

Annual Report 2006



Medicines for Malaria Venture



Medicines for Malaria Venture (MMV) is a nonprofit 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.

Medicines for Malaria Venture (MMV) has received funding and support from the following organizations:

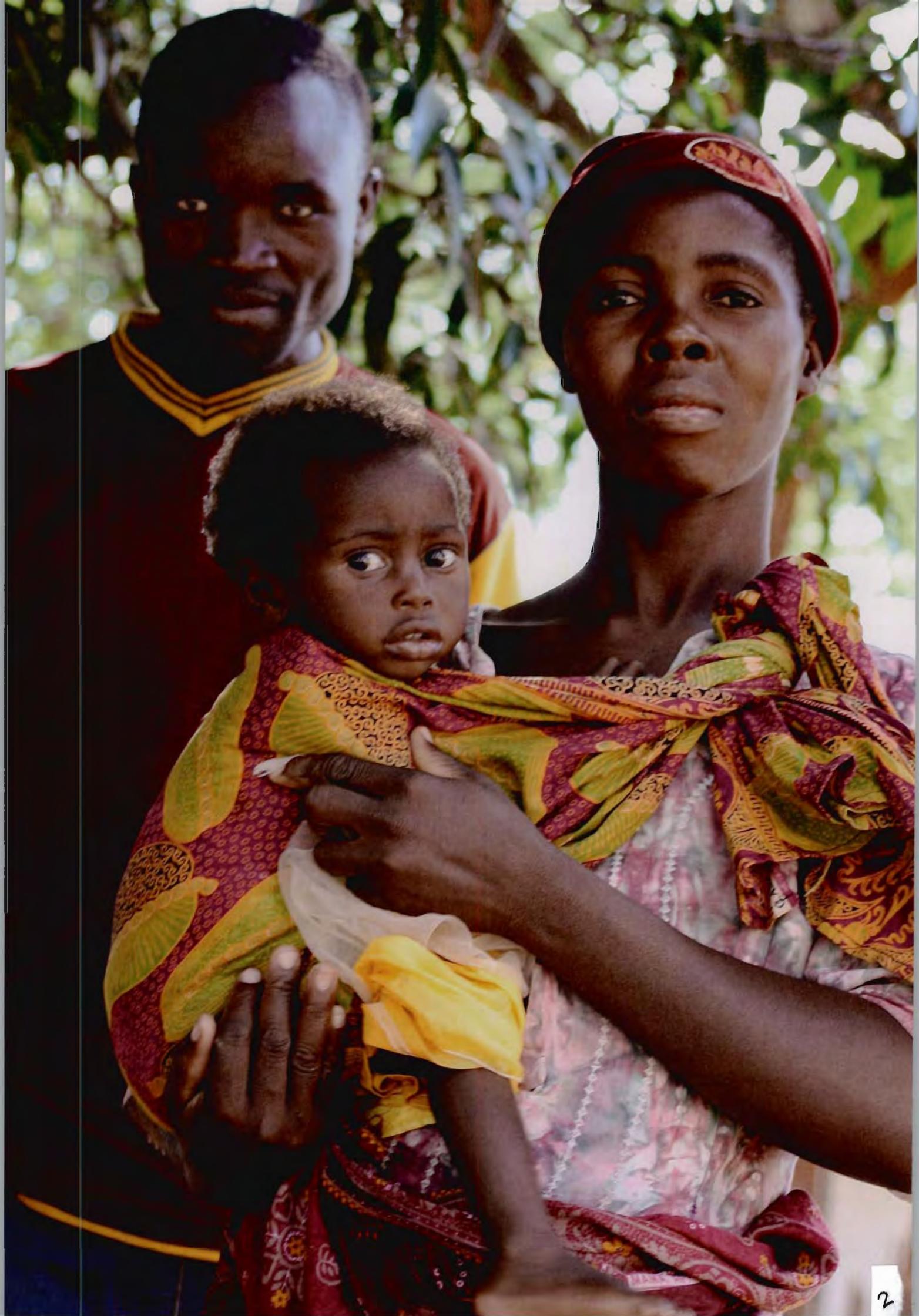
▶ BHP Billiton ▶ Bill and Melinda Gates Foundation ▶ ExxonMobil ▶ Global Forum for Health Research ▶ Google, Inc. ▶ International Federation of Pharmaceutical Manufacturers & Associations ▶ Irish Aid ▶ Netherlands Minister for Development Cooperation ▶ Rockefeller Foundation ▶ Roll Back Malaria Partnership ▶ Swiss Agency for Development and Cooperation ▶ UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) ▶ United Kingdom Department for International Development (DFID) ▶ United States Agency for International Development (USAID) ▶ Wellcome Trust ▶ World Bank ▶ World Health Organization

MMV is also very grateful for the support it has received from a number of private individuals.



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Message from the President & CEO and the Chairman

2006 has been a year of many important transitions for the Medicines for Malaria Venture (MMV). Movement in and out of MMV's research and development (R&D) portfolio, with considerable project advancement, comprises much of the science section of this report. The crucial 'portfolio management' activity that helps makes us a highly cost-effective and productive R&D organization is well illustrated. The other principal factor that makes us operate efficiently, the strength of the public-private partnership model, is also well exemplified. Partnerships like ours are now the norm rather than the exception in global efforts to develop products for diseases that mainly affect the developing world.

The success of this operational model has brought us new donors and stakeholders. Their conviction that our work is a key element in the eventual defeat of malaria has propelled us into becoming a '3D' organization by adding a *deliver* component onto our well established *discover and develop* core. Following wide consultation we have now increased our efforts to ensure that the drugs that should soon emerge from our pipeline will reach those in need quickly and at an affordable cost.

We can take justifiable pride in our portfolio, built with our many partners since 2000, and our management methods that seek to continuously increase portfolio value. Rigorous selection processes are coupled with generous support of the most promising candidates and quick termination of the less successful ones. This is not easy or popular, but essential if our growing R&D expenditure is to be aligned effectively with our highly-focused mission.

By the end of 2006, in accordance with a number of recommendations from our Expert Scientific Advisory Committee (ESAC), we will have added a number of new preclinical projects, re-balanced the array of development projects, and included a new 'mini-portfolio' with the Novartis Institute of Tropical Diseases (NITD) in Singapore. The latter is notable because, for the first time, we and our pharmaceutical partner, Novartis, are specifically targeting the less deadly but equally debilitating *Plasmodium vivax* malaria, found mostly in Asia and South America.

Apart from these significant changes, activities at the discovery end of our portfolio were further boosted by a traditional Call for Proposals that proved highly successful, and illustrated the innovative potential of academia and the biotechnology industry.

Of 107 technically valid applications, seven were chosen to be included in the portfolio, including a recent agreement with the Genzyme Corporation and the Broad Institute (affiliated to MIT and Harvard), all based in Boston, USA.

At the development end of the value chain, several of our drugs went into the decisive stage of Phase III clinical trials. Development highlights now include four new artemisinin-based combination therapies (ACTs) in Phase III clinical trials in Africa and Asia. Regulatory filing of these with a stringent regulatory authority is expected between mid-2007 and 2008. Over 3,600 patients were enrolled in these and other clinical studies in 40 research centres distributed over 20 countries.

This is certainly the largest and most diverse portfolio of anti-malarial drugs being researched and developed in history. The challenge for us will be its continued successful management in terms of science, budgets, and the execution of the legal agreements that apportion rights and obligations to us and our many partners. Indeed, MMV is much better understood today as a global network of contractually-tied partners than as a Geneva-based entity. We now benefit from the support of around 80 partners in 34 countries; benefit achieved through thorough due-diligence, stringent oversight, transparency in decision making, and hard work.

Those who have read earlier annual reports or have attended our annual meeting of stakeholders know that we often assert that despite the growing complexity of operating with many partners, cost-effectiveness and high productivity are characteristics of MMV. But what is the evidence for this? Unlike commercial operations, there are no universally accepted external metrics or templates for comparison. However, a recent study conducted by the London-based Office of Health Economics (OHE) adds

We can be the generation that defeats malaria and sets the timetable for its ultimate eradication.



Dr Christopher Hentschel, President & CEO
Lynda, Baroness Chalker of Wallasey, Chairman

further weight to this assertion. It illustrates that a significant health impact for a very reasonable investment is the likely outcome of MMV's work.

The OHE study¹, conducted on behalf of the Product Development Partnerships Funders' Group, was designed to help inform global public health donors on investment strategies. It used adjusted industry experience and metrics to approximate the cost of producing products from six PDPs (product development partnerships) including MMV, and then, using estimates of uptake and impact of the resulting products, calculated indicative dollars invested per DALY (disability adjusted life year) averted (a measure of the cost-effectiveness in reducing the impact of a disease). There are many caveats regarding the accuracy of this type of calculation, based as it is on many assumptions, but the results are, nevertheless, quite striking. For vaccine portfolios, estimated R&D cost per DALY averted ranged from USD 12 to USD 107 while for drugs, it ranged from USD 12 to USD 17. Both these figures are in the good-to-excellent range when compared with numerous published cost-effectiveness studies for existing global public health programmes.

The OHE findings, though not focused on any particular disease, also inform our belief that, amongst 'neglected diseases', malaria is likely to be an early success for the power of science and innovation to make a real public health difference. Malaria only occurs because of the complex underlying life-cycle of the malaria parasite, which leads to four recognized control and product innovation strategies: products for controlling vectors (insecticides, larvaecides, bednets), products for diagnosing, treating or preventing the disease (diagnostics and drugs), products that prevent parasite reproduction and transmission (gametocidal drugs), and products aimed at enhancing or producing natural immunity to the parasite (none today, but future vaccines). These four approaches are in theory highly synergistic when used together or even in partial combinations. In practice, the benefits of a comprehensive and integrated approach to malaria treatment and control are no longer debated or debatable. Nor is there much remaining debate between the need for product innovations and the scale-up and use of the best tools we have today. By any measure there is still a

mountain to climb in both areas, and the broader community interested in controlling, indeed eventually eliminating, malaria should collectively shore up the enormous resources needed to win the battle against the world's deadliest parasite.

The good news is that the tackling of diseases inextricably linked to poverty in the developing world is now gaining increasing political momentum. Some G8 nations have committed to spending much more on global health and poverty alleviation by 2010, with further increases by 2015. Individual initiatives such as the US President's Malaria Initiative, and the recent commitment from the President of China to fight malaria in Africa; and WHO, Global Fund, World Bank and UNICEF commitments, illustrate that defeating malaria has become a significant factor in global development diplomacy. Many of these remain largely good intentions that are being slowly followed by real resources – we are still far short of what is really needed to defeat malaria. However, it would be churlish not to rejoice at the positive changes being wrought. We are arguably on the brink of a real breakthrough, both in innovation and in being able to deliver the needed interventions to prevent and treat malaria. Malaria control success stories historically limited to Asia, e.g., Vietnam, are now being seen in Africa, too, and are occurring rapidly, as in the case of Zanzibar. Furthermore, this year, for the first time in decades, the concept of 'eradication' as a long-term goal has been used by politicians and global health leaders without causing understandable anguish that they are inevitably setting sights too high. Will this current positive momentum be a real tipping point or just another case of potential unfulfilled?

Our view is that provided we all work together, eschewing narrow interests, doctrines, and competition, we can make something remarkable happen – we can be the generation that defeats malaria and sets the timetable for its ultimate eradication. President John F. Kennedy, a malaria survivor who strongly backed the failed eradication plan of the 1960s, ended one of his memorable 1962 speeches with these words: *"Many years ago the great British explorer George Mallory, who was to die on Mount Everest, was asked why did he want to climb it. He said, "Because it is there." Well, space is there, and we're going to climb it, and the moon and the planets are there, and new hopes for knowledge and peace are there."*

Today, President Kennedy might have been surprised to find that 45 years later most of the challenges he recognized have been overcome – but malaria is still there. The time to set a realistic timetable to finish the job he and his contemporaries started is long overdue.

¹ Case study, Donor Investment Choices: Modelling the value for money of investing in PD PPPs as compared to other health care and non-health care interventions, OHE Consulting, November 2006.



Beyond Phase III: Access becomes a priority

Achievements in 2006

- ▶ Launched MMV access activities at MMV Stakeholders' Meeting in Zambia in May
- ▶ Developed MMV access strategy and work plan
- ▶ Initiated access and launch strategies with commercial partners for three late-stage products
- ▶ Established ADAC – MMV's Access and Delivery Advisory Committee (80% of members from malaria-endemic areas; key competencies represented)
- ▶ Initiated preliminary market information gathering, planned for longer term market analysis work, identified options to improve demand forecasting
- ▶ Developed communications materials on MMV's access activities (including new section on MMV website and information papers for stakeholders)

MMV is now a 3D organization working to "Discover, Develop, Deliver."

Win Gutteridge, Chairperson
MMV Expert Scientific Advisory Committee,
December 2006

Why focus on access?

Medicines for Malaria Venture (MMV) was initially established in 1999 to address the absence of new antimalarial medicines, largely due to the failure of the traditional market-led model of R&D investment. By early 2006, the promise of new antimalarials was close to fulfillment, with four products in the MMV portfolio moving towards Phase III clinical trials.

This unprecedented situation led to the recognition that the development of high quality new antimalarial drugs, principally the artemisinin-based combination therapies (ACTs), is not in itself enough. Widespread, affordable access to the drugs is also a critical factor that requires urgent attention.

However, launching new products into the market in malaria-endemic countries involves a number of risks: the market is dynamic, largely unmapped, and faces a number of bottlenecks in supply, de-

mand, market structures, procurement systems and financing. Although many of these factors cannot be controlled by MMV, their effect on the uptake of products needs to be carefully considered.

In most cases there is a significant time lag between the registration of a product and its widespread adoption, as experienced by Novartis in their scaling up of Coartem[®], which took over five years. New ACTs would benefit from the lessons learned by Novartis. Figure 1 shows an overview of key activities and an estimated timeline, reducing the gap between registration and widespread adoption of new ACTs.

Current efforts to correct this critical lack of access have been applied mainly through the public sector, largely financed through the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). However, the private sector also plays a vital role in treating malaria, providing between 15% and 80% of treatment,

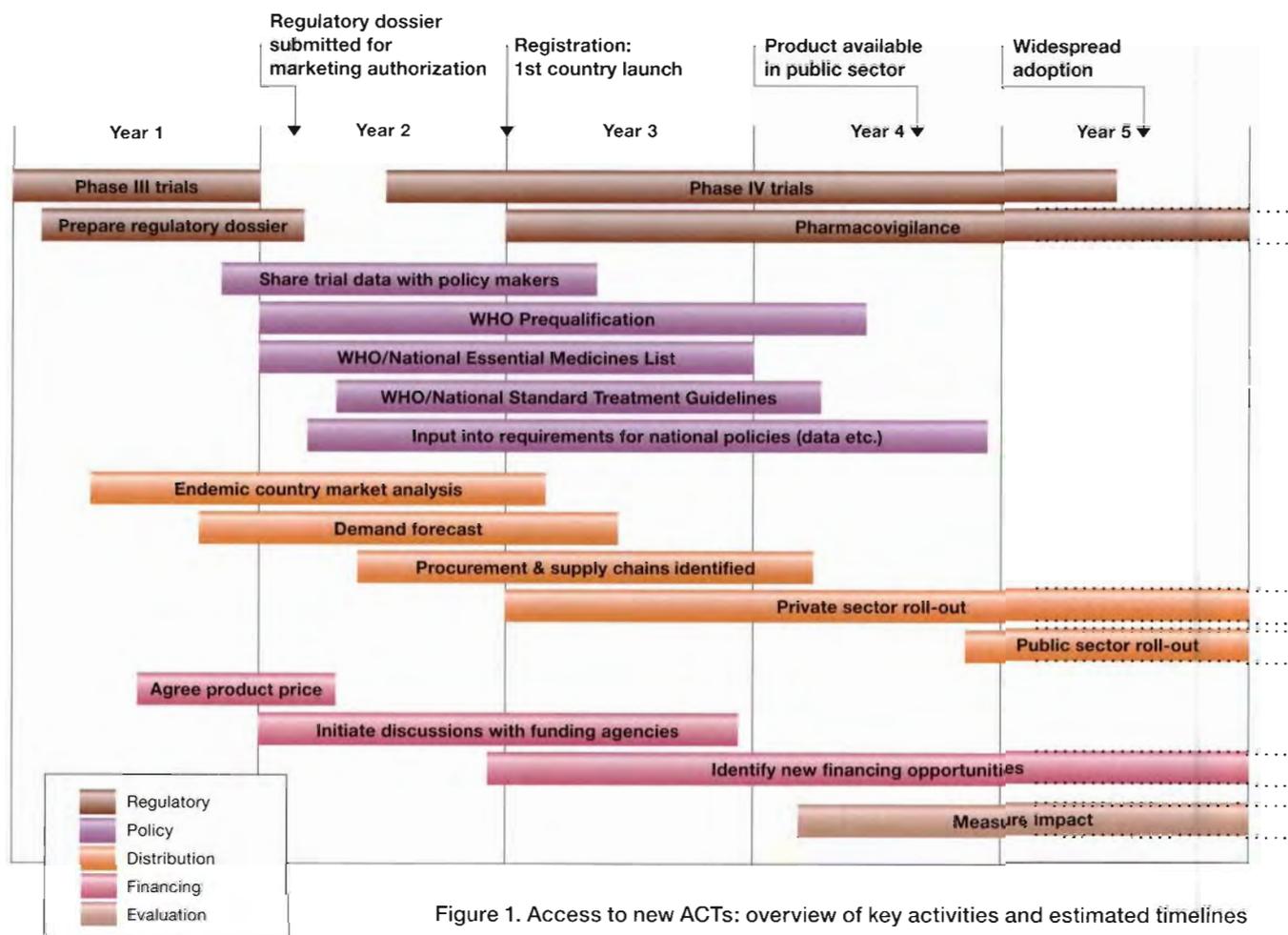


Figure 1. Access to new ACTs: overview of key activities and estimated timelines

depending on the country. The choice of product purchased through this sector is driven largely by cost and availability. This encourages the continued use of ineffective treatment (chloroquine and sulfadoxine-pyrimethamine or SP being the main drugs of choice in the private sector).

The failure to provide access to more effective drugs is clearly evident, as the poor turn to low efficacy drugs, provided through often unregulated local drug outlets. Unfortunately, no concerted effort is being made to address this situation in the private sector.

A coordinated strategy is urgently needed to deliver highly subsidized ACTs through all appropriate distribution outlets. MMV's involvement in access stems from this recognition and the need to ensure that products from the MMV pipeline are launched in a manner that supports availability, affordability and uptake. In particular, this involves meet-

ing the specific needs of MMV's target population with regard to the 'marketing mix', (combination of product, place, promotion and price), especially with regard to price and distribution outlets. MMV recognizes the limitations in what it can achieve in this respect, and will thus focus its efforts on activities where MMV can have greatest impact, based on its areas of competence.

2006: Defining the focus for MMV's access activities

Global access is a new area to MMV. The recommendation by its Board in October 2005, as well as stakeholder encouragement, led MMV to build on the strength of its R&D activities and to expand its mandate to encompass 'delivery'.

The goal of the MMV access activities is to help ensure rapid uptake of products from the MMV pipeline. Products should be widely available in both the public and

private sectors, at affordable prices, with adequate information to ensure appropriate use.

The introduction of new antimalarial drugs on the market within the next two years will present additional choices for the treatment of malaria. Decision makers will need a framework to objectively assess the relative value of each therapeutic choice, and its appropriateness within the local context in terms of resistance, distribution outlets, and level of familiarity with current first-line treatment.

The availability of new tools also provides the opportunity to align the choice of drugs to the ability of the service provider in terms of ease of use, tolerability and other key considerations. This normative function of policy guidance is clearly within the remit of the World Health Organization (WHO). There is nonetheless the need for a consultative process with key stakeholders in defining the evidence base required to guide the decisions,



including the collection of data from Phase IV studies.

Within this context the MMV access strategy has three key objectives:

Shaping the debate

ACTs are a relatively new class of drugs, and are identified by the World Health Organization as the class of drug of choice for treatment of uncomplicated malaria. Further data would be helpful to allow WHO and national decision makers to take informed decisions for continued expansion of the use of ACTs.

MMV will work with partners to frame the questions and gather the data required to expand uptake of ACTs, through the following actions:

- ▀ clarifying the decision-making framework for new product adoption
- ▀ convening a meeting to identify Phase IV research requirements
- ▀ aiming to obtain consensus requirements to expand availability of ACTs in lower level distribution outlets
- ▀ sharing best practices on distribution of ACTs

Faster time to product uptake

Moving new ACTs through the policy and regulatory stages to allow for faster uptake requires a clear understanding of the structure and dynamics of the antimalarial drugs market, as well as key influencing factors in product adoption. MMV will therefore focus activities around the following:

- ▀ better understanding of dynamics of the antimalarial drugs market and country situation
- ▀ understanding the barriers to uptake
- ▀ mapping the critical pathway for early product adoption
- ▀ generating interest in the new ACTs among key stakeholders
- ▀ developing product-specific access plans for drugs within the MMV portfolio

Achieving health impact at the country level

The use of high quality ACTs is mainly limited to the public sector at present. In order to determine optimal solutions for allowing wider availability, MMV will undertake country-level activities to identify best practices in ensuring wider access to ACTs. It will provide the "proof of principle" of improved access resulting in health impact.

MMV will build on the partnership model that it uses in R&D to collaborate with partners at the national and global level.

With this in mind, the focus of MMV's access work will include clarification of areas in which MMV will play a lead role, a collaborative role with other access initiatives, or a role as an interested observer. This final category will include aspects which will have an impact on MMV's ability to achieve results on access issues, but for which it cannot take a lead role (e.g. strengthening health systems); thus MMV will limit its engagement to highlighting the impact of these issues in order to encourage a response from appropriate actors.

2006: Year of transition

It is essential that the right foundations are laid in order to maximize the effectiveness of MMV's future access work. In this respect, 2006 was a year of critical learning and transition as the requirements and opportunities for access were assessed. These requirements include new commitments in staff, resources, and planning.

The first half of 2006 focused on:

- ▀ raising awareness of MMV's new focus on access, and achieving buy-in from key partners through the following activities: a special access meeting at the MMV Stakeholders' Meeting in Zambia; discussion with new donors on access work (Ireland and the Netherlands); reaching out to key stakeholders; and identifying potential partners to contribute technical expertise.



- ▶ working with MMV late-stage product partner companies to clarify and support access expectations, renegotiate contracts to include post-authorization collaborations, and initiate thinking on product launch strategies. Partners agreed that the major objective is to achieve widespread availability of affordable products and promote their rational use.

- ▶ developing an initial work plan, identifying and recruiting staff.

- ▶ establishing the MMV Access and Delivery Advisory Committee (ADAC).

- ▶ assessing information gaps and responses, through identification of market analysis work required, understanding of future market dynamics, clarification of pricing and subsidy.

The last few months of 2006 offered the opportunity to take stock of the developments to date on the access programme and to consolidate activities. Work continued to focus on refining the MMV access strategy, revising the multi-annual work plan, initiating specific market analysis work, developing concepts on 'proof of principle' for launching new antimalarial drugs, working with partner companies on product-specific access narratives, and developing information platforms to share MMV portfolio information with malaria-endemic country stakeholders.

Access and Delivery Advisory Committee (ADAC)

In line with advice provided by MMV's Expert Scientific Advisory Committee (ESAC), MMV established the Access and Delivery Advisory Committee, which met for the first time in July 2006. The committee is composed of 14 members. Eleven of the current ADAC members are from malaria-endemic countries.

The role of ADAC is to:

- ▶ advise MMV on the development and implementation of product access plans to ensure timely and effective delivery of new antimalarial drugs in malaria-endemic countries.

- ▶ provide more general advice and information on appropriate strategies to achieve MMV's access and delivery goals.

The breadth of expertise represented among ADAC members includes the following areas:

- ▶ epidemiology, Phase IV trials, regulatory affairs

- ▶ drug policy, procurement, supply chain management

- ▶ financing, economics of malaria and malaria drugs, demand assessment

- ▶ drug launches, marketing and communications, drug delivery

Additional areas of expertise may be identified as products move along the access pathway. Further members may be invited to join ADAC to ensure a full range of experience in private sector distribution of goods in malaria-endemic countries.

Looking ahead

In 2006, MMV laid solid foundations for its new expanded role. In 2007, MMV will start the implementation of full market analysis and country-level activities to prepare for the launch of new high quality ACTs from the portfolio as they reach regulatory approval. This challenging scenario will demand even further commitment and dedication of all partners in order to ensure the significant health impact that MMV donors and stakeholders seek to achieve.



The Artemisinin Consortium

MMV joins forces with the Institute for OneWorld Health and York University to address the critical issue of satisfying global demand for artemisinin.

Three complementary scientific approaches together aim to improve artemisinin production technologies. This will consequently stabilize the supply of artemisinin, lower the cost of artemisinin production, and ultimately make ACTs cheaper and therefore more accessible to patients who need them. These approaches constitute a revolution.

In 2001, the World Health Organization (WHO) recommended that countries where malaria is resistant to conventional treatments, such as chloroquine, should switch to artemisinin-based combination therapies (ACTs). Since then, orders for ACTs have increased exponentially each year, with WHO alone initially requesting 220,000 treatment courses for the public sector, later increasing their order to 10 million treatment courses in 2004, and to 60 million in 2005. This surge in demand led to a global shortage of ACTs, raising the cost of the drug and making it inaccessible to those populations in desperate need of treatment. In addition, it left the ACT production system straining to keep pace with demand.

Artemisinin, the essential active ingredient of ACTs, costs at least ten times as much as chloroquine. It is extracted from the herb *Artemisia annua*. Cultivation of this plant requires a minimum of six months. The extraction, processing and manufacturing of the final products take an additional three to five months, depending on the product formulation.

It became obvious to WHO, national malaria control programmes, and initiatives researching new treatments for malaria, such as the Institute for OneWorld Health (IOWH) and MMV, that reliable, low-cost supplies of artemisinin were urgently needed if the situation was to be resolved.

In response to this situation, three projects have joined forces to satisfy the projected global demand for ACTs. Known as the Artemisinin Consortium,

this collaboration aims to ensure maximum impact on ACT supply chains, and to ensure that the new technologies do not enter supply chains for substandard drugs or monotherapies. The projects are outlined briefly below:

▀ The Institute for OneWorld Health (IOWH), in partnership with the University of California, Berkeley, and Amyris Biotechnologies, is using synthetic biology to develop microbially-derived artemisinin through fermentation.

▀ The Centre for Novel Agricultural Products (CNAP) at York University is applying fast-track breeding technologies with the aim of creating new, non-GM cultivars of *Artemisia annua* with increased yield of artemisinin.

▀ Medicines for Malaria Venture (MMV) is working towards developing a new class of antimalarial compounds – synthetic peroxides – that is safe, potent, and could mimic the rapid action of artemisinin.

These three complementary scientific approaches constitute a revolution. Together, they aim to improve artemisinin production technologies, which will consequently stabilize the supply of artemisinin, preventing vast fluctuation in prices and shortage-driven price rises; lower the cost of artemisinin production; and ultimately make ACTs cheaper and therefore more accessible to patients.



Microbially-derived artemisinin Institute for OneWorld Health, USA

The Institute for OneWorld Health and its partners, Amyris Biotechnologies and the laboratory of Professor Jay Keasling at the University of California, Berkeley, are using synthetic biology to help reduce the price of artemisinin. The project aims to create, optimize, and scale-up microbial production systems to augment current supplies and make high-quality bulk artemisinin available to ACT manufacturers year-round at a price much lower than the current cost to them.

The project is addressing the price of artemisinin derivatives, which are a significant cost component of ACTs. The price of artemisinin, the starting material for the synthesis of artemisinin derivatives is extremely volatile and in recent years has ranged from USD 400 to USD 1700/kg. The price that the Institute for OneWorld Health project is targeting is USD 100/kg for microbially-derived artemisinin, with the goal of reducing final treatment costs and helping to stabilize the ACT market.

This project aims to develop and validate a cost-effective, commercial-scale process using fermentation combined with synthetic chemistry to produce artemisinin. It is anticipated that bulk production of this important compound will significantly reduce the price of these

medicines, making them accessible to the hundreds of millions of impoverished people who contract malaria each year. The industrial fermentation process also offers advantages in scalability, reliability, and flexibility, which allow for a greater and faster ability to adjust to market changes.

There are two stages in the production of microbially-derived artemisinin: biological and chemical. The biological stage employs an engineered microbe to convert simple sugars into artemisinic acid using microbial fermentation. Several chemical synthesis steps then convert artemisinic acid into the final product, artemisinin.

Production using the highest manufacturing quality standards is expected to begin by 2010, with the goal of making enough medicine for 200 million of the estimated 500 million treatments needed. OneWorld Health is in the process of selecting a manufacturing partner.

High-yielding *Artemisia annua* Centre for Novel Agricultural Products (CNAP), York University, UK

The medicinal plant *Artemisia annua* is currently the sole source of artemisinin and will continue to be an essential element for supply in the foreseeable future. However, it usually yields less than 1% dry weight, making production expensive. High-yielding varieties would reduce the costs associated with both cultivation and extraction, and would improve returns for the farmer.

Based at the Centre for Novel Agricultural Products (CNAP), a research centre in the Department of Biology at York University, this project aims to produce new, non-genetically modified (GM) cultivars of *Artemisia annua* with increased artemisinin yield, using fast-track plant breeding techniques.

A population of *Artemisia annua* seeds with increased genetic variety has been created by means of a chemical treatment, widely used in plant breeding. Two complementary approaches will be used to screen this population for individuals with increased artemisinin yields. The first approach screens their DNA for gene alleles that are predicted to improve yield. The second approach measures the artemisinin levels in leaf tissue.



Once high-yielding individuals have been selected, classical crop breeding methods will be used to convert them into agronomically robust varieties. Field trials in a range of global environments will be conducted on the new varieties. Roll-out will include a sustainable supply of high-quality seed, supplied at cost, accompanied by a handbook for growers. It is vital that the new varieties are not used in the manufacture of monotherapies or substandard drugs. To this end, it is anticipated that seed distribution will be overseen by a stakeholder cooperative, who will ensure that the crop is to be used only by approved ACT manufacturers. The use of hybrids further mitigates this risk, as growers will achieve greatly reduced yields from seed they save from such varieties.

Synthetic peroxides Medicines for Malaria Venture (MMV)

In collaboration with a number of research partners, including the University of Nebraska, Monash University, and the Swiss Tropical Institute, MMV is working towards developing a new class of antimalarial compounds that is safe and potent. This class of synthetic peroxides, coined the 'OZ compounds', could potentially have a different mode of action or molecular target in the parasite, compared with artemisinin.

Many synthetic antimalarial peroxide compounds have been identified as having antimalarial activity, but almost all suffer from low oral activity. Therefore, scientists are eager to discover new peroxide antimalarial agents that can be easily synthesized, are inexpensive, have high oral activity, and which are devoid of the known toxicities associated with artemisinins. The synthetic peroxides appear on initial evidence to be potentially safer in early pregnancy than the artemisinins; and safety in early pregnancy has been one of the concerns about deploying ACTs to women of childbearing age. The goal is to identify new antimalarial agents which have the requisite pharmacokinetic properties to allow curative doses to be administered over a one to three day period.

An extensive investigation of the existing OZ compound library has been undertaken to identify the key features contributing to single-dose cures, which include high oral bioavailability, a longer half-life, and possible prophylactic activity. The research team will select the most promising OZ compound for clinical development during the second half of 2007.



Science Report and Project Portfolio 2006

The MMV portfolio has always been competitive, with only the most promising projects being selected for development.

MMV's hope is that the four new ACTs in its portfolio will enter the market in 2008 and 2009, bringing options for treatment never before available to the malaria community, at a competitive price; and that each individual country will select the drugs most appropriate to the needs of its people.

The four new ACTs are: pyronaridine-artesunate (PYRAMAX®), chlorproguanil-dapsone (Lapdap™)-artesunate (CDA), Coartem® dispersible tablets, and dihydroartemisinin-piperaquine.

In 2006, as the competition for resources became acute, the selection and evaluation process of the MMV portfolio became more critical. Funding was discontinued for projects not able to achieve their milestones and/or unable to meet the overall MMV strategy. At the same time, in order to maintain the portfolio at its optimal efficacy, new projects have been added, including two new mini-portfolios. Several projects were approved but not immediately funded. The net effect is that the portfolio is deeper than ever in the early exploratory and early discovery areas, with only four Phase III projects, which should be filed in 2007 and 2008, remaining in the pipeline on the clinical side. This wealth of new antimalarial products entering the market place in the near future, leads us to the next question: What will be the effect of this competition in the market?

Will competition in the antimalarial drug market benefit the patients? Many experts believe that this competition will cause confusion and that countries in need will not be able to cope. The new influx of drugs will certainly be a challenge for African malaria control programmes, which have never had to deal with more than one first-line drug at a time; but there are advantages to such competition. Many economic theories suggest that no system of resource allocation is more efficient than pure competition, since it causes companies to develop new improved products, services and technologies. We know that up until now this has not happened in the field of

malaria R&D because of the small reward for investment; however, with the investments in new products being made by initiatives such as MMV, the rest of the free market should take over. The first of these effects has already been seen, in the lowering of the cost of Coartem®. The newer products in the MMV pipeline should force the prices paid by public and private markets down even further, especially as a result of competition in the private market, where 70 to 80% of patients obtain their drugs. Currently, doctors treating malaria in Africa have only one GMP fixed-dose ACT to give their patients, and if this is not tolerated, then there are very few other options available.

With MMV and its partners providing a variety of quality products competing in an open market, doctors and patients will have a wider choice. By companies providing product information and training on the new ACTs to doctors and other health personnel, consumers will be better educated and less likely to buy inferior products or counterfeits. Thus, over time, superior products will be recognized and will become the predominant drugs used by the public. The choice will be market driven and not that of a few experts in a distant conference room!

The ever-changing MMV portfolio

There were many changes to the portfolio in 2006. In May, funding for the Pf protein farnesyltransferase project was discontinued due to the inability to make drug-like compounds. Out of the 107 Letters of Interest from the Fifth Call, 16 projects were short-listed. The full proposals were reviewed in Washington, DC, in July, and six of them were recommended for inclusion in the MMV portfolio. These projects are now under contract negotiations.

The MMV ESAC annual project review took place in December. It differed from previous meetings in that projects were evaluated at two levels: initially according to their scientific viability, as before; and then, in a final overview, budgetary requirements were matched to available funding and recommendations made. ESAC recommended that MMV funding for the following projects should be discontinued: RBx11160 + Piperaquine, 4(1H)-pyridone GW308678 (a back-up will be selected to replace it), new dicationic molecules, Cameroonian medicinal plants, and enantioselective 8-aminoquinolines.

A decision on isoquine is pending. Due to the inability to conclude a contract, AQ-13 is no longer under contract negotiation. New projects which were selected in the Fifth Call for Letters of Interest, and which are under contract negotiation, include dihydroorotate dehydrogenase inhibitors, immucillins, TDR22093 series, natural products whole-cell HTS, and natural products as new prototypes. The novel macrolides and tafenoquine projects were approved but not funded. If additional funding becomes available they may be added to the portfolio.

New mini-portfolios

The success of the GSK/MMV mini-portfolio has led to two new mini-portfolios being formed this year. The advantages of the GSK/MMV mini-portfolio are due mainly to the power which comes from being a large professional organization with dedicated staff, and the flexibility to move resources, including personnel, from projects that are not progressing to those which are more likely to achieve their goal if allocated more resources. The addition of the two new mini-portfolios, described below, provides MMV with more depth in the early discovery stages, resulting in a substantial pipeline that has the potential to bring forward the new drugs needed to treat malaria in the future.

Novartis Institute for Tropical Diseases (NITD) Malaria Research Programme is an international public-private partnership developed to bring high-quality drug candidates directed at a curative modality for *Plasmodium vivax*, and a single-dose cure for *Plasmodium falciparum*.

Table 1. Projects discontinued or put on hold in 2006

Project	Dates of funding	Reason for discontinuation of MMV active support
8 aminoquinoline: NPC 1161	May 2003 – Dec 2006	No longer fits the MMV/ESAC strategy.
Cameroonian medicinal plants	March 2005 – Dec 2006	Active molecules did not fit the MMV/ESAC strategy.
New dicationic molecules	April 2003 – Dec 2006	Models did not predict activity of present molecules in man.
Isoquine	Feb 2003 – Dec 2006	On hold until more funding available and re-evaluation of isoquine in the MMV/ESAC strategy.
Tablet, pediatric and intravenous RBx11160	2000 – Dec 2006	Concerns over pharmacokinetics and no longer fits the MMV portfolio strategy.
Pf-Protein farnesyltransferase inhibitors	2Q 2002 – May 2006	Concerns about the pharmacokinetic profile of the most promising molecules.
AQ-13	Never funded	No longer fits the MMV/ESAC strategy.

This ambitious programme is funded by the Wellcome Trust, Medicines for Malaria Venture, Economic Development Board of Singapore, and Novartis. The major collaboration will be between the Novartis Institute for Tropical Diseases, the Genomics Institute of the Novartis Research Foundation, the Swiss Tropical Institute, and the Biomedical Primate Research Centre. The programme is focused on very early exploratory and discovery work which, when successful, will be handed off to MMV for further development.

The Broad Institute of MIT and Harvard and the Genzyme Corporation initiative for novel antimalarials is working in collaboration with MMV to discover new antimalarial drugs. The initiative will use existing leads, drug candidates, and ongoing screens to initiate discovery programmes, including hits from ongoing screens; develop new screens and chemistry programmes based on ongoing discovery biology efforts, small molecule microarray technology, effector screens, and new genome annotation; and generate new fundamental knowledge, tools, and data, such as high throughput gene knockouts, pathway network mapping based on gene expression, metabolomic and proteomic profiling, and the *Plasmodium falciparum* HapMap, to enable a subsequent generation of screens and directed chemistry efforts against novel targets. This initiative is also directed at early exploratory and discovery work, with a hand-off to MMV for clinical development.

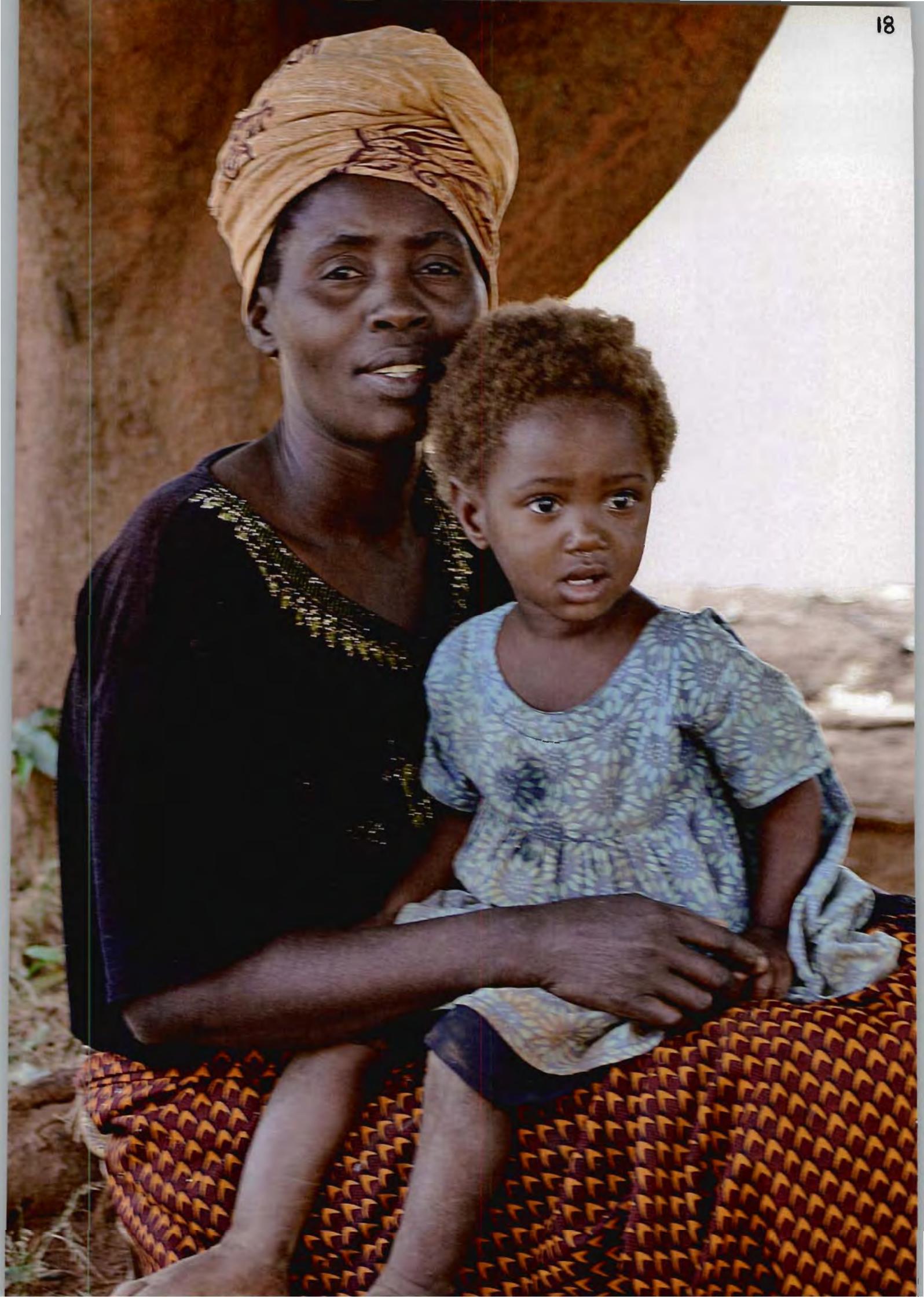
Authorization for Phase III Advancement Committee (APAC)

APAC is a new committee which met for the first time in 2006. Its role is to evaluate projects which have completed Phase II and are ready to proceed to Phase III.

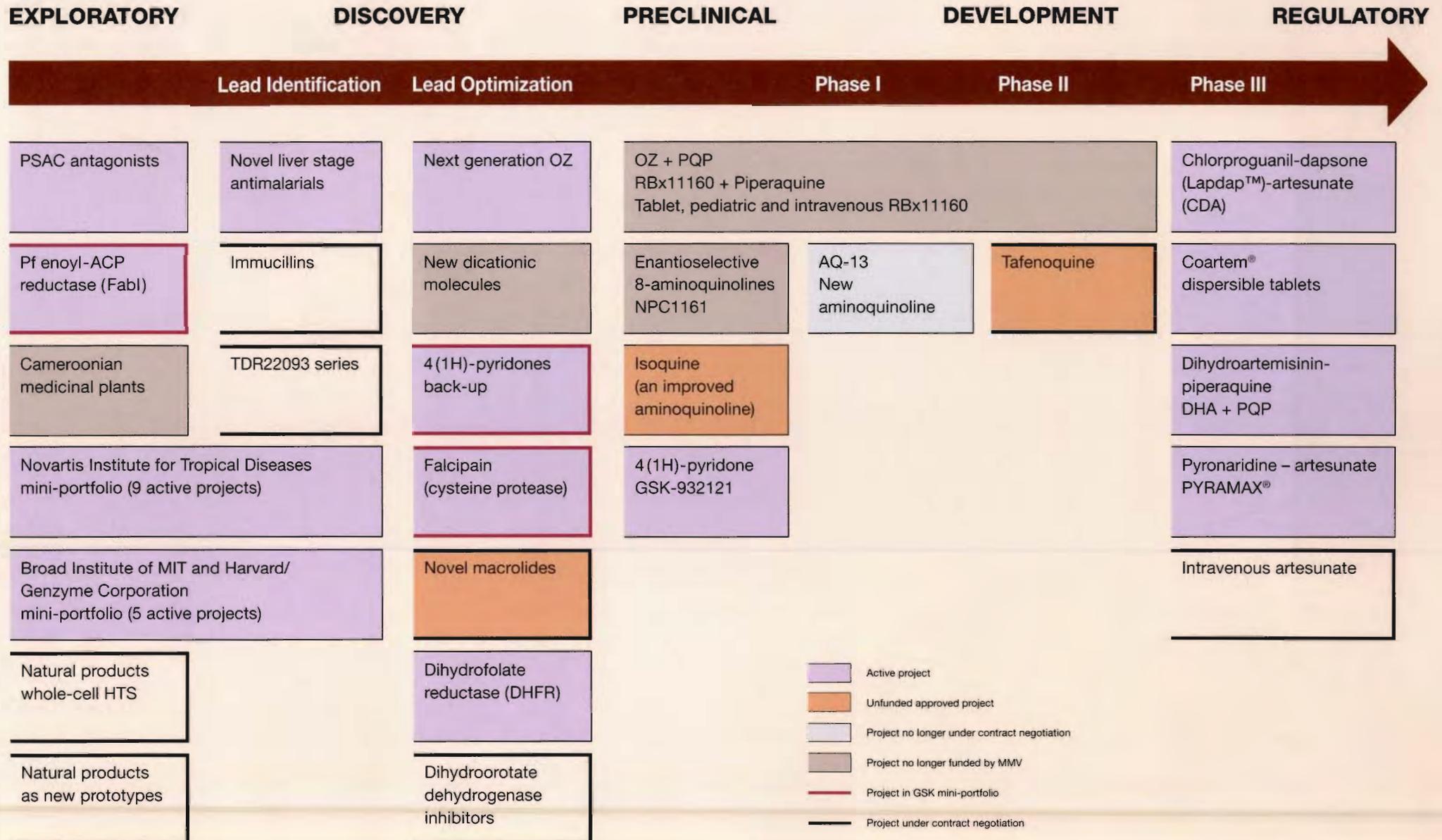
Approval for advancement to Phase III requires that Phase II data support the advancement based on scientific data, and that the drug meets the MMV strategic plan. The pyronaridine-artesunate (PYRAMAX®) project was given the go-ahead for Phase III development.

Table 2. Projects selected in 2006 as a result of MMV's Fifth Call for Letters of Interest

New Projects	Initiation date	Comments
Dihydroorotate dehydrogenase inhibitors	Contract under negotiation	DHOD is an essential enzyme in pyrimidine biosynthesis and a potential antimalarial target. Partners: University of Texas Southwestern Medical Center, USA, University of Washington, USA and Monash University, Australia
Immucillins	Contract under negotiation	Immucillins work by inhibition of purine salvage of <i>P. falciparum</i> . Partners: The Albert Einstein College of Medicine, USA, Industrial Research Ltd., New Zealand and Primate Research Center, The Netherlands
Broad Institute of MIT and Harvard/ Genzyme Corporation mini-portfolio	1 January 2007	The mini-portfolio will work on target identification and validation progressing to lead selection and optimization of drugs to treat malaria. Partners: Broad Institute of MIT and Harvard, USA and Genzyme Corporation, USA
TDR22093 series	Contract under negotiation	Evaluation and SAR development from the screening hit TDR22093. Partners: WHO/TDR, Switzerland and Pharmacoepia, USA
Natural products whole-cell HTS	Contract under negotiation	Screening of natural products. Partners: Griffith University, Queensland Institute for Medical Research, Monash University and Australian Army Malaria Institute
Natural products as new prototypes	Contract under negotiation	Evaluation and SAR development from screen hits. Partners: University of Mississippi, USA



MMV Portfolio - Fourth Quarter 2006



Drug Development and Discovery Projects

Clinical Development Projects

Chlorproguanil-dapsone (Lapdap™)-artesunate (CDA) – Phase III

Project leader: Peter Winstanley,
University of Liverpool, UK

Partners: GlaxoSmithKline, London, UK; UNICEF/
UNDP/World Bank/WHO Special Programme
for Research and Training in Tropical Diseases (TDR),
Switzerland; University of Liverpool, UK; Liverpool
School of Tropical Medicine, UK; London School of
Hygiene & Tropical Medicine, UK

MMV contact: J Carl Craft

Chlorproguanil-dapsone-artesunate (CDA) is a fixed-ratio three-drug combination being developed to treat uncomplicated *Plasmodium falciparum* malaria. A course will comprise one treatment daily for three days, and the anticipated cost is low. Shelf-life is being studied intensively, and it is possible that a claim for a shelf-life of three years will be supported. The clinical programme and pharmaceutical development of CDA have advanced to the final stage before registration.

Two Phase III clinical trials are enrolling patients. The first is a study of CDA vs. Coartem® in adults and children in Burkina Faso, Ghana, Kenya (2 sites), Nigeria (4 sites) and Tanzania. The second study is a comparison of CDA vs. Lapdap™ in adults and children in Burkina Faso, Ghana, Mali and Nigeria (4 sites).

The planning of Phase III b (which will span file submission) and Phase IV (post-licensure) studies have started. Filing will be done in late 2007 or early 2008.

Coartem® dispersible tablets – Phase III

Project leader: Heiner Grueninger,
Novartis Pharma, Switzerland
MMV contact: David Ubben

Novartis and MMV have continued the development of a user-friendly palatable pediatric dispersible tablet containing a fixed-dose combination of artemether and lumefantrine. This pharmaceutical form will be easy and cost-effective to manufacture and can use the well-known WHO package format currently used by Coartem®. Stability studies of the dispersible tablet in hot humid conditions indicate that a shelf-life of two years will be confirmed.

A comparative pharmacokinetic study evaluated the relative bioavailability to healthy volunteers of oral suspensions of the Coartem® dispersible tablet and the crushed commercial tablet formulation of Coartem®. The study showed acceptably similar bioavailability of both artemether and lumefantrine between the dispersible tablet and crushed commercial tablets.

The efficacy and safety of the Coartem® dispersible tablet is now being compared clinically with the marketed crushed Coartem® tablet in an investigator-blinded, multi-centre, Phase III study. It will include 890 infants and children suffering from malaria, with a body weight of between 5 and 35 kg. The study started in July 2006. A futility interim analysis of the first 160 patients was performed by an independent Data Monitoring Board. The board gave the go-ahead to recruit the remaining patients, which is now being done by six centres in Africa (in Benin, Kenya, Mali, Mozambique and Tanzania). Submission to Swissmedic of the registration dossier for the pediatric formulation is planned in 2007, and approvals in Switzerland and in malaria-endemic countries are expected in 2008.



Dihydroartemisinin-piperaquine – Phase III

Project leader: Antonio Longo, Sigma-Tau Industrie Farmaceutiche Riunite, Italy
Partners: Sigma-Tau Industrie Farmaceutiche Riunite, Italy; Chongqing Holley Holding Co. Ltd., China; Oxford University, UK
MMV contact: David Ubben

Dihydroartemisinin-piperaquine (DHA + PQP) is a fixed-ratio drug combination being developed to treat uncomplicated malaria. The combination has already been widely used in South-East Asia in controlled clinical trials.

The two active pharmaceutical ingredients (APIs) contained in DHA+PQP were released on the basis of analyses carried out by Sigma-Tau, and two batches of tablets, one for children and one for adults, were manufactured and released by Sigma-Tau to supply the clinical trials.

A quality system has been established in the Holley production site of DHA in Youyang, China. Youyang is now almost capable of producing DHA at international GMP standard. A similar quality system is being instituted for the Holley finished product production site in Bei-Bei, China. The third party supplier of piperaquine in Mitong, China, will also be upgraded to international GMP standard. These upgrades should be completed early in 2007, allowing Holley to produce both APIs and the finished product that will be fully GMP-compliant.

The non-clinical part of the development plan (toxicology and pharmacokinetics) was started and will be completed by early 2007. This now includes a characterization of all relevant degradation products.

The clinical development plan includes three pharmacokinetic studies and two confirmatory Phase III trials. One Phase III trial is currently ongoing in South-East Asia (India, Laos and Thailand) with a goal of 1050 patients. The comparator is artesunate-mefloquine. The second Phase III trial was completed with 1500 patients in five centres in Africa, with arthemether-lumefantrine as comparator. The pharmacokinetics programme completed in 2006 included one trial in healthy volunteers, one in the pediatric patient population, and one in adults with malaria. All trials were conducted at the highest international Good Clinical Practice (GCP) level.

Pyronaridine-artesunate (PYRAMAX®) – Phase III

Project leader: Larry Fleckenstein, University of Iowa, USA
Partner: Shin Poong Pharmaceuticals, Seoul, South Korea
MMV contacts: Lise Riopel, Isabelle Borghini, Claude Oeuwray

A large multicentre dose-finding study involving 477 patients was completed in March 2006. Study results indicate that all three doses tested yield a very high cure rate and good safety profile. A dose escalation study aimed at assessing the pharmacokinetics and safety of the tablet and granule forms in African children with acute uncomplicated malaria was also completed in 2006. Study results indicate similar efficacy and safety profiles, and therefore justify appropriateness of dose selection in children. Outlines of these two studies were presented at a special session during the 55th ASTMH (American Society of Tropical Medicine and Hygiene) meeting in Atlanta in November 2006.

Following a successful review by MMV's Authorization for Phase III Advancement Committee (APAC), the fixed combination of pyronaridine and artesunate has progressed to Phase III studies to confirm safety and efficacy in patients suffering from acute uncomplicated *Plasmodium falciparum* and *P. vivax* malaria. Three large multicentre comparative studies have been implemented in sub-Saharan Africa and South-East Asia. The pediatric granule formulation will be tested for safety and efficacy in young children and infants in a large Phase III study due to start in 2007.

Shin Poong Pharmaceuticals continues to assess mechanisms by which cost of goods can be reduced further to achieve highly competitive prices in both public and private sectors. Moreover, a new

EU GMP-compliant facility is under construction to ensure that manufacturing capacity for each formulation (tablet and pediatric granules) can meet the market demands for this promising new ACT.

Preclinical Development Projects

Tablet, pediatric and intravenous RBx11160

Project leader: Vijay Batra, Ranbaxy Laboratories, India
Partners: Monash University, Australia; Swiss Tropical Institute, Switzerland; University of Nebraska Medical Center, USA
MMV contacts: J Carl Craft, Jörg Möhrle

In 2006, two pharmacokinetic studies with RBx11160 in Thai volunteers and patients were conducted to investigate the influence of malaria on the pharmacokinetic properties of the compound. A Phase II dose-ranging study was initiated in June in adult patients in Africa, India and Thailand to identify the best dose for future studies of RBx11160 in combination with piperazine.

Development of both a pediatric formulation and an intravenous formulation progressed for the RBx11160 compound. Preclinical regulatory studies with the intravenous formulation were performed and completed in 2006. The product development team had chosen piperazine as the first partner drug for development with RBx11160. In 2006,

a Phase I trial of piperazine in healthy volunteers, and regulatory, preclinical studies of the combination of RBx11160 and piperazine were completed.

Further Phase I studies of the combination treatment were initiated to establish the safety profile of this combination. Data from the RBx11160/piperazine project were presented at a special session during the 55th ASTMH meeting in Atlanta in November 2006.

After review of the preliminary data and other portfolio priorities, MMV has decided to stop funding the project. Ranbaxy will continue development of RBx11160, alone and in combination with partner drugs for the treatment of malaria.

Enantioselective 8-aminoquinolines

Project leader: Larry Walker, University of Mississippi, USA
Partner: National Institutes of Health, USA
MMV contacts: Ian Bathurst, Pascal Fantauzzi, Isabelle Borghini-Fuhrer

There is increasing concern that morbidities resulting from *Plasmodium vivax* malaria have been underestimated and that chloroquine resistance is spreading. The need for a new, safe, effective and affordable treatment for both the acute and relapse phase of *P. vivax* malaria is pressing.

To date, 8-aminoquinolines are the only compounds that have been shown to be efficacious as anti-relapse therapy. However, most products of this class show unacceptable toxicity for widespread use in malaria-endemic countries, the primary concern being the propensity to cause methaemoglobinemia and haemolysis, especially in individuals deficient in glucose-6-phosphate dehydrogenase (G6PD).

NPC1161B is the (-)enantiomer of the 8-aminoquinoline racemic mixture NPC1161C. While it retains very potent pharmacological activities both *in vivo* and *in vitro*, it was shown to be significantly less toxic than the (+)enantiomer or the racemic mixture in the models tested so far. This remains to be confirmed in humans.

A cost-efficient and commercially feasible route of synthesis for the active enantiomer has been developed, and GMP drug substance should be available early in 2007.

An antimalarial efficacy study in the Rhesus monkey (*Macaca mulatta*)/*Plasmodium cynomolgi* malaria model was conducted.

Results indicate excellent efficacy for radical cure with a 3-day regimen, especially in combination with rapidly acting blood schizonticide. Methaemoglobin generation was seen only at high doses and there was no occurrence of haemolysis, suggesting a favourable safety profile.

In vitro metabolic studies were conducted in order to better understand the mechanism of toxicity to red blood cells and to determine species specificity.

Isoquine (N-tert butyl form)

Project leader: Martin Bates, GlaxoSmithKline, UK
Partners: University of Liverpool, UK;
GlaxoSmithKline, Tres Cantos, Spain and USA
MMV contact: David Ubben

Isoquine is being developed in partnership with GlaxoSmithKline and the University of Liverpool, where it was discovered. It is an amodiaquine-like compound that has been redesigned and synthesized to remove the structural cause of toxicity of its class while retaining full antimalarial activity. The aminoquinoline class of drugs has been the most successful antimalarial to date. However, widespread resistance to chloroquine and growing resistance to amodiaquine have rendered most of the compounds useless in broad areas where malaria is endemic.

Although the positive results obtained to date justify further development work, more convincing evidence of a safety advantage in humans of NPC1161 over existing 8-aminoquinolines is crucial. MMV decided to suspend funding of this project — until there are compelling safety data in man, especially in G6PD-deficient patients. A pharmaceutical partner will be essential to move this project ahead.

Isoquine, a second generation aminoquinoline, retains the easy synthesis of amodiaquine from inexpensive precursors. It promises a new generation of affordable, well-tolerated, and effective antimalarial drugs.

During 2006, the N-tert butyl form advanced through the Good Laboratory Practice (GLP) preclinical testing needed to begin testing in healthy volunteers. At the same time, the team addressed the question as to whether there is potential for cross-resistance to amodiaquine, which is now widespread in Africa. The experiments demonstrated that isoquine was consistently active in parasites cultured from malaria patients treated clinically with amodiaquine, even from areas where clinical failures to amodiaquine treatment were frequent. The team is also considering potential agents to combine with N-tert butyl isoquine.

Entry into the clinic was scheduled for early 2007; however, at the December 2006 ESAC meeting the project was put on hold pending availability of additional funding.



Discovery Projects – Lead Optimization

Next generation OZ (synthetic peroxide)

Project leaders: Jonathan L. Vennerstrom, University of Nebraska Medical Center, USA; Susan A. Charman, William N. Charman, Monash University, Australia; Sergio Wittlin, Swiss Tropical Institute, Switzerland

Partners: Fulcrum Pharma, UK; Hoffmann-La Roche, Switzerland; Basilea Pharmaceutica, Switzerland

MMV contact: J Carl Craft

The project objective for 2006 was to identify next generation ozonides (OZ) that will provide single-dose oral cures for patients with uncomplicated *Plasmodium falciparum* malaria. The screening and selection strategy focused on optimizing the PK-PD relationship of these ozonides in order to provide single-dose cures, outstanding prophylactic potential, optimized bioavailability, and low cost of goods.

Specifically, current studies are focused on identifying further compounds with increased half-lives after oral administration, to allow for extended exposure following a single dose. Detailed mechanistic studies provided valuable insight into the factors controlling the half-life for this series of compounds.

New dicationic molecules

Project leader: Richard R. Tidwell, University of North Carolina, USA
Partner: Swiss Tropical Institute, Switzerland
MMV contact: Ian Bathurst

Pentamidine, a dicationic-type molecule, has been used to treat *Pneumocystis carinii* pneumonia, antimony-resistant leishmaniasis, and early stage African trypanosomiasis (sleeping sickness), but its use has been limited by toxicity. DB289 (an improved pentamidine) is a compound being developed for treating African trypanosomiasis, which has also been tested in a Phase II proof-of-concept study to treat malaria. Its demonstrated activity in humans is a good proof of concept for the new dicationic molecules.

The dicationic molecules concentrate selectively in *Plasmodium falciparum*-infected red blood cells, where they enter and kill the parasites. The exact mechanism of action of these compounds is not well understood, but they are believed to interfere with mitochondrial function in a manner that may or may not include binding to the minor groove of DNA, among other potential targets.

New lead ozonides were identified that are curative with a single dose in the murine malaria model, and are as effective as mefloquine as a prophylactic agent but with a faster mode of action. They have an extended half-life relative to the RBx11160/OZ277 compound in rats, and have high and reproducible oral bioavailability. Several potential drug candidates will soon undergo toxicological studies with the aim of selecting the best candidate in 2007.

The next generation OZ project was selected by the Expert Scientific Advisory Committee (ESAC) as MMV Project of the Year for 2006. This team also received the Project of the Year award in 2001 for work with the first generation ozonide project.

Recent chemistry work has demonstrated that superior compounds with excellent selective activity against malaria can be designed.

After progressing both the selected and the new compounds through *P. falciparum* *in vitro* assays, and studying the corresponding pro-drug's pharmacokinetic and metabolic properties, the best compounds were tested in the *P. falciparum* severely compromised immune deficient mouse model, and then in the Aotus monkey model. Unfortunately none of the rodent models were predictive of the primate model system and ESAC recommended the project be discontinued.

4(1H)-pyridones – Preclinical/Back-up

Project leaders : Martin Bates, GlaxoSmithKline, UK;
Domingo Gargallo, GSK, Tres Cantos, Spain
MMV contacts : David Ubben (preclinical), Ian
Bathurst, Pascal Fantauzzi (back-up)

Following the termination of the 4(H)-pyridone derivative GW844520 in late 2005, the work on back-up compounds was intensified to find a new candidate lacking the toxicological properties of GW844520. Pyridone derivative GW308678 was progressed as the lead back-up compound, and achieved candidate selection in March 2006. This compound has a shorter half-life and lacks the toxicological properties which had led to the termination of the previous pyridone development. GW308678 is a potent selective inhibitor of the *Plasmodium falciparum* mitochondrial function, via inhibition of its electron transport chain. It has also been demonstrated to have *in vitro* activity against isolates carrying resistance determinants to marketed antimalarial compounds.

In 2006, development continued on this compound, focusing on its safety assessment and formulation. The inability to obtain high exposure in some species used for testing is being addressed.

In December, compound GSK932121A, that displayed similar biological properties but had a better physicochemical and pharmacokinetic profile than GW308678, was selected as a further back-up candidate for development.

Plans for 2007 include preclinical development of GSK932121A, and identification of further back-up structures.

Falcipain (cysteine protease)

Project leader : Philip J. Rosenthal, University of
California, San Francisco, USA
Partners : GlaxoSmithKline, Tres Cantos,
Spain and USA
MMV contact : Pascal Fantauzzi

Plasmodium falciparum malaria parasites reside within red blood cells during the portion of their life cycle that is responsible for clinical malaria. While inhabiting red cells, the parasites take up and degrade human haemoglobin as a key source of amino acids. A number of proteases participate in haemoglobin degradation, including cysteine-class proteases known as falcipains. Inhibitors of cysteine proteases block haemoglobin degradation, causing the accumulation of undegraded haemoglobin in the parasite food vacuole, which results in parasite death. Therefore, the falcipains are exciting potential drug targets.

promising bioavailability, pharmacokinetic, and safety properties. Six lead compounds effectively cleared parasites in a new *P. falciparum* murine model, and additional series of related compounds are being optimized.

Plans for 2007 include selection of a lead candidate for preclinical studies, identification of back-up leads, determination of falcipain structures complexed with inhibitors, and evaluation of the impact of falcipain inhibitors on *P. vivax*.

Various series of falcipain inhibitors, such as azepanones and acyl hydrazones, were developed for this project, but were later abandoned because of high potential cost of goods and poor pharmacokinetic properties. Recently, detailed exploration of a new class of small molecules has identified multiple compounds with low nanomolar antimalarial activity and

Dihydrofolate reductase (DHFR)

Project leader: Yongyuth Yuthavong,
BIOTEC, Thailand
Partners: London School of Hygiene & Tropical
Medicine, UK; Monash University, Australia
MMV contact: Pascal Fantauzzi

Drugs which inhibit the folate pathway have been widely used for the treatment of *Plasmodium falciparum* malaria, but their efficacy is declining due to the emergence of drug resistance. Resistance develops through mutations in the dihydrofolate reductase (DHFR) enzyme. However, the folate pathway remains a good target for chemotherapy because resistant mutations depend on the structure of antifolates, and the enzyme is limited in its mutation capability.

This project aims to utilize structural biology and knowledge of resistance mechanisms to rationally design, synthesize and identify inexpensive, orally-active inhibitors of wild-type (WT) and quadruple mutant (QM) DHFR enzymes. The structural basis for resistance to 'rigid DHFR inhibitors' such as cycloguanil and pyrimethamine, occurs as a result of amino acid mutations within the enzyme active site, sterically prohibiting the binding of rigid inhibitors. The structural flexibility

in the scaffold of the 'flexible DHFR inhibitors' developed in this project accommodates the effect of steric changes that occur in the binding site of the enzyme upon mutation, allowing them to bind to both the WT and QM enzymes.

The main achievements of the project during 2006 were the optimization of the antimalarial activity and ADME (absorption, distribution, metabolism and excretion) characteristics of the flexible inhibitor series. Significant advances have been made in understanding the binding of this series and in developing new design concepts to drive the synthetic chemistry programme. The goals for 2007 include the interpretation of toxicology results for a set of representative inhibitors, optimization of the activity and pharmacokinetics of the best compounds, combination studies, and compound nomination as a preclinical development candidate by the end of the year.

Discovery Projects – Lead Identification

Novel liver stage antimalarials

Project leader: Michael P. Kozar, Walter Reed Army
Institute of Research (WRAIR), USA
Partner: WRAIR, USA
MMV contact: Ian Bathurst

A novel imidazolidinedione compound, identified as WR182393, was found to have radical curative and causal prophylactic activity in Rhesus monkeys infected with *Plasmodium cynomolgi* when given intramuscularly. Unfortunately, the compound was not active when administered orally, and solubility in water and organic solvents was poor. On further investigation, WR182393 was found to be a mixture consisting of two major components, WR283246 (A) and WR288568 (B), and a small amount of chlorproguanil (1-2%), the starting material for the synthesis of WR182393.

To overcome the poor solubility and separate the components (A and B), they were derivatized as carbamates. Both carbamate derivatives (A-1 and B-1) were shown to be more efficacious than the parent mixture in non-human primates; however, neither compound showed significant causal prophylactic activity when given orally.

In a simulated stomach acid solution both A-1 and B-1 were shown to be chemically unstable, which may be responsible for the poor oral efficacy of the carbamates. These results suggested that acid-stable carboxamide derivatives of A and B may obviate the poor oral efficacy of A-1 and B-1. Initially, three carboxamide derivatives of component B

were prepared and all were orally active at <10 mg/kg in the mouse causal prophylaxis model. However, all three carboxamides were metabolized to their triazine derivatives in both human and mouse microsome preparations, suggesting that imidazolidinedione carboxamides may be prodrugs of the corresponding triazines.

Scale-up synthesis of the active compounds will be followed by confirmation of the oral bioavailability and efficacy of the triazine analogues in the combined causal prophylactic and radical curative model in Rhesus monkeys.

Discovery Projects – Exploratory

Plasmodial surface anion channel (PSAC) antagonists

Project leader: Sanjay Desai, NIAID, Washington, DC, USA
Partners: Broad Institute, USA; NIAID, USA
MMV contact: Ian Bathurst

The plasmodial surface anion channel (PSAC) is a novel ion channel found on *Plasmodium falciparum*-infected human red blood cells. This channel is strictly conserved in rodent and primate malaria models, where functional homologues exhibit nearly identical activities. Because PSAC dramatically increases host cell permeability to amino acids, purines, vitamins, and precursors for phospholipid biosynthesis (all required for *in vitro* parasite growth), it may serve an essential role in parasite nutrient acquisition.

PSAC has been validated as an anti-malarial target because most available antagonists inhibit *in vitro* growth of *P. falciparum* at concentrations modestly higher than needed to inhibit channel activity. However, most available antagonists also inhibit human transporters and are, therefore, not sufficiently specific for clinical use.

The project, using high-throughput screening (HTS) technology, has identified groups of structurally related compounds that target this ion channel. Current goals include the generation of one or more therapeutic lead series by identifying high affinity PSAC antagonists that kill parasites. By interfering with nutrient uptake, these compounds should produce a cure for malaria with short, sub-acute therapy. This MMV-funded research aims to use PSAC antagonists to develop a compound with desirable properties for further drug development.

***P. falciparum* enoyl-ACP reductase (FabI)**

Project leader: José F. García-Bustos,
GlaxoSmithKline, Tres Cantos, Spain
MMV contacts: Ian Bathurst, Pascal Fantauzzi

FabI is the only known enoyl-ACP reductase in *Plasmodium falciparum*. Phylogenetically, this enzyme is in the same group as the plant and bacterial enoyl reductases, forming part of a type II fatty acid synthase (FAS II) system, clearly different from the FAS I system present in animals. In bacteria, FabI has been shown to be essential for fatty acid synthesis and is the molecular target for several antimicrobials, including isoniazid and triclosan. *P. falciparum* is sensitive to triclosan, and Pf FabI has been shown to be inhibited by this compound. FabI is an attractive target because it has been validated pharmacologically to a given extent with triclosan.

The leads developed in 2005 lacked whole-cell inhibition; therefore new chemical series were identified in 2006, and subsequent design and synthesis of chemical library compounds were carried out. These new compounds have potent antiplasmodial activity and will be tested against *P. falciparum* transfectants to genetically validate FabI as their target. Additionally, these two inhibitors demonstrated good oral activity *in vivo* in a *P. falciparum* murine model. Future developments for 2007 include target validation studies, optimization of physicochemical properties, potency, and determination of efficacy parameters in *in vivo* models.

Antimalarial constituents of Cameroonian medicinal plants

Project leader: Simon Mbua Ngale E'fange,
University of Buea, Cameroon
Partners: Swiss Tropical Institute, Switzerland;
Monash University, Australia; University of Buea,
Cameroon; University of Minnesota, USA; Scynexis,
North Carolina, USA
MMV contact: Ian Bathurst

This project capitalizes on the discovery of a set of mono- and bicyclogarnesyl sesquiterpenes that display activity against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. Isolated from a Cameroonian spice as part of a screening programme designed to identify novel antiplasmodial chemotypes, the compounds, some of which have not been previously reported in the literature, provide the platform upon which researchers at the University of Buea in Cameroon, in collaboration with other partners, have initiated this drug discovery effort.

Scale-up isolation of the bioactive metabolites, yielding multi-gram quantities, and re-testing against *P. falciparum* *in vitro* has been achieved during the first half of Year One of the project. Preliminary ADME (absorption, distribution, metabolism and excretion) studies suggest that the compounds possess acceptable pharmacokinetic properties.

However, as none of the active molecules identified to date fit the MMV /ESAC strategy, ESAC recommended the project be discontinued.

The discovery, which links plant and animal secondary metabolites, provides new insights into the search for bioactive secondary metabolites. Researchers have found that at least one of the bioactive metabolites is a novel endoperoxide. However, this structural feature is absent from other bioactive constituents of the plant; therefore, it is not clear that the endoperoxide moiety plays an important role in the antiplasmodial activity of these metabolites.



Project Support Programmes

During 2006, MMV supported a number of additional programmes, some of which are summarized below:

Antimalarial drug screening at the Swiss Tropical Institute

The Swiss Tropical Institute (STI) was founded in 1943 as a public organization with the mandate to contribute to the improvement of the health of populations internationally and nationally, through excellence in research, services, teaching and training. Funding from MMV has resulted in the expansion of the antimalarial drug screening efforts at STI. A master agreement between STI and MMV was formalized at the end of 2003, allowing the two organizations to have a flexible working relationship without the need to negotiate a new contract for each project, and allowing resources to be moved from one project to another more easily.

During 2006, STI collaborated with MMV on a number of projects that focused on the discovery of new antimalarial drugs. Both institutions support the increased participation of qualified scientists from malaria-endemic countries, especially in Africa, in the ongoing drug screening efforts. In this context, two talented young scientists (Mrs. Beatrice Irungu from the Kenya Medical Research Institute (KEMRI) in Nairobi, Kenya, and Mrs. Oyin

Abiodun from the College of Medicine in Ibadan, Nigeria) attended a one-year training in malaria drug discovery at STI. It is hoped that this will help to build capacity and transfer technology in this critical area of antimalarial drug discovery.

Artemisinin extraction benchmarking study

Traditionally, the majority of *Artemisia annua* grown worldwide is processed through solvent extraction, using hexane and petroleum ether. The only other considered alternative has been supercritical CO₂ (scCO₂). While petroleum ether and hexane are cheap to buy, both solvents represent a considerable safety hazard and could be harmful to the environment.

Following the worldwide exposure *A. annua* has received as a treatment for malaria, a number of other technologies which claim to have greater efficiency, are safer, or are more environmentally friendly, are now being promoted. These processes were initially developed for the extraction of essential oils, fragrances and other pharmaceutical products, but initial trials on *A. annua* have been successful and indicate that they could be used as an alternative to existing technologies.

The lack of accurate data on hexane extraction, together with the emergence of these new technologies, makes it difficult for new and existing *Artemisia* producers to assess the efficiency, financial viability, safety and environmental impacts of the individual processes, and thereby to select the process which is best for their application.

With support from the Dutch Government, a study was commissioned that examined the new technologies that could be used for the extraction of artemisinin, and developed a benchmarking procedure through which these new technologies could be compared with existing extraction methods such as hexane. The need for flexible extraction technologies was also reviewed, both in order to ensure the financial viability of an extraction plant and also to provide potential for other crops to be grown by farmers in addition to *Artemisia annua*.

The technologies compared included extraction using hexane/petroleum ether, scCO₂, ethanol, HFC-134a and ionic liquids. The results show that the new technologies, specifically HFC-134a and ionic liquids, have particular potential, being equal or better in extraction efficiency, extraction time, running and capital costs, than hexane. Both technologies are also safer and are potentially more environmentally friendly (accepting that care has to be taken to ensure complete recycling and capture of the solvents).



For a summary report, commissioned by MMV, please see:

Lapkin AA, Plucinski PK, Cutler M. Comparative Assessment of Technologies for Extraction of Artemisinin. *J. Nat. Prod.*; 2006; 69(11) pp 1653-1664

Artemisinin in pregnancy

MMV has been funding research into the mechanism of the toxic effects on the embryo of drugs containing artemisinin. Artemisinins have been shown to be embryo lethal and teratogenic when given to mice and rabbits in doses equivalent to the exposure in man. GSK and Nerviano Medical Sciences, sponsored by MMV, worked on developing a better understanding of the cause and effects. Prior to the recent work, it was felt that the effect might not be seen in primates because of the difference between an amniotic sac pregnancy and a placental pregnancy. Experiments in primates, however, demonstrated a similar effect to that observed in the mouse. Further studies showed that this is due to the effect of artemisinins on embryonic blood cell formation. As the primitive red blood cells appear, these haemoglobin- and mitochondria-containing cells are damaged, resulting in death of the embryo due to severe anaemia. At lower doses the damage results in cardiac malformations as well as limb abnormalities.

The window of vulnerability is very short — only 3 to 5 days, depending on the species — and occurs at a time when women would not necessarily know that they are pregnant. Because of this, it is impossible to predict the consequences of treating pregnant women during the first trimester of pregnancy.

Albert Schweitzer Clinic, Gabon

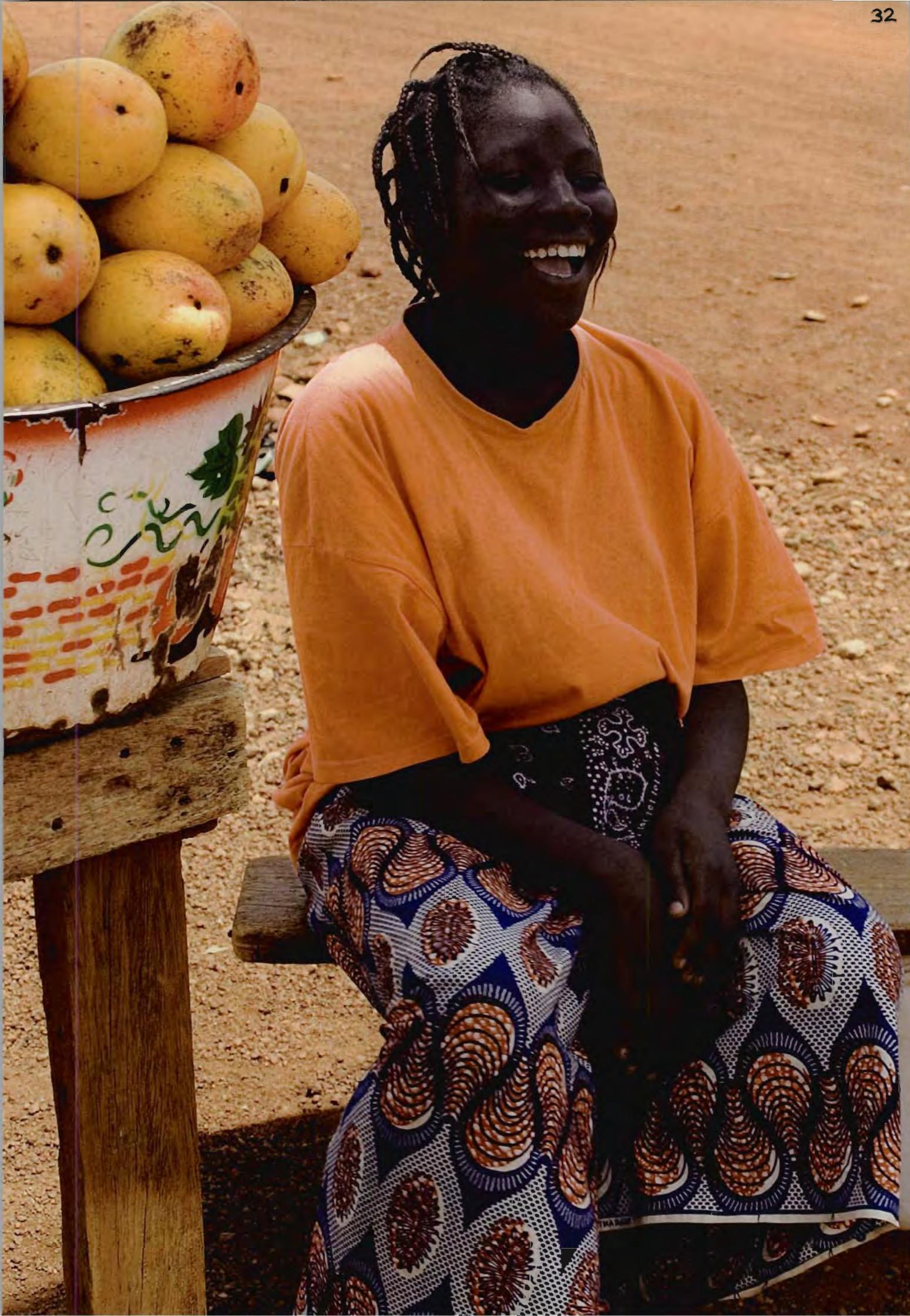
To conduct clinical trials to the standards required for inclusion in a registration dossier, MMV relies on a handful of clinical research centres in sub-Saharan Africa. Among them, the Medical Research Unit (MRU) of the Albert Schweitzer Hospital (ASH) in Lambaréné, Gabon, has special expertise in severe malaria.

At least one of the new products in MMV's current portfolio has the potential to be developed for severe malaria. A fully equipped and qualified clinical trial site, with the medical and research equipment to ensure safety of the study participants with severe malaria, is a requirement.

Funds provided by MMV through the special support of the Dutch Government have enabled the transformation and refurbishment of the old facility into a state-of-the-art clinical trial unit for conducting all-Phase safety and efficacy studies for antimalarial drugs, mainly in pediatric patients. It also enabled the setting-up of high standard laboratory infrastructure and the up-grading of equipment in order to:

- ▶ conduct clinical and research laboratory analyses at the standards required for regulatory drug studies;
- ▶ improve diagnostic capabilities to treat severe diseases;
- ▶ become a reference laboratory for various research and clinical analyses relating to malaria.

In addition, with such a structure in place, the MRU will serve as a training centre for clinical research and implementation of quality systems for the developing network of clinical trial centres in Africa.



MMV Project of the Year 2005: Pyronaridine Artesunate (PYRAMAX®)

A novel combination treatment for acute *Plasmodium falciparum* and *Plasmodium vivax* malaria

Today, artemisinin-based combination therapy (ACT) is the treatment of choice for acute malaria, as prescribed by the World Health Organization (WHO) in 2001. In early 2006, WHO urged the malaria community to stop the production and use of monotherapies. This counsel has been fully supported by MMV.

ACTs come in many shapes, sizes, and dosages: some require administration of several tablets more than once a day, or for longer than three days; some do not have patient-adapted pediatric formulations; and some are unaffordable and thus inaccessible to the vulnerable populations of malaria-endemic countries. Many currently-marketed ACTs continue to be given in co-blisters which are relatively expensive and prone to misuse. These limitations give rise to problems of compliance, which increase morbidity and mortality.

In an effort to address this critical lack of effective, affordable, easy-to-use, and accessible new antimalarial drugs, MMV launched a Call for Proposals in 2000. One of the most promising proposals accepted came from the South Korean pharmaceutical company Shin Poong Pharmaceuticals and the WHO Special Programme for Research and Training in Tropical Diseases (TDR), combining the artemisinin derivative, artesunate, with

a known antimalarial drug, pyronaridine. Pyronaridine is active against multiple chloroquine-resistant malaria *in vitro* and *in vivo* models. It was used for almost 20 years as monotherapy to treat malaria in the Hunan and Yunan provinces in China, where it was discovered in the 1970s. As the drug has not been used outside China, the rapid development of resistance once it is combined with artemisinin is less likely. Studies conducted by Looosewaan¹, Ringwald², and others, demonstrated that pyronaridine was an effective antimalarial drug in both African and Asian patient populations.

Pyronaridine artesunate (PYRAMAX®) is being developed as a 3-day treatment for acute uncomplicated malaria caused by *Plasmodium falciparum* or *Plasmodium vivax*. It is presented in two fixed-dose formulations: the tablet formulation contains 180:60 mg pyronaridine-artesunate for patients over 20 kg; and the pediatric formulation, in granular form, contains 60:20 mg pyronaridine-artesunate for infants over 5 kg.

Securing good stability is a critical measure of success in the development of artemisinin-based fixed-dose combinations, given that artesunate is very unstable when exposed to light, humidity, and high temperatures. Shin Poong developed a novel formulation technology

The PYRAMAX® project has been a leading example of virtual drug development within MMV's portfolio

to protect artesunate from pyronaridine and also to increase the stability of the combination. Once produced, PYRAMAX® tablets and granules will have a shelf-life of three years, which is longer than for other artesunate combinations and will be a key advantage in developing countries where storage facilities are not impervious to heat, light and humidity.

The PYRAMAX® project has been a leading example of virtual drug development within MMV's portfolio and could well be one of MMV's first-to-market products. A rigorous and exhaustive development programme was designed and undertaken, ensuring that PYRAMAX® was subjected to international regulatory standards at the manufacturing, non-



clinical, and clinical levels (GMP/GLP/GCP). The combination drug will be distributed to the public and private sector at an affordable price. Commercial scale manufacturing will take place in an EU GMP facility currently under construction in South Korea specifically for the product.

The early promise of PYRAMAX® in terms of efficacy, safety and tolerability from a large Phase II dose-finding trial in eight sites spread over six countries in Africa and South-East Asia, is now to be confirmed in Phase III pivotal trials in malaria patients which were implemented in the beginning of 2007. These trials will study the use of PYRAMAX® in patients with both *Plasmodium falciparum* and *Plasmodium vivax* malaria.

The PYRAMAX® team

By focusing on quality, deliverables, and world-class expertise, the pyronaridine artesunate team, comprising MMV, Shin Poong Pharmaceuticals and the University of Iowa, has achieved an efficient and cost-effective means of virtual drug development.

The Chair of the Product Development Team is Professor Larry Fleckenstein of the University of Iowa.

The PYRAMAX® team are grateful to the skills and dedication of the scientists at the clinical sites who have worked on the Phase I and Phase II trials: Prof. IJ Jang, Seoul National University, South Korea; Prof. S Looareesuwan, Mahidol University, Thailand; Prof. O Gaye, University of Dakar, Senegal; Dr. E Tjiitra, National Malaria Control Programme, Indonesia; Dr. D Socheat, National Malaria Control Programme, Cambodia; Dr. B Kalifa, Farafenni Hospital, The Gambia; Dr. P Piola, Mbarara Hospital, Uganda, and Prof. Kremsner, Albert Schweitzer Hospital, Lambaréné, Gabon.

Figure 2. Pyronaridine Artesunate Clinical Trial centres



The expertise, motivation and diligence of a number of specialist organizations have contributed to the success of the programme, including the Korean Institute of Toxicology, Fulcrum Pharma Developments, Family Health International, Akos Healthcare Group Ltd., LIFECORD (Korea), MicroConstants, and Hesperion.

The next challenge will be to ensure that the drug is accessible to the most vulnerable patients. To achieve this, MMV will join forces with Shin Poong, which has over 20 years of experience in registration, distribution, and marketing in Africa, Asia, and South America, and has been collaborating with the established WHO distribution network.

A registration plan is underway with Shin Poong to address access to markets of the approved product. The target is to submit a registration package in early 2008 to the European Agency for Evaluation of Medicinal Products (EMA) and to the Korea Food and Drug Administration (FDA). This will occur in parallel with submissions at the national level in key malaria-endemic countries, in conjunction with the work of MMV's Access and Delivery Advisory Committee that is preparing for the imminent launch of several MMV products by the end of 2008.

References

- 1 Looareesuwan S, Kyle DE, Viravan C, Vanjanonta S, Wilairatana P, Wernsdorfer WH. Clinical Study of pyronaridine for the treatment of acute uncomplicated falciparum malaria in Thailand. *Am J Trop Med Hyg.* 1996 Feb;54(2):205-209.
- 2 Ringwald P, Bickii J, Basco LK. Randomised trial of pyronaridine versus chloroquine for acute uncomplicated falciparum malaria in Africa. *Lancet.* 1996 Jan 6;347(8993): 24-28.



Behind the Scenes: the MMV Teams

MMV Board Members

Seated from left to right:

Win Gutteridge Chairperson, MMV Expert Scientific Advisory Committee (ESAC), (*Board Observer*)

Lynda, Baroness Chalker of Wallasey Chairman, Africa Matters Ltd UK (*Chairman, MMV Board*)

Anarfi Asamoah-Baah Assistant Director-General, HIV/AIDS, Tuberculosis & Malaria, World Health Organization, Switzerland

Standing from left to right:

Leon Rosenberg Department of Molecular Biology, Princeton University, USA

James Cochrane Vice Chair TNT nv and Former Director, GlaxoWellcome plc, UK

R A Mashelkar Director General, Council of Scientific and Industrial Research (CSIR), India

Regina Rabinovich Director, Infectious Disease Programme, Bill and Melinda Gates Foundation, USA

Chris Hentschel President and Chief Executive Officer, Medicines for Malaria Venture (MMV), Switzerland

Trevor Jones Former Director-General, The Association of the British Pharmaceutical Industry (ABPI), UK

Not pictured:

Pascoal Mocumbi High Representative, European and Developing Countries Clinical Trials Partnership (EDCTP)

Carlos Morel Scientific Coordinator, Oswaldo Cruz Foundation (FIOCRUZ), Brazil

MMV Access and Delivery Advisory Committee (ADAC)

Awa Marie Coll-Seck Executive Secretary, Roll Back Malaria Partnership (*Chairperson, ADAC*)

Dora Akunyili Director General, National Agency for Food & Drug Administration & Control, Nigeria

Joseph Amoussou Retail Pharmacist, Benin

Issa Diop Former Director, Centrale d'Achat (Central Procurement Agency), Senegal

Win Gutteridge Consultant and Visiting Professor, LSHTM, UK (*Chairperson, MMV ESAC*)

Paul Lalvani Consultant, Procurement and Supply Chain Management, USA (India)

P A Narayan Marketing (Pharmaceuticals), India

Daniel Ngamije Head, National Malaria Control Programme, Rwanda

Naawa Sipilanyambe Acting Head, National Malaria Control Programme, Zambia

Bob Snow Head, Malaria Epidemiology, Public Health Group, KEMRI/Wellcome Trust Programme, Nairobi, Kenya and the University of Oxford, UK

Francisco Songane Head, Neonatal, Maternal and Child Health Partnership, Mozambique

Ambrose Talisuna Assistant Commissioner, Ministry of Health; Head, Division, Epi. & Surveillance, Uganda

Marcel Tanner Director, Swiss Tropical Institute, Switzerland

Geoff Targett Deputy Director, Gates Malaria Partnership, UK

MMV Expert Scientific Advisory Committee (ESAC)

Win Gutteridge Consultant and Visiting Professor, LSHTM, UK (*Chairperson, ESAC*)

Richard Auty Chairman, MNLpharma Ltd.; Director, Salient Consulting Ltd. and Visiting Professor of Medicine, University of Malawi

George Aynilian Director of drug development with expertise in clinical research, international regulatory affairs and over 15 years of drug development experience

Bill Charman Dean, Monash University, Melbourne, Australia

Virander Chauhan International Centre for Genetic Engineering & Biotechnology (ICGEB), New Delhi, India

David Floyd Chief Scientific Officer and Executive Vice-President, Pharmacopela Drug Discovery, USA

Brian Greenwood Professor, Clinical Tropical Medicine, LSHTM, UK; Director, Malaria Centre and Gates Malaria Partnership

David Matthews Expertise in medicinal chemistry and structural-based drug design; Scientific Founder, Agouron Pharma (now Pfizer, La Jolla)

Maria Paris Senior Medical Director, ENANTA Pharmaceuticals, USA

Meg Phillips Professor, University of Texas Southwestern Medical Center, USA

Zulfiqarali Gulamhussien Premji Professor of Clinical Parasitology with over 25 years of experience in teaching, research and clinical work

David Roos Professor of Biology and Director, University of Pennsylvania Genomics Institute, USA

Jürg Seiler Former group leader, Swissmedic; Consultant in non-clinical pharmacology/toxicology and regulatory affairs

Dennis Schmatz Vice-President, Merck Research Laboratories, USA; Head, Tsukuba Research Institute, Japan

Bob Snow Head, Malaria Epidemiology, Public Health Group, KEMRI/Wellcome Trust Programme, Nairobi, Kenya and University of Oxford, UK

Henrietta Ukwu Vice-President, World Wide Regulatory Affairs, Wyeth Research Inc., USA

Thomas E Wellems Chief, Laboratory of Malaria Vector Research, NIAID/NIH, USA

Kitima Yuthavong Vice-President, Thailand Centre of Excellence for Life Sciences, Thailand

MMV Team

Chris Hentschel President and Chief Executive Officer

Jaya Banerji Communications Manager

Ian Bathurst Director, Drug Discovery and Technology

Isabelle Borghini-Fuhrer Associate Director, Clinical Sciences

Renia Coghlan Global Access Programme Officer

Diana Cotran Vice-President, Operations

Maud Couturier Administrative Assistant

J Carl Craft Chief Scientific Officer

Christine Crettenand Finance Assistant

Pascal Fantauzzi Associate Director, Drug Discovery

Penny Grewal Director, Global Access

Marion Hutt Business Development Manager

Erin Kimaoui Administration & Publications Officer/Assistant to the President and CEO

Maud Lugand Administrative Assistant

Jörg Möhrle Associate Director, Clinical Development

Claude Oeuvray Associate Director, Clinical Development

Peter Potter-Lesage Chief Financial Officer and Donor Relations

Lise Riopel Director, Clinical Development

David Ubben Director, Clinical Development

P V Venugopal Director, International Operations

Anna Wang Vice-President, Public Affairs



Financial Information

Medicines for Malaria Venture receives funding and support from government agencies, private foundations, international organizations, corporations and corporate foundations, and private individuals. These funds are used to finance the MMV portfolio of research and development projects to provide new, affordable medicines for the treatment and prevention of malaria. As a nonprofit Swiss Foundation under statutes dated 15 November 1999, MMV is exempt from cantonal and federal taxes and is the equivalent of an exempt organization within the meaning of Section 501(c)(3) of the United States Internal Revenue Code.

Financial year to 31 December 2006 - Summary

This seventh year of operations has indeed been a year of active transition for MMV with important and far-reaching financial implications. With four projects in late stage Phase III clinical trials, two new mini-portfolios and several other new entries into the Discovery Phase, malaria drug R&D expenditure increased dramatically (by 73%) while overall expenditure reached USD 51.5 million. Moreover, as the mission of MMV extended to embrace the facilitation of Access & Delivery, this new item represented USD 0.7 million in 2006. Significant new funding commitments by the government of Ireland – Irish Aid, the Netherlands Ministry of Foreign Affairs, and the Rockefeller Foundation, augmented the amount of funds pledged from USD 250 million to over USD 273 million to 2010.

The financial infrastructure and procedures of MMV have again evolved to meet the growing needs of the organization. Another financial assistant will join the team early in 2007.

KPMG provide audit services to MMV, and UBS, a major Swiss bank, manages the global banking relationship, offering services such as current accounts, investments and cash-management facilities in multiple currencies.

Interest on investments increased very substantially in 2006 to USD 1,280,111 reflecting active treasury management, considerably larger cash balances, and rising interest rates on international money markets. The Foreign Exchange Reserve created in 2003 to hedge against adverse fluctuations in future years, increased in 2006 to USD 459,667 due to a small exchange gain of USD 61,461 mainly as a result of lower USD exchange rates against other currencies in the latter part of the year.

International Financial Reporting Standards (IFRS) - Transition

The transition to International Financial Reporting Standards (IFRS) was completed with success. The 2005 MMV Financial Statements were the first to be issued under these standards and the organization's operating procedures are in line with requirements. Now mandatory for European listed companies, IFRS offers a real drive to greater disclosure, transparency and international comparison of financial figures.

Financial year to 31 December 2006 - Detail

Income

Overall Income decreased by 32% to USD 30,618,703 as compared with USD 44,770,355 in 2005, USD 28,797,559 (adjusted) in 2004, USD 21,712,944 in 2003, USD 10,586,792 in 2002, USD 13,599,677 in 2001 and USD 7,606,949 in 2000.

Research & Development Expenditure

Scientific project-related expenditure increased substantially to USD 46,943,252 as against USD 27,166,334 in 2005, USD 23,805,411 (adjusted) in 2004, USD 16,950,454 in 2003, USD 10,353,468 in 2002, USD 6,709,653 in 2001 and USD 2,280,748 in 2000.

Foundation Capital

By 31 December 2003, the stipulated foundation capital of USD 4,000,000 was fully subscribed (in a Swiss foundation it is a legal requirement that the Foundation Capital should be constituted without delay so as to provide a degree of financial security for the foundation). The Foundation Capital remains unchanged at 31 December 2006.

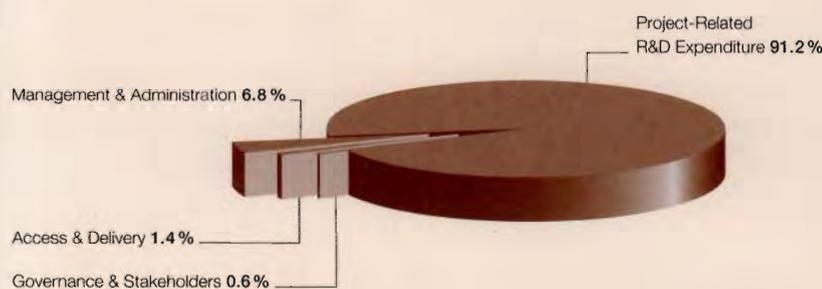
Donations & Pledges 2006

Cash received at bank amounted to USD 23,107,042 with USD 10 million received in December 2005 from the Bill & Melinda Gates Foundation recognized as income for 2006, and USD 3,919,607 from the Netherlands Government deferred to 2007.

Management & Administration

Management and Administration costs increased only slightly during 2006, although staff headcount went up by 50% from 14 to 21. However, the ratio of Management & Administration expenditure to overall spending decreased measurably to 6.8% compared with 11.1% in 2005.

MMV – 2006 Expenditure – Total: USD 51.5 million



Fundraising

Continued progress in fundraising was a feature of 2006:

Donor (new pledges)	Amount	Period
Netherlands Ministry of Foreign Affairs	EUR 7 million	4 years
Government of Ireland – Irish Aid	EUR 9 million	3 years
Rockefeller Foundation	EUR 0.45 million	1 year

MMV is grateful for these and previous commitments from its many donors.

Financial year ahead to December 2007

MMV operates in a complex multi-currency environment. The bulk of donations are received in US dollars, although other currencies are sometimes involved. Outflows for projects are mostly in USD, the standard currency used in the various agreements signed with project partners. Many operational expenses, however, are in Swiss Francs. The resulting exposure or exchange risk is hedged according to the budget in January and at mid-year, to provide a nominal fixed USD/CHF budget rate for the period. The accounts are kept in US dollars.

The philosophy underlining MMV's financial management is that of prudent, conservative control, including appropriate return on interim treasury investments. Forecasting various long-term funding and income scenarios enables MMV to manage the growing R&D portfolio more effectively. It also provides a base analysis for fundraising activities aimed at financing the portfolio in line with the projections of the MMV Business Plan 2003–2007, the Boston Consulting Group's 'Planning for Success' process completed in 2005, and further ongoing consultations with several donors. Moreover, currently in preparation is a new Business Plan 2007–2012, also in conjunction with the Boston Consulting Group.

Research & Development, Access and Facilitation of Delivery: Sustainability

In particular, 2006 was critical in beginning to prepare MMV's drug pipeline for market access. Thus, while 2005 allowed significant improvements to financial sustainability for drug R&D, 2006 saw substantial growth in our needs for staff and financial resources to prepare for scale-up and launch activities. In effect, a second and critical series of investments are now urgently needed to enable a further 'downstream' extension of the public-private partnership model that will underpin MMV's fundamental goal – that of achieving a major health impact from its products.

Although fundraising remains successful and the contingent assets to 2010 amounted to over USD 112 million at 31 December 2006, expected effective cash flow for 2007 at USD 50 million is

a major constraint at the time of writing (March 2007), obliging the organization to slow certain critical Research and Development projects and to label others as 'approved, but as yet unfunded'.

Financial Modelling

Financial modelling (below) suggests that, in spite of the increase in pledged funding for MMV in 2006, access and delivery activities remain substantially unfunded. Our current forecasts for future MMV overall spending are USD 60 to 65 million in 2006, and thereafter an average of USD 60 to 70+ million annually, representing a mixture of R&D, product launch and access-related spending.

Since its foundation, Medicines for Malaria Venture has been granted multi-year pledges of funding for its R&D portfolio, notably from the Bill & Melinda Gates Foundation, the UK Department for International Development, the Swiss Agency

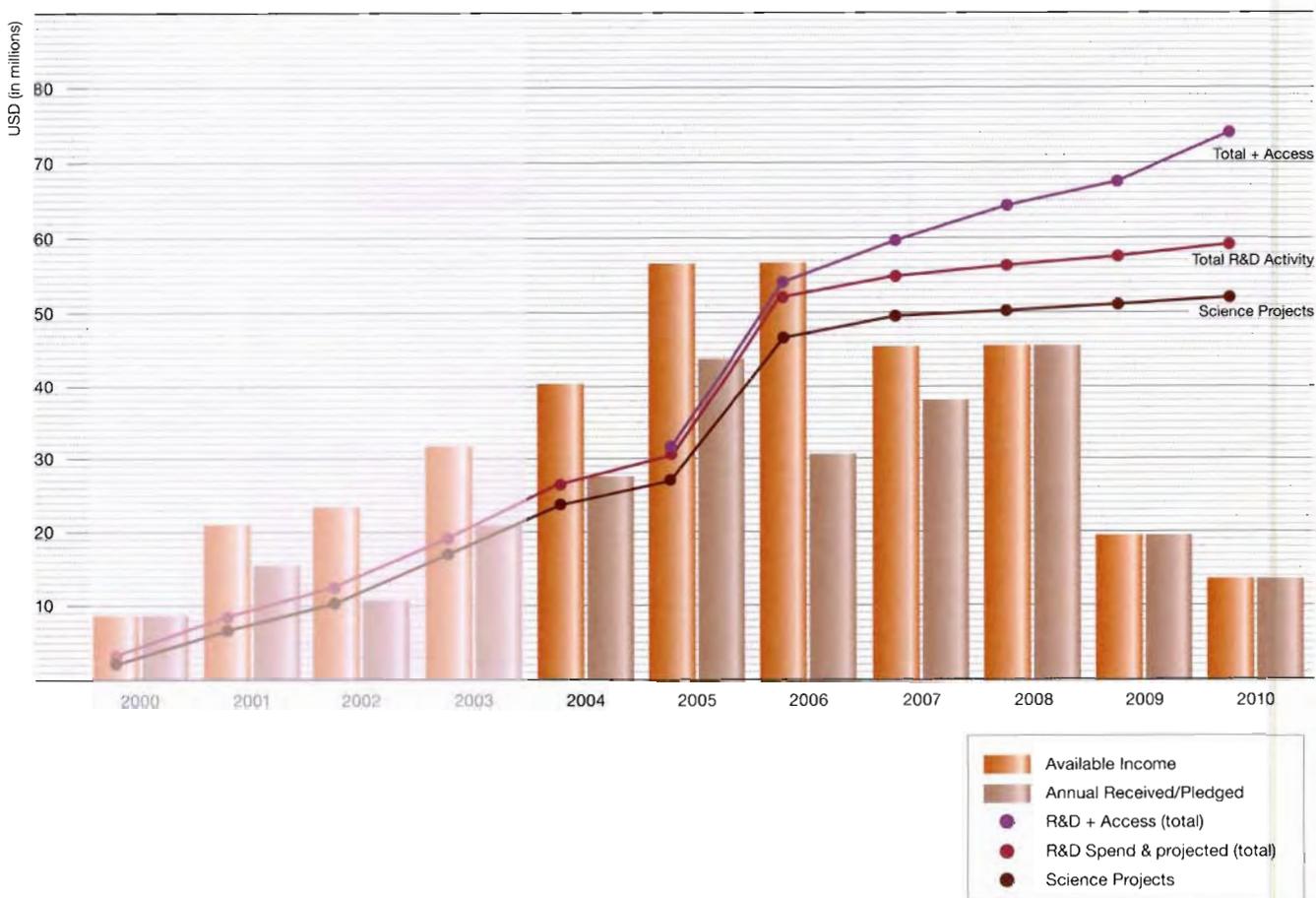
for Development and Cooperation, the Rockefeller Foundation, USAID, Exxon-Mobil, the Dutch Government, Irish Aid, BHP Billiton and the Wellcome Trust.

These statements and all forward-looking financial figures should be considered as management's best estimates based on information available at the time of printing (April 2007).

Financial Tables

The financial tables that follow – Balance Sheet, Statement of Income & Expenditure, Cash Flow and Notes – represent MMV in its seventh full year of operation. These tables are extracted from IFRS full International Financial Reporting Standards compliant accounts. We are one of the first product development public-private partnership and among the first nonprofit organizations to report using these widely accepted international standards.

Figure 3. MMV actual and projected Income & Expenditure 2000-2010



MMV Balance Sheet at 31 December

ASSETS	Notes	2006 USD	2005 USD
CURRENT ASSETS			
Cash and cash equivalents	3	19 826 097	37 672 107
Donations Receivable	6	0	4 577
Accounts Receivable		36 354	75 101
Recoverable Withholding Tax		466 685	223 201
Project-related prepaid expenses		25 645	5 621 519
Total CURRENT ASSETS		20 354 780	43 596 505
LONG-TERM ASSETS			
Guarantees	14	74 213	43 381
Fixed assets, net	4	220 578	52 883
Total LONG-TERM ASSETS		294 790	96 264
TOTAL ASSETS		20 649 570	43 692 769
LIABILITIES AND CAPITAL & RESERVES			
CURRENT LIABILITIES			
Accrued R&D Commitments	7	5 794 953	2 047 249
Deferred Income	6	3 919 607	10 000 000
Other Creditors		328 990	314 722
Accrued Expenses		778 486	561 226
Short-term Provisions	5	160 000	246 965
Total CURRENT LIABILITIES		10 982 036	13 170 162
CAPITAL & RESERVES			
FOUNDATION CAPITAL		4 000 000	4 000 000
OPERATIONS RESERVE		5 207 866	23 772 497
FOREIGN EXCHANGE RESERVE		459 667	398 206
DONOR RESTRICTED RESERVE		0	2 351 903
TOTAL CAPITAL & RESERVES		9 667 534	30 522 607
TOTAL LIABILITIES AND CAPITAL & RESERVES		20 649 570	43 692 769

MMV Statement of Income & Expenditure for the year ended 31 December

INCOME	Notes	2006 USD	2005 USD
DONATION REVENUES			
Private Foundations & Individual Donors		14 889 579	37 375 004
UN Agencies		750 000	750 000
Government Agencies		12 797 857	4 879 963
Corporates & Corporate Foundations		750 000	750 000
Total DONATIONS RECEIVED	6	29 187 435	43 754 967
OTHER INCOME			
Financial Income, net	9	1 289 113	635 425
Project Balance Reimbursements	7	97 556	65 866
Other		44 598	314 096
OTHER INCOME		1 431 267	1 015 387
TOTAL INCOME		30 618 703	44 770 355
EXPENDITURE			
RESEARCH & DEVELOPMENT EXPENDITURE			
Project-Related Variable Expenditure	7-8	46 646 940	26 844 576
Expert Scientific Advisory Committee Expenses		296 312	321 758
RESEARCH & DEVELOPMENT EXPENDITURE		46 943 252	27 166 334
ACCESS EXPENDITURE			
Access-Related Variable Expenditure	8	697 556	0
Access & Delivery Advisory Committee		34 278	0
ACCESS EXPENDITURE		731 834	0
FOUNDATION BOARD & STAKEHOLDER EXPENSES	12	291 300	136 952
GENERAL & ADMINISTRATION EXPENSES			
Staff-Related Benefits - Compensation	8	1 915 567	1 735 094
Office and Occupancy	10	565 200	391 881
Travel Expenses		196 638	194 638
Fundraising		168 571	264 924
Professional & Legal Fees		121 747	402 967
Training, Education & Journals		81 312	153 927
IT Expenses		153 704	87 366
Communications		187 728	127 267
Depreciation	4	103 638	56 193
Other		13 284	5 455
GENERAL ADMINISTRATION EXPENSES		3 507 390	3 419 712
TOTAL EXPENDITURE		51 473 776	30 722 999
NET RESULT		(20 855 073)	14 047 356
ALLOCATIONS			
TRANSFER FROM/(TO) OPERATIONS RESERVE		18 564 631	(11 747 389)
TRANSFER FROM/(TO) DONOR RESTRICTED RESERVE		2 351 903	(2 351 903)
TRANSFER (TO)/FROM FOREIGN EXCHANGE RESERVE		(61 461)	51 937
		20 855 073	(14 047 355)

MMV Statement of Cash Flows to 31 December

	Notes	2006 USD	2005 USD
EXCESS OF INCOME/(EXPENDITURE) FOR THE YEAR		(20 855 073)	14 047 356
(Decrease)/Increase in Provisions		(86 965)	(19 035)
Depreciation	4	103 638	56 193
OPERATING RESULT BEFORE WORKING CAPITAL CHANGES		(20 838 400)	14 084 514
CASH FLOWS FOM OPERATING ACTIVITY			
Decrease/(Increase) in Donations Receivable	6	4 577	(4 577)
Decrease/(Increase) in Project Balance Reimbursements	7	0	647 466
Decrease/(Increase) in Accounts Receivable		38 747	(54 250)
Increase in Recoverable Withholding Tax		(243 484)	(177 255)
Decrease/(Increase) in Project-related Prepaid Expenses		5 595 876	(4 190 400)
Increase in Accrued R & D Commitments		3 747 706	871 257
Decrease/(Increase) in Deferred Income		(6 080 393)	10 000 000
Increase in Other Creditors		14 268	240 597
Increase in Accrued Expenses		217 260	85 900
CASH FLOW RESULTING FROM OPERATING ACTIVITY		3 294 559	7 418 739
CASH FLOWS FROM INVESTMENT ACTIVITY			
Decrease/(Increase) in Guarantees		(30 832)	6 749
(Increase) in Fixtures and Installations	4	(81 410)	(17 123)
(Increase) in Office Furniture	4	(76 452)	(3 303)
(Increase) in Computers and Equipment	4	(113 471)	(31 123)
CASH FLOW RESULTING FROM INVESTMENT ACTIVITY		(302 166)	(44 800)
NET VARIATION OF CASH AND CASH EQUIVALENTS		(17 846 007)	21 458 453
CASH & CASH EQUIVALENTS AT BEGINNING OF YEAR		37 672 107	16 213 654
CASH & CASH EQUIVALENTS AT END OF YEAR		19 826 097	37 672 107

MMV Statement of recognized Income & Expenditure

	Capital Fund USD	Operations Reserve USD	Restricted Reserve USD	Foreign Exchange Reserve USD	Total Capital & Reserves USD
BALANCE AT 1 JANUARY 2005	4 000 000	12 025 109	0	450 143	16 475 252
Allocation of result for the year	0	11 747 389	2 351 903	(51 937)	14 047 355
BALANCE AT 31 DECEMBER 2005	4 000 000	23 772 498	2 351 903	398 206	30 522 607
Allocation of result for the year	0	(18 564 631)	(2 351 903)	61 461	(20 855 073)
BALANCE AT 31 DECEMBER 2006	4 000 000	5 207 867	0	459 667	9 667 534

Notes to the financial statements for the year ended 31 December 2006

1. Organization

MEDICINES FOR MALARIA VENTURE (MMV) is a Swiss Foundation, established as a not-for-profit legal entity, registered in Geneva under statutes dated 15 November 1999. It is managed by a foundation council, a chief executive officer and three senior managers.

With its head office in Geneva, the aim of MMV is to bring public and private sector partners together to fund, and provide managerial and logistical support for, the discovery and development of new medicines for the treatment and prevention of malaria. The products should be affordable and appropriate for use by populations in developing countries.

As with all Swiss foundations, Medicines for Malaria Venture is monitored by the Swiss Federal Supervisory Board for Foundations.

2. Significant accounting policies

The financial statements were approved for issue by the MMV Board on 20 March 2007.

The significant accounting policies adopted by MMV in the preparation of the financial statements are set out below.

Statement of compliance

The financial statements have been prepared in accordance with International Financial Reporting Standards (IFRS) and its interpretations adopted by the International Accounting Standards Board (IASB) and comply with Swiss law.

Basis of preparation

The financial statements are presented in US dollars, since a majority of MMV's activities is conducted in this currency. They are prepared on the historical cost basis.

Fair value is the amount for which a financial asset, liability or instrument could be exchanged between knowledgeable and willing parties in an arm's length transaction.

The preparation of financial statements in conformity with IFRS requires management to make judgements, estimates and assumptions that affect the application of policies and reported amounts of assets and liabilities, income and expenditure. The estimates and associated assumptions are based on historical experience and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis of making the judgements about carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates. If in the future such estimates and assumptions, which are based on management's best judgement at the date of the financial statements, deviate from the actual circumstances, the original estimates and assumptions will be modified as appropriate in the year in which the circumstances change.

Judgements made by management in the application of IFRS that have significant effect on the financial statements and estimates with a significant risk of material adjustment in the next year are discussed below.

The accounting policies set out below have been applied consistently to all periods presented in these financial statements.

Foreign currency transactions

Transactions in foreign currencies are translated at the foreign exchange rate ruling at the date of the transaction. Monetary assets and liabilities denominated in foreign currencies at the balance sheet date are translated to USD at the foreign exchange rate ruling at that date. Foreign exchange differences arising on translation are recognized in the statement of revenue and expenditure. Non-monetary assets and liabilities that are measured in terms of historical cost in a foreign currency are translated using the exchange rate at the date of the transaction.

The following exchange rates were used at year-end:

2005	1 CHF = USD	0.7588
	1 EUR = USD	None
	1 GBP = USD	1.7168
2006	1 CHF = USD	0.8192
	1 EUR = USD	1.3187
	1 GBP = USD	1.9572

Cash and cash equivalents

Cash and cash equivalents comprise cash balances and short-term money market deposits with original maturities of three months or less.

Fixed or tangible assets

Fixed assets are stated at cost less accumulated depreciation. Depreciation is charged to the income statement on a straight line basis over the estimated useful lives of the assets. The estimated useful lives of assets are as follows:

office furniture	5 years
fixtures and installations	3 years
computers and equipment	3 years

Impairment

The carrying amounts of the MMV's assets are reviewed at each balance sheet date to determine whether there is an indication of impairment. If any such indication exists, the asset's recoverable amount is estimated. An impairment loss is recognized in the income statement whenever the carrying amount of an asset exceeds its recoverable amount.

Provisions

A provision is recognized in the balance sheet when MMV has a present legal or constructive obligation as a result of a past event, and it is probable that an outflow of economic benefits will be required to settle the obligation.

Employee benefits

MMV maintains a defined contribution plan for its employees. Contributions to the defined contribution pension plan are recognized as an expense in the statement of income and expenditure as incurred.

Foundation capital

The Capital Fund is fully subscribed at USD 4,000,000 as stipulated under the original legal statutes. Under normal circumstances, Foundation Capital may be used during the year to meet cash flow shortfalls, but should be replenished before closing at year end. Under exceptional circumstances, Foundation Capital serves to maintain the viability of the organization, for 6 to 9 months, until other funding sources can be found.

Revenue recognition

An unconditional grant is recognized as revenue in the statement of revenue and expenditure when the grant becomes receivable. Any other grant which has performance or other conditions is recognized in the balance sheet initially as deferred income when there is reasonable assurance that it will be received and that the foundation will comply with the conditions attaching to it, and recognized as revenue when these conditions are satisfied. Exceptionally, contributions may be restricted to specific activities by donors. In this case, such donations are attributed to the Donor Restricted Reserve which is used as those activities progress.

A reconciliation between donations received in cash and income recognized in the income and expenditure account is shown in note 6.

Operations reserve

The accumulated Operations Reserve represents excess of income over expenditure since the inception of MMV, and is available to be utilized for future operation and project funding costs as the rapidly evolving research and development project pipeline dictates.

Foreign exchange reserve

Expenditure for operational costs in Geneva is denominated in Swiss Francs. The Foreign Exchange Reserve serves as a segregated fund for use to reduce the impact of future adverse currency fluctuations.

Donor-restricted reserve

The Donor-restricted Reserve was created during 2005 in connection with a contribution from the Netherlands Government. The use of these funds is restricted to five specified clinical trial capacity-building and artemisinin yield improvement projects additional to the principle R&D portfolio. This reserve was fully used in 2006 for those projects.

Financial income/(expense), net

Financial income/(expense), net comprises interest on funds invested and foreign exchange gains and losses.

Research and development expenditure

Expenditure and grants allocated for research and development activities undertaken with the prospect of gaining new scientific or technical knowledge and understanding are recorded on the basis of contracts with grantees. In the event that a portion of a grant is unpaid at the year-end, it is included under current liabilities. Expenses paid before year-end for the following period are recorded as Project-related Prepaid Expenses in the current assets and as Prepaid in note 7.

Regulatory and other uncertainties inherent in the development of new products in this sector preclude MMV from capitalizing development costs.

Income tax

MMV has received exoneration from income tax from the Geneva cantonal and Swiss federal authorities from the year 2000 for an indeterminate period.

Accounting estimates and judgements

Certain critical accounting judgements in applying the organization's accounting policies are described as follows.

Revenue recognition – MMV enters into complex grant contracts that contain numerous provisions related to performance, reporting and spending. These criteria are monitored by both the scientific programme and finance teams to assess progress according to grant milestones and objectives. The evaluation of progress requires judgement, as it is based on subjective evaluations and discussions with programme participants and sponsors.

Research and Development Expenditure – MMV's research and development expenditure is generally not direct expenditure, but is in the form of grants and contracts with external parties who perform certain tasks at MMV's request. These requests are formalized by contracts and agreements that outline the requested services and development effort. Progress against expectations is difficult to measure, and measurement criteria are generally not defined in grant agreements. Additionally, actual research and development timing and execution are often different than the original plans. These factors lead to subjectivity in the timing and recognition of research and development expenditure.

Fair value

The fair value of cash, other assets, deferred income and other creditors are not materially different from the carrying amounts.





3. Cash and cash equivalents

	2006 USD	2005 USD
Cash	1 417	415
Bank balances	1 024 680	1 419 652
Money market deposits	18 800 000	36 252 040
	19 826 097	37 672 107

4. Fixed assets

2005	Fixtures Installations USD	Office Furniture USD	Computers & Equipment USD	Total USD
COST:				
At 1 January 2005	28 643	107 841	111 658	248 142
Additions	17 123	3 303	31 123	51 459
At 31 December 2005	45 765	111 144	142 781	299 690
ACCUMULATED DEPRECIATION:				
At 1 January 2005	28 643	81 965	80 007	190 614
Charge for the year	5 708	22 079	28 406	56 193
At 31 December 2005	34 350	104 044	108 413	246 807
NET BOOK VALUE:				
AT 31 DECEMBER 2005	11 415	7 100	34 368	52 883

2006	Fixtures Installations USD	Office Furniture USD	Computers & Equipment USD	Total USD
COST:				
At 1 January 2006	45 765	111 144	142 781	299 690
Additions	81 410	76 452	113 471	271 333
At 31 December 2006	127 175	187 596	256 252	571 023
ACCUMULATED DEPRECIATION:				
At 1 January 2006	34 350	104 044	108 413	246 807
Charge for the year	32 844	18 564	52 230	103 638
At 31 December 2006	67 194	122 608	160 643	350 446
NET BOOK VALUE:				
AT 31 DECEMBER 2006	59 981	64 988	95 609	220 578

5. Provisions

Statements of movement in provisions:

	Service-Related Provisions USD	Unused Vacation reserve USD	Total Provisions USD
Balance at 1 January 2005	180 000	86 000	266 000
Use/release 2005	(28 845)	(6 000)	(34 845)
Allocation for the year	15 810	0	15 810
Balance at 31 December 2005	166 965	80 000	246 965
Use/release 2006	(166 965)	0	(166 965)
Allocation for the year	0	80 000	80 000
BALANCE AT 31 DECEMBER 2006	0	160 000	160 000

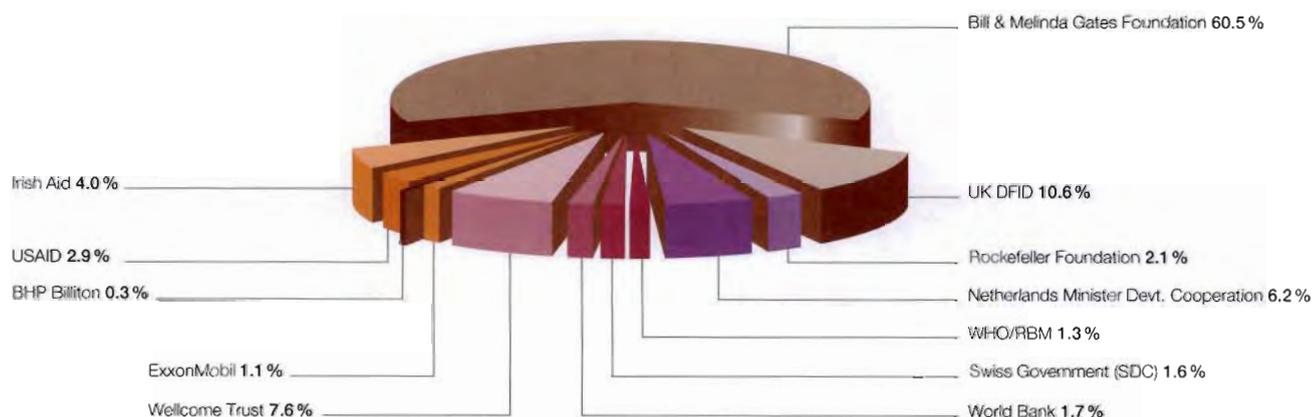
6. Donations

Below is a summary of donations received or committed during 2006:

	Cash received 2006 USD	Income recognized from previous year USD	Income deferred to following year USD	Current year income to be received USD	Total income as per I&E account USD
Bill & Melinda Gates Foundation	-	10 000 000	-	-	10 000 000
Rockefeller Foundation	450 000	-	-	-	450 000
Wellcome Trust	4 427 300	-	-	-	4 427 300
Swiss Government (DEZA/SDC)	649 200	-	-	-	649 200
UK Government (DFID)	5 425 100	-	-	-	5 425 100
Dutch Government (NMDC)	5 315 164	-	(3 919 607)	-	1 395 557
US Government (USAID)	1 500 000	-	-	-	1 500 000
Irish Aid	3 828 000	-	-	-	3 828 000
World Bank via Global Forum	750 000	-	-	-	750 000
ExxonMobil	500 000	-	-	-	500 000
BHP Billiton	250 000	-	-	-	250 000
Individual donors	12 279	-	-	-	12 279
TOTAL RECEIVED	23 107 042	10 000 000	(3 919 607)		29 187 435

Figure 4. Funding from Foundation to end 2010 (as of December 2006)

Total received/pledged: USD 273 million



7. Project-related variable expenditure

PROJECT	Recognized in 2006 USD	Awarded in 2006 USD	Paid in 2006 USD	Relating 2006 Paid 2007 USD
CLINICAL DEVELOPMENT PROJECT				
Chlorproguanil-dapsone (Lapdap™)-artesunate ¹	3 998 215	3 998 215	3 998 215	
Pyronaridine-artesunate ²	6 823 463	6 823 463	5 830 896	992 567
Coartem® dispersable tablets ³	2 956 579	2 956 579	2 205 531	751 048
DB289 (an improved pentamidine) ⁴	1 036 996	1 036 996	1 036 996	
RBx11160 + Piperazine ⁵	7 025 448	7 025 448	5 494 223	1 531 225
Dihydroartemisinin-piperazine ⁶	7 808 924	7 808 924	5 558 825	2 250 099
AQ-13 ⁷	113 000	113 000	113 000	
PRECLINICAL TRANSITION PROJECTS				
Isoquine (an improved aminoquinoline) ⁸	476 508	476 508	312 916	163 592
4 (1H)-pyridones ⁹	484 481	484 481	452 481	32 000
DISCOVERY PROJECTS				
* Falcipain (cysteine protease) ¹⁰	483 157	483 157	483 157	
Protein farnesyltransferase (Pf-PFT) ¹¹	283 173	283 173	283 173	
Dihydrofolate reductase (DHFR) ¹²	776 171	776 171	772 382	3 790
New dicationic molecules ¹³	1 330 245	1 330 245	1 321 859	8 386
* 4 (1H)-pyridones (back-ups) ¹⁴	-	-	-	
Enantioselective 8-aminoquinolines ¹⁵	840 117	840 117	791 219	48 898
Novel liver stage antimalarials ¹⁶	1 230 965	1 230 965	1 230 965	
EXPLORATORY PROJECTS				
* <i>P. falciparum</i> enoyl-ACP reductase (FAB1) ¹⁷	509 708	509 708	509 708	
PSAC antagonists ¹⁸	248 358	248 358	248 358	
Cyclofarnesyl-sesquiterpenes (Cameroonian medicinal plants) ¹⁹	8 705	8 705	8 705	
Next Generation OZ ²⁰	843 695	843 695	830 348	13 347
MINI-PORTFOLIO				
GSK Tres Cantos mini-portfolio ²¹	2 307 165	2 307 165	2 307 165	
NITD Singapore mini-portfolio ²²	544 110	544 110	544 110	
ENABLING PROJECTS				
STI Services - Discovery ²³	621 270	621 270	621 270	
GSK Tres Cantos Support Group ²⁴	352 063	352 063	352 063	
Artesunate Segment II Study ²⁵	521 055	521 055	521 055	
Nerviano Medical - Toxicology ²⁶	14 674	14 674	14 674	
Gabon/Albert Schweitzer Hospital ²⁷	552 000	552 000	552 000	
DXP/DXS Screening ²⁸	52 000	52 000	52 000	
Discovery technologies ²⁹	23 600	23 600	23 600	
ARTEMISININ RESEARCH				
Carbon-14 labelled artemisinin ³⁰	17 438	17 438	17 438	
Artemisinin cultivars ³¹	960 000	960 000	960 000	
Artemisinin extraction benchmarking ³²	124 608	124 608	124 608	
Artemisinin extraction technology ³³	18 069	18 069	18 069	
TOTAL	43 385 959	43 385 959	37 591 006	5 794 953

* Projects managed within the GSK mini-portfolio

- 1 GlaxoSmithKline, UK; University of Liverpool, UK; WHO/TDR, Switzerland
- 2 Shin Poong Pharma, Korea; University of Iowa, USA
- 3 Novartis Pharma AG, Switzerland
- 4 Imtech International, USA; University of North Carolina, USA
- 5 Ranbaxy Laboratories, India; University of Nebraska, USA; Monash University, Australia; Swiss Tropical Institute, Switzerland
- 6 Sigma-Tau Industrie Farmaceutiche, Italy; University of Oxford, UK; Hologic Pharma, China
- 7 Tulane University, USA; Imtech International, USA
- 8 GlaxoSmithKline, UK; University of Liverpool, UK
- 9 GlaxoSmithKline, UK
- 10 GlaxoSmithKline, Spain; University of California San Francisco, USA

- 11 University of Washington, Seattle, USA; Yale University, USA
- 12 BIOTECH, Thailand; Monash University, Australia; London School of Hygiene & Tropical Medicine, UK
- 13 University of North Carolina, USA; STI, Switzerland
- 14 GlaxoSmithKline, Spain
- 15 University of Mississippi, USA
- 16 Walter Reed Army Institute of Research, USA
- 17 GlaxoSmithKline, Spain; Texas A&M University, USA; Albert Einstein College of Medicine, USA
- 18 National Institutes of Health, USA; Broad Institute of MIT and Harvard
- 19 University of Buea, Cameroon
- 20 University of Nebraska, USA; Monash University, Australia; Swiss Tropical Institute, Switzerland

- 21 GlaxoSmithKline, Spain
- 22 Novartis Institute for Tropical Diseases (NITD), Singapore
- 23 Swiss Tropical Institute, Switzerland
- 24 GlaxoSmithKline, Spain
- 25 Shin Nippon Biomedical Laboratories, Japan
- 26 Nerviano Medical Services, Italy
- 27 University of Tuebingen, Germany
- 28 Texas A&M University, USA
- 29 Sanaria Inc, USA
- 30 Research Triangle Institute (RTI), USA
- 31 University of York, UK
- 32 FSC Development Partners Ltd, UK
- 33 Bionigs, UK

7. Project-related variable

expenditure (continued)

Project-related variable expenditure represents the awards to the projects as specified on the previous page, directly managed and supervised by MMV. It also includes all legal advice/services for contract negotiations (IPR), organization and travel for project meetings/reviews, MMV scientific personnel compensation and various scientific project consultancies. Expenditure for this MMV support totalled USD 3,260,981 and USD 2,287,018 in 2006 and 2005, respectively.

Project balance reimbursements

Refer to unused balances of project grants previously committed, which are returned to MMV by the project partners, as stipulated in the individual contractual agreements on termination or reorganization of R&D projects.

8. Personnel expenses

There were 21 employees as at 31 December 2006 (2005: 14). The Pension Expense concerns MMV payments to a defined contribution plan.

Salaries and related charges are included under Project-Related Variable Expenditure, Access-Related Variable Expenditure and Staff-Related Benefits/Compensation.

9. Financial income (expense), net

Financial income (expense)	2006 USD	2005 USD
Interest income	1 280 111	703 332
Financial expense	(52 458)	(15 970)
Exchange gain (loss)	61 461	(51 937)
Net	1 289 144	635 425

10. Leases

MMV has several operating leases. These leases generally run for a period of 5 years, with an option to renew the lease after that date. During the year ended 31 December 2006, USD 369,755 was recognized as an expense in the income statement in respect of operating leases (2005: USD 209,139). Lease expenses are included under Office & Occupancy in the Income Statement.

11. Contingent assets

As per contractual agreements, and depending on satisfactory reporting to donors, contingent assets related to donations are as follows:

	2006 USD	2005 USD
Less than one year	34 150 000	23 336 859
Between one and five years	112 438 235	123 769 620
More than five years	0	0

12. Related parties

MMV has a related party relationship with its board members and executive officers.

In addition to their salaries, the organization also contributes to a defined contribution pension plan for all staff on a ratio of 75% employer and 25% employee.

Total remuneration is included in Project-Related Variable Expenditure, Access-Related Variable Expenditure and Staff-Related Benefits/Compensation.

Board members serve on a voluntary basis and receive no remuneration. They are compensated for travel and accommodation for participation in board meetings and receive a per diem allowance to cover incidental expenses during these events.

There were no loans to directors or executive officers for the year ended 31 December 2006 or 31 December 2005.

13. Credit risk

In accordance with MMV credit policy, exposure to credit risk, principally as regards contributions, is monitored on an ongoing basis.

MMV's liquid assets are kept in cash or low-risk short-term deposits.

At the balance sheet dates there were no significant concentrations of credit risk. The maximum exposure to credit risk is represented by the carrying amount of each financial asset in the balance sheet, principally accounts receivable, short-term deposits and cash.

14. Guarantees

Guarantees concern office rental only and are recoverable on vacating the premises subject to the prevailing contracts.

15. Capital commitments and contingencies

As at 31 December 2006, there were no significant capital expenditure commitments. As a condition to MMV's business credit card relationship with its bank it has signed the bank's general terms and conditions agreement. This agreement requires that MMV pledge certain of its assets to secure unpaid credit card transactions.

Report of the Auditors to the Board of MMV



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Report on summarized financial statements to the management of **Medicines for Malaria Venture, Geneva**

We have audited the financial statements of Medicines for Malaria Venture for the year ended December 31, 2006 from which the summarized financial statements were derived, in accordance with Swiss Auditing Standards and with the International Standards on Auditing. In our report dated 20 March 2007, we expressed an unqualified opinion on the financial statements from which the summarized financial statements were derived.

In our opinion, the accompanying summarized financial statements are consistent, in all material respects, with the financial statements from which they were derived.

For a better understanding of the organisation's financial position and the results of its operations for the period and of the scope of our audit, the summarized financial statements should be read in conjunction with the financial statements from which the summarized financial statements were derived and our audit report thereon.

KPMG Ltd

William D. Laneville
Auditor in Charge

Pierre Henri Pigeon

Geneva, March 20, 2007

Enclosure:

- Summarized financial statements

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Curing Malaria Together



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