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Status Report

Pharmaceutical Industry R&D for Diseases of the Developing World – 2010

This document lists research-based pharmaceutical company[1] projects[2] to develop new medicines and vaccines for the ten diseases of the developing world (DDW) prioritized by the Programme for Research and Training in Tropical Diseases (TDR), co-sponsored by the UNICEF, the UNDP, the World Bank and the WHO. The diseases are, in order of decreasing mortality: tuberculosis, malaria, human African trypanosomiasis (sleeping sickness), leishmaniasis, dengue, onchocerciasis (River blindness), American trypanosomiasis (Chagas disease), schistosomiasis, leprosy and lymphatic filariasis. Data on projects published in 2005 by the Pharmaceutical R&D Policy Project[3] under Dr. Mary Moran, George Institute, and subsequently by the IFPMA show the evolution and status of industry R&D for DDW.

Industry DDW R&D – Evolution, 2005-2010

	2005	2006	2007	2008	2009	2010
Medicines	32	43	50	58	75	91
Vaccines	(not counted)	6	8	9	9	11

Industry DDW R&D – Status Overview as of November 2010

Diseases	Ongoing Medicines R&D Projects	Ongoing Vaccines R&D Projects	Approvals Since 2005	R&D Projects Stopped Since 2005
Tuberculosis	28	3	0	6
Malaria	36	5	2	13
Other Tropical Diseases	27	3	3	8
Totals	***91***	***11***	***5***	***27***

71 of these R&D programs are by companies working with Product Development Partnerships[4], while 20 are by companies on their own (21%). 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
GlaxoSmithKline	DDW Drug Discovery Center	Tres Cantos, Spain	Malaria Tuberculosis Kinetoplastids	2002
Lilly*	Lilly TB Drug Discovery Initiative (not-for-profit) in the Infectious Disease Research Institute	Seattle, USA	Tuberculosis	2007
Merck & Co., Inc.	MSD Wellcome Trust Hilleman Laboratories	New Delhi, India	Vaccines for the developing world	2009
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

* Also supported by provision of compound library by Merck & Co., Inc.

NOTE: Items added to this Status Report since the previous one have a light grey background.

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Tuberculosis

Disease impact: Estimated 1.6 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, GlaxoSmithKline, Lilly, Novartis & sanofi-aventis.

Products approved since 2005: None to date.

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

Notes: The Critical Path to TB Drug Regimens (CPTR) initiative will test promising combinations of TB drug candidates and includes scientists from the US FDA and AstraZeneca, Bayer HealthCare, GlaxoSmithKline, Johnson & Johnson, Novartis, Otsuka, Pfizer and sanofi-aventis. Daiichi Sankyo TB compound library screening program was previously managed by its Ranbaxy affiliate. Lupin of India has licensed Gatifloxacin from Kyorin Pharmaceutical of Japan for tuberculosis.

Company	Partners	Project	Phase
Abbott	TB A	Compound screening	Lead identification
AstraZeneca	TB A	Joint research collaboration agreement	Discovery
AstraZeneca	*company*	DNA synthesis / repair inhibitors	Lead identification
AstraZeneca	*company*	Screening, target identification (multiple)	Lead identification
AstraZeneca	*company*	AZD5847	Phase I
AstraZeneca	NM4TB	Compounds	Lead identification
Bayer HealthCare	TB A, BMRC, UCL	Moxifloxacin	Phase III
Daiichi Sankyo	DBT	Compound library screening	Discovery
GlaxoSmithKline	TB A	Antimicrobial screening program	Lead identification
GlaxoSmithKline	TB A	Whole-cell screening program	Lead identification
GlaxoSmithKline	TB A	Mycobacterial gyrase Inhibitors / MGI	Lead optimization
GlaxoSmithKline	TB A	InhA inhibitors	Lead identification
GlaxoSmithKline	TB A	Malate synthase Inhibitors	Lead identification
GlaxoSmithKline	TB A	Whole-cell hit to lead screening program	Lead identification
J&J (Tibotec)	TB A	Diarylquinoline TMC207	Phase II
J&J (Tibotec)	TB A	Next generation diarylquinoline	Lead optimization
Lilly	NIH	CPZEN-45	Preclinical
Lilly	NIH	Screening program	Discovery
Novartis	TB A	Nitroimidazole PA-824	Phase II
Novartis	TB A	Portfolio	Discovery
Novartis	GC11	Mini-portfolio	Discovery
Novartis	NIAID	Anaerobic screen and other cell-based TB screens	(?)
Otsuka	*company*	Nitroimidazole (OPC-67683)	Phase II
Otsuka	*company*	Nitroimidazole backup compound	Preclinical
Pfizer	*company*	PNU-100480	Phase I
sanofi-aventis	*company*	Rifapentine (new regimen development)	Preclinical
sanofi-aventis	*company*	Antimycobacterial screening program	Discovery
sanofi-aventis	*company*	Target selection & screening (3 groups)	Discovery
sanofi-aventis	TB A	Portfolio	Discovery

Vaccines			
Crucell	Aeras	Aeras-402 vaccine (AdVac®)	Phase I / II
GlaxoSmithKline	Aeras	Vaccine (GSK M72) (Mtb72F/AS)	Phase II
sanofi-aventis	SSI, Aeras, Intercell	Vaccine HyVac4 IC31 (AERAS-404)]	Phase I

Malaria

Disease impact: 243 million cases & 863,000 deaths/year, 90% in sub-Saharan Africa, mostly children.

Available therapies: WHO recommends Artemesinin combinations to slow continually evolving resistance.

Access & Capacity Building: Programs by Abbott, 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), Pediatric Coartem® Dispersible (Novartis/MMV) (2009).

Projects stopped since 2005: Artemifone (Bayer HealthCare/MMV), Peptide deformylase inhibitor (GSK/MMV), protein franesyltransferase inhibitors (BMS/MMV), intrarectal quinine (sanofi-aventis), 4(1H)-pyridone derivate (GSK/MMV), Fatty Acid Bionsynthesis/Fab I (GSK/MMV), chloroproguanil-dapsone-artesunate (GSK/MMV), Falcipain Inhibitors / Cysteine Protease (GSK/MMV/UCSF), Novel Macrolide (GSK/MMV), P. falciparium vaccine (sanofi-aventis/Inst. Pasteur), n-tert butyl Isoquine (GlaxoSmithKline/Liv/MMV), Novel Macrolide (GSK/MMV), 4(1H) pyridones Lead - GSK 932121 (GSK/MMV).

Notes: Ranbaxy's RBx 11160 initially with MMV. Sigma-Tau & Pfizer will jointly market Eurartesim®. Bayer HealthCare stopped Artemifone in 2005; the University of Hong Kong has taken it to Phase II with MMV.

Company	Partners	Project	Phase
Abbott	NYU	Lopinavir / ritonavir (potential preventive therapy)	Preclinical
Abbott	Penn	Inhibitors of human calpain	Lead identification
Abbott	MMV	Compound screening	Lead identification
AstraZeneca	MMV	Compound screening	Lead identification
Daiichi Sankyo	MMV	Compound screening	Lead identification
Eisai	*company*	Compound screening	Discovery
Eisai	Academia	Compound screening	Discovery
Genzyme	MMV, BI	Mini-portfolio	Lead generation
Genzyme	MMV, BI	Aminoindole	Lead optimization
Genzyme	MMV	DHODH	Lead optimization
GlaxoSmithKline	MMV, WRAIR	Tafenoquine (radical cure of P vivax)	Phase I
GlaxoSmithKline	MMV	Pyridone back-up	Lead optimization
GlaxoSmithKline	MMV	DHODH inhibitors	Lead identification
GlaxoSmithKline	MMV	Anti-malarial whole-cell inhibitors	Discovery
Holley Pharm	MMV	Duo Cotecxin® (Dihydroartemisinin & Piperaquine)	Registration
Merck & Co., Inc.	MMV	MK4815	Preclinical
Merck KGaA	TDR	Lead optimization	Lead optimization
Novartis	Well, MMV, BPRC, STI	Mini-portfolio	Discovery
Novartis	Well, MMV, BPRC, STI,	Imidazolopyrazines, pyrrolidines, & imidazolopiperazines	Lead optimization
Novartis	Drex, Wash,	Pyrazoles	Lead optimization
Novartis	Well, MMV, BPRC, STI	Spiroindolone (NITD 609)	Preclinical
Novartis	MMV	Coartem® Dispersible	Phase IV
Pfizer	TDR, MMV	Compound library screening	Lead generation
Pfizer	MMV, LSHTM	Azithromycin/chloroquine in IPTp for pregnant women	Phase III
Pfizer	*company*	Azithromycin/chloroquine	Phase III

Ranbaxy	MMV	Arterolane (RBx 11160) & piperaquine	Phase III
sanofi-aventis	iOWH	Semi-synthetic artemisinin	Discovery
sanofi-aventis	MMV, DNDi	Artesunate-amodiaquine winthrop ASAQ FDC	Phase IV
sanofi-aventis	*company*	Bis-thiazolium (SAR97276A/T3)	Phase II
sanofi-aventis	CNRS	Thiazolium back-up	Discovery
sanofi-aventis	*company*	Ferroquine (SSR97193)	Phase II
sanofi-aventis	*company*	Trioxaquine (SAR116242/PA1103)	Preclinical
sanofi-aventis	Palumed	Trioxaquine back-up	Discovery
sanofi-aventis	MMV, DNDi	Orthologue screening	Lead generation
Sigma-Tau	MMV	Eurartesim® (dihydroartemisinin & piperaquine)	Registration
Sigma-Tau	WRAIR, MMV, EDCTP	Intravenous artesunate (in children)	Phase II
Shin Poong	MMV, Iowa	Pyronaridine artesunate / Pyramax®	Registration
Vaccines			
Amgen	*company*	MSP1-42 and AMA-1 vaccine	Phase I
Crucell	MVI	AdVac®-based malaria vaccine	Phase I
Crucell	NIAID	AdVac®-based malaria vaccine	Phase I
GlaxoSmithKline	MVI	RTS,S/AS01E vaccine	Phase III
Merck & Co., Inc.	NYU	CSP synthetic peptide (NANP)6-OMPC conjugate	Discovery

Human African Trypanosomiasis (Sleeping Sickness)

Disease impact: Estimated 50-70,000 cases infected per year, but totals have surged in 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, only effective for stage 1 Gambiense form), Eflornithine (1991, effective for late-stage disease, less adverse effects than melarsoprol).

Access / Capacity Building: Programs by Bayer HealthCare, Novartis & sanofi-aventis,

Products approved since 2005: Nifurtimox oral & Eflornithine IV combination (sanofi-aventis & Bayer HealthCare / TDR, DNDi, Epicentre, MSF, STI) registered & included in WHO essential medicines list (May 2009)

Projects stopped since 2005: Compound screening (Pfizer/TDR).

Company	Partners	Project	Phase
GlaxoSmithKline	DNDi	Exploratory e-transport & cysteine protease inhib	Discovery
Merck & Co., Inc.	DNDi	Target screening and hit optimization	Discovery
Merck KGaA	TDR	Target screening and hit optimization	Discovery
Novartis	DNDi	Compound screening	Discovery
Pfizer	DNDi	Compound library screening	Discovery
sanofi-aventis	DNDi	Fexinidazole (antiprotozoal compound)	Preclinical
sanofi-aventis	MMV	Focused compound library screening	Discovery

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: The number of treatments has increased in the past decade, but there are numerous drawbacks to each of the treatments, such as difficulty to administer, length to treat, toxicity, cost, and increasing parasitic resistance to treatment: Pentavalent antimonials: toxic & increasingly ineffective due to resistance, 30-days of hospital-based parenteral treatment; Amphotericin B: dose-limiting toxicity, 15-20 days of hospital-based IV treatment; Paromomycin: registered in India, but efficacy in Africa not yet determined; Liposomal amphotericin B (AmBisome®): excellent, but IV, registration being broadened; Miltefosine: first orally available drug registered in India, but expensive and teratogenic (through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of developing countries as of 2007).

Access / Capacity Building: Programs by Gilead Sciences, Novartis & sanofi-aventis.

Products approved since 2005: Miltefosine / Impavido® (Zentaris – sold to Paladin Labs in 2008 – TDR), Paromomycin IM (iOWH).

Projects stopped since 2005: Compound screening (Pfizer/TDR).

Note: Gilead Sciences is donating AmBisome® to DNDi for clinical studies.

Company	Partners	Project	Phase
Abbott	DNDi	Compound screening	Lead identification
GlaxoSmithKline	*company*	Sitamaquine (WR6026)	Phase IIb
GlaxoSmithKline	DNDi	Exploratory e-transport & cysteine protease inhib	Discovery
Merck & Co., Inc.	DNDi	Target screening and hit optimization	Discovery
Novartis	DNDi	Compound screening and hit optimization	Discovery
Pfizer	DNDi	Compound library screening	Discovery
sanofi-aventis	MMV	Focused compound library screening	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 million infections per year, of which 250-500,000 are the potentially fatal hemorrhagic form.

Available therapies: None.

Access / Capacity Building: Novartis.

Products approved since 2005: None to date.

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

Company	Partners	Project	Phase
Novartis	*company*	NS5 polymerase	Discovery
Novartis	NTU, SIB, Sch, Brist, WC	NS5 methyltransferase	Discovery
Daiichi Sankyo	ICGEB, DBT	Compound library / Plant extract screening	Discovery
Toyama Chemical	*company*	RNA polymerase inhibitors	Preclinical
Vaccines			
GlaxoSmithKline	WRAIR, PDVI	Tetravalent live attenuated vaccine	Phase II
Merck & Co., Inc.	*company*	Tetravalent subunit	Preclinical
sanofi-aventis	PDVI	Tetravalent live attenuated chimeric vaccine	Phase IIb

Onchocerciasis (River Blindness)

Disease impact: Negligible directly attributable mortality, but extensive long-term morbidity. 37 million infected 99% of whom in sub-Saharan Africa.

Available therapies: Ivermectin allows safe & effective treatment.

Access / Capacity Building: Program by Merck & Co., Inc.

Products approved since 2005: None to date.

Projects stopped since 2005: Compound screening (Pfizer/TDR).

Company	Partners	Project	Phase
Pfizer	TDR	Moxidectin	Phase III

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, Novartis, Roche & sanofi-aventis.

Products approved since 2005: None to date.

Projects stopped since 2005: Compound screening (Pfizer/TDR).

Company	Partners	Project	Phase
Abbott	DNDi	Compound screening	Lead identification
GlaxoSmithKline	DNDi	Exploratory e-transport & cysteine protease inhib	Discovery
Merck & Co., Inc.	DNDi	Target screening and hit optimization	Discovery
Pfizer	DNDi	Compound library screening	Discovery
Merck & Co., Inc.	*company*	Posaconazole	Phase IIb
Novartis	DNDi	Compound screening and hit optimization	Discovery
Eisai	DNDi	E1224	Phase I

Schistosomiasis

Disease impact: Estimated 150,000 deaths per 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 (TDR), Compound screening (Pfizer/TDR).

Company	Partners	Project	Phase
Merck KGaA	TDR	Compound library screening	Discovery

Leprosy

Disease impact: Negligible direct mortality, extensive long-term morbidity, 212,802 new cases in 2008.

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, over 120 million have already been affected by it. Over 40 million of them are seriously incapacitated and disfigured by the disease.

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

Access / Capacity Building: Programs by GlaxoSmithKline & Merck & Co., Inc.

Products approved since 2005: None to date.

Projects stopped since 2005: None to date.

(ends)

(Updated: 4 November 2010)

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 George Institute), 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:

- Aeras - Aeras Global TB Vaccine Foundation
- BI - Broad Institute, USA
- BMRC - British Medical Research Council
- BPRC - The Netherlands Primate Centre
- Brist - University of Bristol, UK
- CNRS - Centre national de la recherche scientifique, France
- DBT - Department of Biotechnology, India
- DNDi - Drugs for Neglected Diseases initiative
- Drex - Drexel University, USA
- EDCTP - European & Developing Countries Clinical Trials Partnership
- Epicentre - Epicentre Biotechnologies
- GC11 - Consortium 11 of Grand Challenges in Global Health
- ICGEB - International Centre for Genetic Engineering and Biotechnology, India
- Iowa - Iowa University, USA
- iOWH - Institute for OneWorld Health
- Intercell - Intercell AG
- Inst. Pasteur - Institut Pasteur, France
- Liv - Liverpool University, UK
- LSHTM - London School of Hygiene and Tropical Medicine, UK
- MVI - Malaria Vaccine Initiative
- MMV - Medicines for Malaria Venture
- NIAID - National Institute of Allergy and Infectious Diseases, USA
- NIH - National Institutes of Health, USA
- NM4TB - New Medicine for Tuberculosis
- NTU - Nanyang Technology University, Singapore
- NYU - New York University, USA
- Palumed – Palumed SA
- PDVI - Pediatric Dengue Vaccine Initiative
- Sch - Schroedinger LLC
- SIB - Swiss Institute of Bioinformatics
- SSI - Statens Serum Institute
- STI - Swiss Tropical Institute
- TB A - Global Alliance for TB Drug Development
- TDR - Programme for Research and Training in Tropical Diseases (UNICEF, UNDP, World Bank & WHO
- UCL - University College London, UK
- UCSF - University of California, San Francisco, USA
- Iowa - University of Iowa, USA
- Penn - University of Pennsylvania, USA
- Wash – University of Washington, USA
- WC - Wadsworth Center, New York, USA
- WRAIR - Walter Reed Army Institute of Research, USA
- Well - Wellcome Trust, UK

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), 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 industry, including the biotech and vaccine sectors. Its members comprise 26 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), the IFPMA's Ethical Promotion online resource (www.ifpma.org/EthicalPromotion/) and its Developing World Health Partnerships Directory (www.ifpma.org/HealthPartnerships) help make the industry's activities more transparent. The IFPMA supports a wide range of WHO technical activities, notably those relating to medicine efficacy, quality and safety. 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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