	Project	Phase
GlaxoSmithKline	<i>company</i>	Sitamaquine (WR6026)	Phase IIb
GlaxoSmithKline	DNDi	Exploratory e-transport & cysteine protease inhib	Discovery

## 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:** None.

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

**Projects stopped since 2005:** NS3 helicase and protease inhibitors (Novartis).

Company	Partners	Project	Phase
Novartis	<i>company</i>	NS5 polymerase	Discovery
<b>Vaccines</b>			
GlaxoSmithKline	WRAIR, PDVI	Tetravalent live attenuated vaccine	Phase II
sanofi-aventis	PDVI	Vaccine	Phase IIb

## 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, but resistance may become an issue.

**Access / Capacity Building:** Donation program by Merck & Co., Inc.

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

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

Company	Partners	Project	Phase
Wyeth	TDR	Moxidectin	Phase II

## American Trypanosomiasis (Chagas Disease)

**Disease impact:** Estimated 14,000 deaths per year. Approximately 8 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. Roche donated manufacturing process for benznidazole to the Brazilian government.

**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.

Company	Partners	Project	Phase
GlaxoSmithKline	DNDi	Exploratory e-transport & cysteine protease inhib	Discovery
Schering-Plough	PHRI, SFBR	Posaconazole	Preclinical/Clinical

## Other Tropical Diseases

### Schistosomiasis

**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:** Oxomiquine & Praziquantel (TDR).

### 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:** Donation programs by GlaxoSmithKline and Merck & Co., Inc.

**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 specific disease target, or 2) a program to screen compounds against a specific 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:
  - Advinus Therapeutics Institute (ATI)
  - Aeras Global TB Vaccine Foundation (Aeras)
  - British Medical Research Council (BMRC)
  - Centers for Disease Control and Prevention (CDC)
  - Centre national de la recherche scientifique (CNRS)
  - Columbia University (Col)
  - Consortium 11 of Grand Challenges in Global Health (GCGH) (GC11)
  - Drugs for Neglected Diseases initiative (DNDi)
  - Epicentre Biotechnologies (Epicentre)
  - European & Developing Countries Clinical Trials Partnership (EDCTP)
  - Global Alliance for TB Drug Development (TB A)
  - Harvard Medicine (Harvard)
  - Institute for OneWorld Health (iOWH)
  - Institut Pasteur (Inst. Pasteur)
  - Intercell AG (Intercell)
  - Johns Hopkins University (JHU)
  - Liverpool University (Liv)
  - Malaria Vaccine Initiative (MVI)
  - Medicines for Malaria Venture (MMV)
  - National Institute of Allergy & Infectious Diseases (NIAID)
  - National Institute of Health (NIH)
  - Oxford University (Oxon)
  - Pediatric Dengue Vaccine Initiative (PDVI)
  - Population Health Research Institute (PHRI)
  - South African TB Vaccine Initiative (SATVI)
  - Southwest Foundation for Biomedical Research (SFBR)
  - Statens Serum Institute (SSI)
  - Swiss Tropical Institute (STI)
  - Texas A&M University (Tex)
  - University College London (UCL)
  - University of California, San Francisco (UCSF)
  - University of Iowa (Iowa)
  - Walter Reed Army Institute of Research (WRAIR)
  - Wellcome Trust (Wellcome)
  - WHO/UNICEF/UNDP/World Bank Special Program for Research & Training in Tropical Diseases (TDR)
- (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 26 leading international companies and 44 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/healthpartnerships](http://www.ifpma.org/healthpartnerships)) 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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