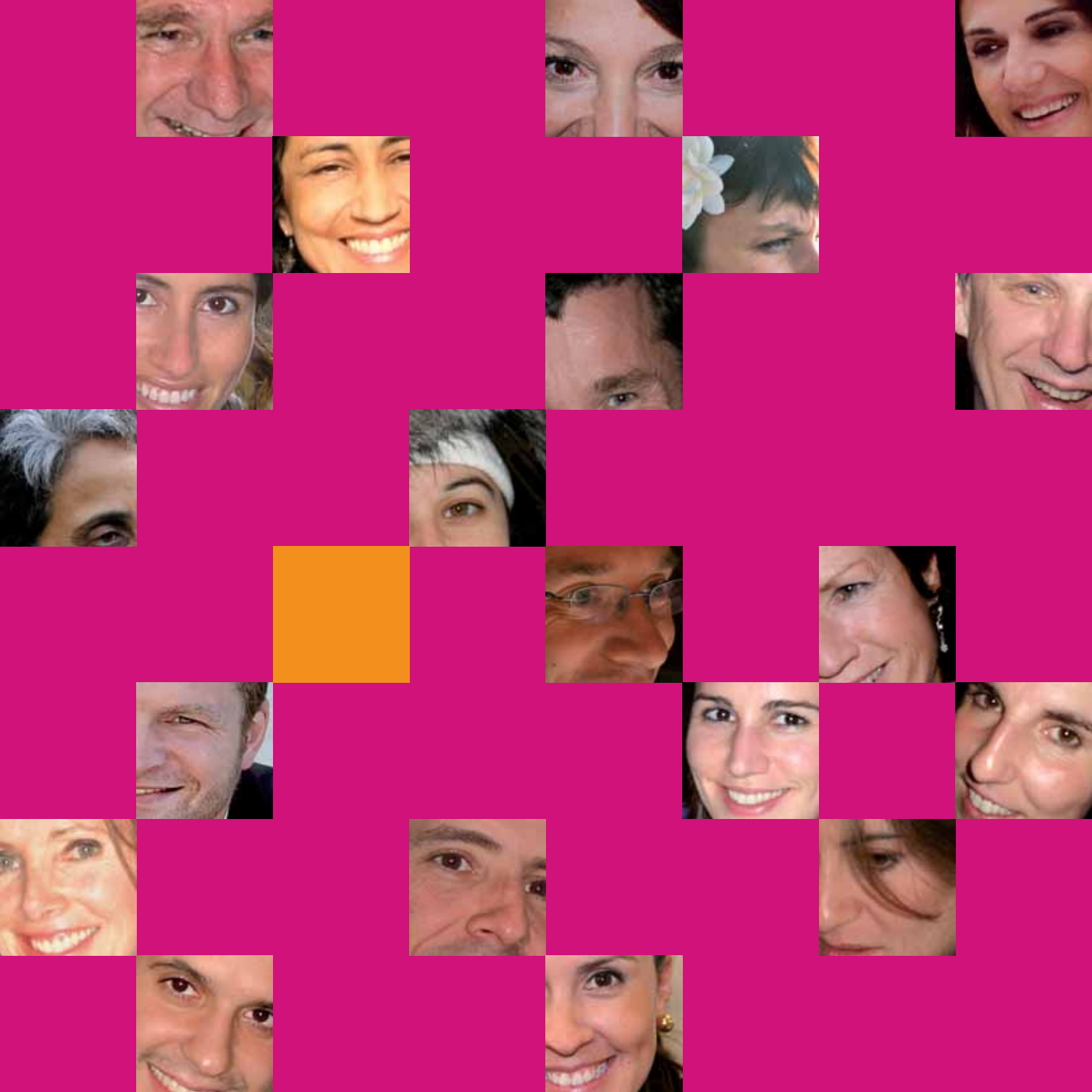
Medicines for Malaria Venture I Anniversary Book

Medicines for Malaria Venture

2009



“In MMV’s short 10 year history there have been numerous challenges that have shaped our development. These challenges – overcome in the true MMV spirit of tenacity and determination – are reflected by our achievements detailed in this book. In this brief period, MMV has blossomed into a successful and multi-skilled organization that has proved to be the leading PDP at the fore-front of the fight to defeat malaria.”

Lynda, Baroness Chalker of Wallasey, Chairman of the Board

“This year, we are proud to celebrate our 10th anniversary, and also the culmination of several years work with the launch of our first medicine – Coartem® Dispersible – especially formulated for children. As we move forward, our sights are now firmly set on the ultimate goal of malaria eradication. Alongside our partners we will con-tinue to discover and develop the next generation of affordable and effective medicines, and ensure their availability to vulnerable people the world over. The next decade will surely be as amazing as the last!”

Chris Hentschel, President and CEO

1999

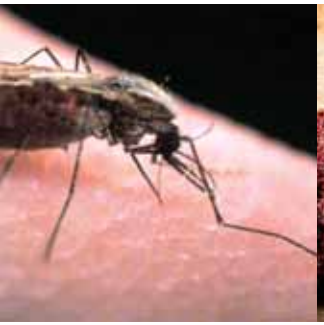
1st call for proposals
focuses on drug discovery to target *Plasmodium falciparum.*

Results
100 proposals: 6 approved

Portfolio status
6 projects: 3 exploratory, 3 discovery
0 projects terminated

Gro Harlem Brundtland officially launches MMV on 3 November under the umbrella of the WHO Special Program for Research and Training in Tropical Diseases (TDR).

MMV adopts the mission to *Discover and Develop* new effective and affordable antimalarials.



MMV sets out with initial seed finance of USD 4 million from the Governments of Switzerland, the UK (Department for International Development) and the Netherlands; The World Bank; and Rockefeller Foundation.

2000

Call for proposals
None

Results
N/A

Portfolio status
6 projects: 3 exploratory, 3 discovery
1 project terminated

MMV recruits its first team of two, including Dr Chris Hentschel, Chief Executive Officer. Initially housed in the TDR offices, MMV rapidly becomes an independent foundation under Swiss law, and takes up permanent residence in the International Center Cointrin, Geneva.

MMV establishes its first alliance with industry (Glaxo Wellcome) and academia (University of Bristol and London School of Hygiene and Tropical Medicine) to work on the enzyme lactate dehydrogenase. This new alliance is a huge turning point for MMV – opening up a new world of possibilities through access to the pharmaceutical industry's chemical and natural product libraries. Moreover, it lays the foundation for fruitful relationships with Pharma in the future.

Dame Bridget Ogilvie chairs MMV's first Board meeting and Dr Simon Campbell chairs the first Expert Scientific Advisory Committee meeting, both held in Geneva.

MMV adopts its first business plan, on the strength of which the Bill & Melinda Gates Foundation awards its first major donation of USD 25 million over 5 years.

ExxonMobil Foundation makes its first pledge.

2001

2nd call for proposals
focuses on development and discovery.

Results
84 proposals: 7 approved

Portfolio status
6 projects: 3 exploratory, 3 discovery
0 projects terminated

MMV Project of the Year 2001 goes to synthetic peroxides.

Partners: University of Nebraska/Monash University/Swiss Tropical Institute/Roche

These compounds hold the potential to provide a synthetic alternative to the artemisinin derivatives, and therefore a medicine free from the vagaries of agricultural production.

MMV holds its first Stakeholders' meeting at the Olympic Museum in Lausanne.

MMV discusses the idea of a novel concept – the mini-portfolio – with legal counsel (Stephen Whybrow, of Cameron McKenna). The mini-portfolio will allow the efficient distribution of resources within a group of discovery projects held by MMV and an industrial partner.

By the end of 2001 the rapidly expanding team comprises the CEO, Human Resources and Administration Manager, Chief Scientific Officer, Chief Financial Officer, Personal Assistant to the Management Team and a Delhi-based Director of International Operations.

2002

3rd call for proposals
focuses on discovery, development and natural products.

Results
106 proposals: 7 approved

Portfolio status
13 projects: 3 exploratory, 4 discovery, 5 preclinical, 1 clinical development
1 project terminated

MMV Project of the Year 2002 goes to protein farnesyltransferase inhibitors.

Partner: University of Washington

The project has progressed rapidly from lead identification to optimization.

TDR, MMV and Shin Poong Pharmaceutical, Co. Ltd. sign an agreement to develop pyronaridine-artesunate (Pyramax®), just as the potential combination therapy embarks on preclinical development.

The Wellcome Trust donates £1.8 million over 5 years. MMV is honoured to be the first PDP to receive a Wellcome Trust grant.

2003

Call for proposals
None

Results
N/A

Portfolio status
16 projects: 1 exploratory, 6 discovery, 4 preclinical, 5 development
3 projects terminated

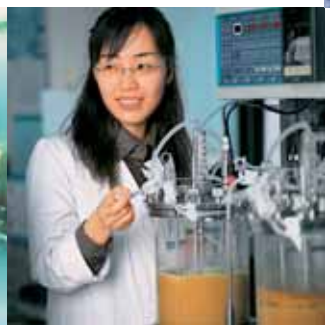
MMV Project of the Year 2003 goes to 4(1H)-pyridones.

Partner: GlaxoSmithKline

The project has moved rapidly – within 1 year – from discovery to development.

MMV and Novartis sign an agreement to make a paediatric formulation of Coartem® (artemether-lumefantrine) – Coartem® Dispersible.

The Gates Foundation pledges its continued support with USD 40 million over 5 years. This allows MMV to release the brakes previously applied to some projects and significantly accelerate others.



New 3D logo highlights the three components of MMV's mission: *Discover, Develop, Deliver.*

MMV updates its business plan to incorporate the need to ensure access to products emerging from the project pipeline.

MMV and GSK sign the first mini-portfolio agreement, comprising four promising discovery projects.


Medicines for Malaria Venture
awing Competition

2004

4th call for proposals
focuses on populating the portfolio with promising projects.

Results
81 proposals: 5 approved

Portfolio status
21 projects: 3 exploratory, 8 discovery, 4 preclinical, 6 development
2 projects terminated

MMV Project of the Year 2004 goes to the falcipain project focusing on cysteine proteases.

Partner: University of California San Francisco

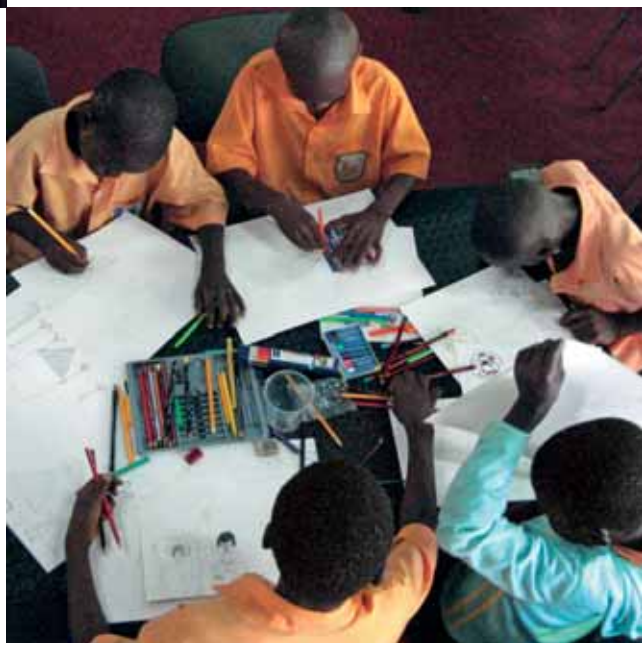
The project team has made impressive progress.

First children's drawing contest takes place at the first ever Stakeholders' meeting to be held in an African capital – Maputo, Mozambique.

President Joacquim Chissano of Mozambique delivers a poignant keynote speech at the Stakeholders' meeting in Maputo, stating: *"One day our children will be born free from malaria. With our determination and perseverance, that future is attainable".*

USAID and BHP Billiton pledge their support to MMV.

MMV joins hands with Sigma-Tau Industrie Farmaceutiche Reunite, Oxford University and Holley Pharmaceutical Co. Inc. to develop a high-quality medicine to treat uncomplicated malaria – dihdroartemisinin-piperaquine (Eurartesim™).



and develop a new antimalarial ready to be delivered to those in need

2005

Call for proposals
None

Results
N/A

Portfolio status
21 projects: 12 discovery, 2 preclinical, 7 clinical
3 projects terminated

MMV Project of Year 2005 goes to pyronaridine artesunate (Pyramax®).

Partner: Shing Poong Pharmaceutical Co. Ltd

The project progressed rapidly from Phase I into Phase II of the clinical development trials.

The R&D agenda continues to evolve, addressing other aspects of malaria control, for example, prophylaxis, *Plasmodium vivax*, severe malaria and transmission blocking drugs. The pipeline shows signs of blossoming, with three projects in the final phase of clinical development.

2005 is MMV's 5th anniversary. Serendipitously, in Roman numerals the year 2005 is written as MMV.

Significant new funding comes in from the Wellcome Trust (£10 million over 5 years), UK DFID (£10 million over 5 years) and BMGF (USD 100 million over 5 years).

A Burkina Faso clinical trial site is the first to enroll a patient for a clinical development project and first to receive MMV support for capacity building.

An independent review of MMV by major donors and Stakeholders states, *"MMV has made tremendous progress, clearly ahead of its predicted milestones, towards achieving its goals. It has successfully mobilized academic institutions and pharmaceutical companies in highly productive partnerships."*

The Moran *et al* report, 'The New Landscape of Neglected Disease Drug Development', funded by the Wellcome Trust, positions MMV as a leading public–private partnership.

Discover, develop, deliver: it takes between 13–15 years to discover

► Lead identification

Time: 1–2 years

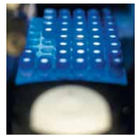
The development of an entirely new medicine begins with a broad array of compounds, each tested for their potential antimalarial activity via a range of screening methods, such as high-throughput screening. Compounds that demonstrate antimalarial activity are initially designated as 'hits'. The antimalarial activity and drug-like quality of these hits must be improved and confirmed through chemical manipulations and repeated *in vitro* and *in vivo* studies, in order to fit the required profile. Only then can the compounds be upgraded from 'hit' to 'lead' status.

Combining compound libraries and drug discovery expertise from both academic and industrial partners, one of MMV's lead identification projects is led by scientists at the University of South Florida. The team is undertaking a huge screening effort in search of the next elusive compounds to be designated with "hit" status. The project utilizes the chemical diversity of natural product extracts from Antarctica to Southeast Asia as the primary source of compounds. This strategy maximizes the potential of discovering novel chemistry – directly from nature.

► Lead optimization

Time: 2–4 years

Lead compounds – once identified – are optimized until they have the ideal properties to be a drug candidate. Compounds must not only demonstrate antimalarial activity but must have pharmacological properties in line with our target product profiles. Further chemical modifications are made to improve the lead molecule's drug-like properties, including its ability to be appropriately absorbed, distributed, metabolized and excreted by the body – whilst maintaining or even improving it's antimalarial activity.

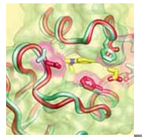


Demonstrating the unique power of public–private partnerships in drug discovery, one of our partners, Novartis, has completed an intense screening effort of both their synthetic and natural product compound libraries. As one of the largest pharmaceutical companies in the world, Novartis has the capacity required to power a project through the entire drug discovery and development process. From this latest screening effort, around 6,000 hits were identified and confirmed. To date, two of these compounds have progressed through lead identification and been optimized. These two successful compounds are now undergoing evaluation as potential drug candidates.

► Preclinical development and candidate selection

Time: 1.5 years

A drug candidate's predicted safety in man is determined via *in vitro* and *in vivo* pre-clinical tests, which assess antimalarial activity and toxicology, as well as the feasibility of manufacturing at low cost. These data form the basis of the decision to start clinical trials in man.



One of our preclinical projects, from a collaboration originally led by scientists at BIOTEC Thailand, aims to develop a curative antimalarial drug active against the drug-resistant strains of malaria currently emerging in Southeast Asia and around the world. The project team is targeting the malaria parasite's dihydrofolate reductase (DHFR) enzyme in its naturally occurring and resistant forms. Blocking the activity of this enzyme compromises the parasite's ability to proliferate, thereby leading to its eventual demise. The lead DHFR-targeting compound from the project is now being prepared for future clinical studies.

► Clinical Phase I

Time: 1 year

This is the first opportunity to examine the safety of a potential new medicine in man. A small group of healthy human volunteers receive an initial dose of the drug, which has been deemed to be safe in preclinical studies. Provided no unexpected adverse events occur, the dose is then escalated, at graded intervals, up to a level at which efficacy can be expected. All the while, patients are continuously monitored in order to detect potential adverse events at the earliest opportunity.

Fully synthetic peroxides provide an exciting prospect as future antimalarials since, by definition, they are not reliant on the vagaries of agriculture for their production. In concert with the University of Nebraska, Monash University, and the Swiss Tropical Institute, MMV has supported this project since its inception. Although, this chemical class holds the potential to provide a fast-acting and effective antimalarial, selected candidates also have a relatively long half life and thus could provide a reduced treatment regimen.

▼ Clinical Phase II

Time: 1–2 years

Once the drug has been established to be safe in man at a potentially effective dose, it is ready to be tested for efficacy in addition to safety in malaria patients. The aim of this stage is to attain 'proof of concept', which provides the first evidence that the treatment is efficacious in humans. Furthermore, it allows for the determination of precisely what the optimum treatment and non-toxic dose should be. Only then can the drug be tested in a larger Phase III trial.

Artemisone, a potent artemisinin derivative, identified by the Hong Kong University of Science and Technology, is one example from the MMV portfolio of a project in Phase II trials. It is hoped that artemisone will prove to be a vital tool to treat patients who have exhibited malaria resistant to current drug therapy, such as those recorded in Cambodia.

► Clinical Phase III

Time: 3 years

The definitive test of a drug's safety and efficacy occurs in the form of a randomized, controlled Phase III trial in a large patient group. The new medicine is compared head-to-head with the best currently available treatment.

Two new medicines that have recently completed successful Phase III trials include: Eurartesim™ (dihydroartemisinin-piperaquine) developed in partnership with Sigma-Tau Pharmaceuticals and Pyramax® (pyronaridine-artesunate) developed with Shing Poong Pharmaceutical Co. Ltd. Eurartesim has now been submitted for regulatory approval. It provides a once-a-day therapy and is the best ACT currently in development to provide protection against new infections. Pyramax is also exciting, as it has been proven to be highly effective against both P. falciparum and the blood stages of P. vivax malaria.

► Registration and launch

Time: 1 year

Once a drug has been proven to be safe and efficacious in Phase III trials, the preclinical, clinical and manufacturing data are combined and submitted for stringent regulatory approval. All MMV-supported medicines are submitted for the most rigorous regulatory approval in addition to WHO prequalification. This ensures that all our medicines meet the highest national and international standards of quality. The new medicine can then be marketed and sold in the country or countries that have approved it.

Coartem® Dispersible (artemether-lumefantrine) was developed in partnership with Novartis specifically for children – the most vulnerable victims of malaria. The new medicine was approved by Swissmedic in December 2008 and launched in February 2009. Coartem Dispersible is the culmination of over 4 years of dedicated work and is a huge MMV success story.

2006

5th Call for proposals
focuses on discovery and natural products.

Results
105 proposals: 7 approved

Portfolio status
39 projects: 29 discovery, 3 preclinical, 7 clinical development
7 projects terminated

MMV Project of the Year 2006 goes to next generation OZ (synthetic peroxide).

Partners: University of Nebraska; Monash University; Swiss Tropical Institute and Roche

The synthetic peroxides hold the promise of generating a fast-acting antimalarial of the future.

Former Irish President Mary Robinson announces a donation of €9 million over 3 years from the Irish government at the Stakeholders' meeting in Zambia.

The newly created Access and Delivery department transforms MMV into a 3D organization – *Discover, Develop, Deliver*. The Access and Delivery Advisory Committee (ADAC) is established.

Lynda, Baroness Chalker of Wallasey succeeds Dame Bridget Ogilvie as Board Chairperson.

Dutch Government funds enable the refurbishment of an old research facility in Gabon into a state-of-the-art clinical trial unit (Albert Schweitzer Clinic) to conduct safety and efficacy studies for antimalarial drugs, particularly in paediatric patients.

MMV establishes two new mini-portfolios, one with Novartis Institute for Tropical Disease, and the other with Broad Institute of MIT/Harvard & Genzyme Corporation.

2007

Call for proposals
None

Results
N/A

Portfolio status
39 projects: 29 discovery, 3 preclinical, 7 clinical development
5 projects terminated

MMV Project of the Year 2007 goes to Queensland natural products.

Partner: The Nature Bank at Eskitis Institute, Griffith University

This project combines the chemical diversity of natural products with the technological power of high-throughput screening in the search for the next generation of antimalarials.

The Pivotal Phase III study of dihydroartemisinin-piperaquine (Eurartesim™), with the contracted service of MDS Pharma Services, wins the Good Clinical Practice Journal (GCPj) Award, honouring excellence in clinical research.

Regulatory dossier for Coartem® Dispersible is submitted to Swissmedic.

MMV completes two major Phase III studies – Eurartesim™ and Pyramax®.

President Museveni of Uganda inaugurates the Stakeholders' meeting in Kampala, Uganda.

MMV takes to the road in Africa (Kenya, Mozambique, Tanzania, Uganda, Togo and Benin) for 5 weeks, drawing attention to the new products soon to emerge from the portfolio.

Access Symposium in Uganda sparks keen interest in the critical need for improved access to effective antimalarial treatment in Africa.

The Gates Foundation donates an additional USD 37 million over 2 years and the NIH awards its first donation of USD 5.6 million over 5 years.

The World Bank Independent Global Program Review considers MMV 'a successful product development public–private partnership.'

2008

6th Call for proposals
focuses on products for uncomplicated malaria and prophylaxis.

Results
166 proposals: 9 approved

Portfolio status
50 projects: 37 discovery, 6 preclinical, 6 development (2 in late-stage clinical development, 1 registered)
4 projects terminated

MMV Project of the Year 2008 and first-ever MMV Drug Innovation Award goes to Coartem® Dispersible.

Partner: Novartis

Coartem Dispersible *is the first MMV-supported medicine to be approved by a stringent regulatory authority.*

Coartem® Dispersible is approved by Swissmedic – a stringent regulatory authority.

Our fourth artemisinin combination therapy (ACT), Dacart™ (GSK) completes its Phase III studies, but is discontinued due to side effects of haemolysis in patients with G6PD-deficiency. Nonetheless, the studies were useful in terms of the lessons they provided.

Prime Minister of Uganda, Rt. Honorable Apolo Nsibambi launches the MMV–MOH pilot to study the effects of providing a heavily subsidised ACT through private channels in four rural districts of Uganda. This work aims to inform the Affordable Medicines Facility – malaria (AMFm).

MMV launches revised 5-year business plan with a new vision to target eradication.

Spanish government becomes MMV's 6th public sector donor with a grant of €3 million for 2008.

2009

7th Call for proposals
focuses on powering the malaria eradication agenda; projects targeting the liver stage and gametocytes are requested.

Results
70 proposals; 6 selected for full application

Portfolio status
52 projects by the 2nd quarter: 40 discovery, 4 preclinical, 8 clinical development

MMV receives its fifth and largest grant from the Gates Foundation of USD 115 million in addition to new funding from DFID of USD 30 million – both to support MMV over 5 years. This renewed support demonstrates both the Gates Foundation and DFID's continued belief in MMV's ability to succeed.

Coartem® Dispersible is launched in three African countries as well as Switzerland. The regulatory dossier for Eurartesim™ is submitted to EMEA, the European stringent regulatory authority. The dossier for Pyramax® is being prepared for submission in 2010.

Senegal's Minister of Health, Mme Therese Coumba Diop, offers her country's continued support to MMV's mission at the Stakeholders' meeting in Dakar.

MMV continues to work towards eradication by supporting the first cellular assay to screen compounds for activity against the hypnozoite of *P. vivax*.

In MMV's 10th year, the dedicated, multi-skilled team of two has blossomed to 40.

Medicines for Malaria Venture (MMV) is a not-for-profit organization dedicated to reducing the burden of malaria in disease-endemic countries by discovering, developing and delivering new affordable antimalarial drugs through effective public–private partnerships. Our vision is a world in which these innovative medicines will cure and protect the vulnerable populations at risk from malaria, and help to ultimately eradicate this terrible disease.

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Medicines for Malaria Venture

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Dr Simon Sargent (Glaxo Wellcome)
Sir Richard Sykes (Glaxo Wellcome)
Prof. Marcel Tanner (Swiss Tropical Institute)

MMV has received funding from the following entities (in addition to numerous individuals)

BHP Billiton
Bill and Melinda Gates Foundation
Exxon Mobil Corporation
Irish Aid
National Institutes of Health
Netherlands Minister for Development Cooperation
Rockefeller Foundation
Roll Back Malaria Partnership
Spanish Agency for International Cooperation for Development
Swiss Agency for Development and Cooperation
United Kingdom Department for International Development
United States Agency for International Development
Wellcome Trust
World Bank

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Thank you