Our vision is a world in which affordable drugs will help eliminate the devastating effects of malaria and help protect billions of people at risk. Through successful public-private partnerships, Medicines for Malaria Venture discovers, develops and delivers safe and effective antimalarial drugs appropriate for the neediest population. With the largest-ever portfolio in development, MMV ensures that antimalarial drugs are delivered as “public goods” and ultimate health impact is made in disease endemic countries. As a nonprofit organization leveraging public sector financial resources, MMV improves the economic prospects of new drug innovation by attracting, funding and partnering with pharmaceutical companies, academic and other research institutions.

Curing Malaria Together
Mission

Medicines for Malaria Venture is a nonprofit foundation 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 has received funding and support from the following organizations:

- Bill and Melinda Gates Foundation
- ExxonMobil
- Global Forum for Health Research
- International Federation of Pharmaceutical Manufacturers Associations
- Netherlands Minister for Development Cooperation
- Rockefeller Foundation
- Swiss Agency for Development and Cooperation
- United Kingdom Department for International Development
- World Bank
- World Health Organization
- Roll Back Malaria
- UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)
- The Wellcome Trust
- BHP Billiton
- United States Agency for International Development

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Drawings: courtesy of the children of Maputo, Mozambique, who took part in the drawing contest in 2004.
The environment leading to MMV’s establishment is worth recalling. There had for several decades been major breakthroughs in basic and applied medical science that had dramatically reduced the disease burden in the industrialized world. In contrast, the burden of avoidable disease in developing countries was worsening, and investments in relevant health innovations were declining.

The result is perhaps best exemplified in the 2003 World Health Report which details an appalling 40 to almost 50 year difference in life expectancy between parts of sub-Saharan Africa and the industrialized world. While there were many factors compounding this desperate health inequity, the resurgence of malaria in Africa was clearly one, and in particular the inability of Africa’s rural health systems to provide prompt effective treatment for malaria. This was exacerbated by the increasing problem of drug resistance and by the fact that antimalarial drug innovation had practically ceased due to “market failure,” a term that obscures the true complexity of the problems MMV and the malaria control community faced.

MMV was founded in this rather bleak setting in November 1999 with a very clear and highly focused vision. Put simply, MMV would reverse the decline in malaria drug innovation by exploiting an innovative public-private partnership model, focused on developing antimalarial drugs as global public goods. Performance metrics were clear from the start, albeit rough and ready. To quote from a WHO press release, “MMV’s goal is that new antimalarials are brought to the market and are accessible to those that need them... it is expected that the first products developed through MMV could be available before 2010.”

While initially couched in rather vague terms, this goal was soon backed by a detailed business plan which incorporated year by year targets for the growth and development of the MMV portfolio, as well as potential sources and detailed use of funds, and the expected in-kind industry contributions.

The business plan projected that by 2005 MMV would have grown its portfolio to 11 research and development (R&D) projects of which two or three would have been selected for development. It was hoped that one of these might have advanced to efficacy testing in humans (Phase II clinical trials). In fact, after five years of operation, MMV and its partners have performed much better. At the time of writing, we have more than 20 projects (some with back-ups), nine of which are in development. Most remarkably, five of these are already in Phase II or later clinical development. While the risk of failure with these projects always remains, no one today can argue with the notion that MMV has made a very real and positive difference to the chances of developing important new antimalarial drugs before 2010.

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In Roman numerals the year 2005 is written MMV, a piece of serendipity that we regard as auspicious for our fifth anniversary. As this report illustrates, 2004/5 has indeed been a significant year for MMV, one based on solid achievements that amply affirm the vision and strategies developed by our founders in the late 1990s.

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Because MMV’s statutes rightly require periodic Board turnover, succession planning is crucial. In 2006, Dame Bridget Ogilvie will relinquish the Board Chair position after two three-year terms and other new Board members will be sought and nominated. While this is an ongoing process, we are delighted to be able to announce that Baroness Lynda Chalker of Wallasey has agreed to succeed to the Board Chair position.

After many years in British politics, most recently as Minister for Overseas Development, Baroness Chalker is currently Chairperson of Africa Matters Limited, an independent consultancy on African business and development issues. She brings with her an unparalleled mix of global political, development and business experience as well as a unique direct style that will serve MMV well through the many challenges ahead, not least those related to the delivery part of our discover, develop, deliver mission.

Today we can confidently predict that MMV’s achievements, well exemplified in the extensive scientific section of this report, will act as a springboard for the next five years.

Furthermore, we know that our continuing progress will rely not on serendipity but on the hard and focused work of MMV’s staff, and of our many partners around the world. While a lot has been achieved already, we do not want to overstate what is possible or likely. “Under-promise, over-deliver” have been our watchwords from the start and we are happy to stick with them.
While malaria control programmes, malaria product innovation, and indeed malariologists themselves waned after the eradication era, resistance to antimalarial drugs and to insecticides began to take hold. Unlike AIDS, malaria is a rarity in high-income countries. The world’s poor on the whole do not benefit from drugs developed for the specialized travelers market in wealthy countries. The market in the industrialized countries totals between USD 200-300 million per year, well off the radar screen for the research-based pharmaceutical industry. The market for innovative new antimalarial drugs is further hampered by competing counterfeit and sub-standard drugs, and poor regulatory infrastructure in many disease endemic countries. The net result is that we are now paying for this lack of innovation with the resurgence of drug resistance and our lack of armaments to fight the disease.

Today it is evident that the old and extraordinarily cheap first-line drug treatments, chloroquine and sulfadoxine-pyrimethamine, have been rendered useless in many parts of Africa and Asia. Partly as a consequence of this, malaria silently kills more than 3000 children every day. Antimalarial monotherapy – and even combination therapy if it is poorly thought out and implemented – is now understood as a Darwinian “numbers game” which drugs eventually lose as selection pressure mounts.

Fortunately, some effective treatments do exist today, thanks to drugs derived from military rather than civil investment in innovation. The Chinese initiated the development of the artemisinin drugs during the Vietnam War and they have continued working on them since. As a result, artemisinin combination therapies (ACTs) are by far the best class of antimalarial drugs available today, both in terms of efficacy and prospective longevity. However, ACT drugs are still not ideal. Containing processed plant extracts, their production is lengthy and relatively costly. Today, the cost of the most effective ACT is USD 2.40 per treatment. Although sold to the public sector in developing countries at cost, the price is still 10-30 times more than the traditional first-line cures. Quality and stability of artemisinins can also be an issue. Scale-up requires more farmland, dedicated extraction plant and is relatively capital intensive.

To address the immediate cost problem of ACTs, the US National Academies of Science Institute of Medicine (IOM) recently advocated annual donor subsidies of USD 300-500 million in order for ACTs to be affordable as first-line drugs in sub-Saharan Africa. While this is a fitting response to an acute and growing crisis, it is not surprising that potential recipient countries worry about sustainability. All of these factors suggest that scaling up existing ACTs, the development of cheaper ACTs with more complete safety data, and the simultaneous development of even better, cheaper drugs should be regarded as equal priorities if the growing malaria burden in Africa is to be reversed. We should not now repeat the mistakes of the eradication era by thinking that all that is needed is already available.

Investment in drug innovation suffers as a public investment case because it comes at a significant, though often exaggerated, upfront price while the hoped-for benefits are distant.
Medicines for Malaria Venture - Annual Report 2004

and uncertain. Regulated quality manufacturing, distribution and appropriate medical use take significantly more resources before any real public health impact can be achieved. Nevertheless, for malaria a number of analyses suggest that the returns can be striking. It has been estimated that malaria costs Africa at least USD 12 billion in lost Gross Domestic Product (GDP) per year, while on the individual level the burden falls particularly heavily on the poorest who can spend a staggering 30% of their income on malaria-related expenses. Macroeconomic studies reinforce the link to underdevelopment: the national incomes of countries with a substantial amount of malaria have grown by an estimated 1.3% per year less than those without such a burden.

Conversely, effective intervention can thrust an economy just as powerfully in a positive direction. The Commission on Macroeconomics and Health (CMH) reported that global health improvements have contributed as much, or more, to improvements in economic welfare as have innovations and expansion in material goods and services. Given greater international commitment to financing malaria product innovation and control, there is every reason to believe that the burden of malaria can be substantially reduced. The recent Copenhagen Consensus initiative concluded that malaria constituted one of the most tractable of global challenges and found that deploying effective malaria drugs had one of the highest cost–benefit ratios when opportunities for global investment across a number of sectors are compared. Overall this study calculated that to halve the malaria burden in sub-Saharan Africa by 2015, USD 824 million would be needed annually for a package of interventions. The direct economic benefit of the successful implementation of such a package would be USD 14 billion per year. The cost of research and development (R&D) of new products is small on this global investment scale and hence was not directly calculated into the price. However, the potential benefits are large, and given the correlation between the malaria burden and the availability of effective drugs, it could be pivotal. This economic case becomes even more compelling if one takes into consideration the macroeconomic benefits and the improved general health resulting from better malaria control.

The question should therefore not be whether we can afford malaria drug innovation, but why there are no global financing mechanisms to fund such R&D. Fortunately, the scale and importance of the innovation gap has not been overlooked by certain donors, most significantly the Bill and Melinda Gates Foundation. The real difference they are making should encourage governments and multilateral donors to step up to the challenge as well.

The only historical harbinger for disease-financing mechanisms such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, is the highly successful March of Dimes, targeting polio. Inspired by a very visible President Roosevelt, the March of Dimes funded mainly polio treatment and care, but it reserved a small percentage of its assets for innovation. With the benefit of hindsight we can see that this percentage led to the Salk vaccine, changed history, and has now all but defeated the disease.

Public-private partnerships for drug development are relatively new entities. They were launched amid scepticism. However, organizations such as Medicines for Malaria Venture have proved to the cynics that “virtual” R&D with public and private sector collaborators can be a very successful framework for building a strong pipeline of new tools to tackle neglected diseases. MMV’s portfolio of R&D projects is no doubt impressive. Nevertheless, as the most promising projects are in or approaching a critical stage where drugs are advancing through the expensive phases of clinical trials, their successes will be highly dependent on sustainable funding. It was therefore the recommendation of the Institute of Medicine of the National Academies (IOM) that the global community increase its funding for antimalarial R&D for which MMV is the main driver.

Comparing the cost of antimalarial R&D to commercial drug development, for which the amount of up to USD 1 billion has been quoted, is not a particularly useful exercise given the many differences in approach. However, the truth is that for the public good we can do much more than is being done today, and do it in a very cost effective manner. It plainly makes economic sense not to risk investments already made but rather to secure more resources in order to accelerate drug development, so that life-saving drugs become accessible to the poorest as quickly as possible. In parallel, we must ensure that health care delivery systems are strengthened so that the drugs reach those most in need.

By Professor Anne Mills, London School of Hygiene and Tropical Medicine, UK

Malaria costs Africa at least USD 12 billion in lost Gross Domestic Product (GDP) per year.
In the MMV portfolio of 21 projects, three are positioned to start Phase III clinical trials in 2005. Regulatory submissions could be as early as 2007. Three projects have moved into Phase II in 2004 and one additional project will start Phase II in 2005. The "OZ" project (MMV Project of the Year 2001) moved through preclinical, Phase I and into Phase II, all during 2004 — a record by industry standards. MMV has six projects in clinical development which could produce new antimalarial drugs before 2010.

If we only hit the industry average in clinical development, at least three new drugs should be available to treat malaria before 2010.

Are we pushing too many new drugs out of the pipeline at once? At present there is only one fixed-dose artemisinin combination therapy (ACT) available to be used by endemic countries. Not only is it relatively expensive – even though it is sold at cost – there is currently not enough of it. Because of the time lag between ordering the drug and delivery times, which is affected by planting and growing seasons, shortages of this plant-based drug are inevitable. Ideally, Roll Back Malaria (WHO/RBM) would like to have an effective and affordable first and second-line drug for each country. There are no ideal drugs to fill the second-line drug category. Since no drug will fit the needs of every country, at least three or four options will be needed.

We are hoping to have several lower-cost ACTs (e.g. chlorproguanil-dapsone-artesunate (CDA) and Artekin™) approved within the next three years. Our main contribution to the antimalarial arsenal will be the development of newer antimalarial combination therapies which do not rely on artemisinin production, such as the synthetic peroxides – better known as OZ. In principle, these synthetic drugs will be superior drugs not only in safety and efficacy, but will also cost less and be much easier to manufacture, thus mitigating the problems of shortage.

MMV's projects are evaluated continuously by the project management teams against set milestones. Once a year, the entire portfolio is assessed by the Expert Scientific Advisory Committee (ESAC) made up of the most experienced chemists, biologists, clinicians, malariologists and drug development experts. Their insights and contributions to the success of MMV's pipeline are invaluable. Finally, our rapid advances are made possible by MMV's partners, nearly 40 in total, in academic research institutes and industry. Currently, there are about 300 scientists and clinicians around the world working on antimalarial projects supported by MMV. We may manage our portfolio like a virtual pharmaceutical company, but the work and the progress are far from virtual.
Expanding our focus and deliverables

During the last five years we have focused on developing drugs that would be used primarily to treat uncomplicated *Plasmodium falciparum* malaria, but there are other malaria indications which are in need of new drugs, as outlined below.

**Intermittent preventive treatment in pregnancy (IPTp)**

Pregnant women are particularly susceptible to developing severe malaria with few symptoms to alert them. Developing drugs for pregnant women is very difficult since the drugs must be safe and effective for the mother without causing damage to the developing fetus. As a result, testing of drugs is seldom done in pregnancy, particularly during clinical trials. This type of critical data is seldom collected in an organized fashion. Instead it comes with experience after the drug is on the market, when women take it without knowledge of their pregnancy or of the potential danger of the drug. There are also situations where there was no other choice if the mother’s life was to be saved. Unfortunately this type of data is difficult to collect and analyse. There is an urgent need for studies in pregnancy in a more controlled environment and with adequate follow-up.

Studies in pregnant women are difficult to conduct unless the embryo toxicology studies are clean. Artemisinin-based drugs have not had clean embryo toxicology in animal studies. However, accidental treatment of pregnant women suggests that artemisinin may be safe in humans. MMV and GlaxoSmithKline (GSK) are collaborating on a fetal toxicity study in monkeys to help answer this question. If the study proves that there is no fetal toxicity, then clinical trials designed for studying the use of artemisinin during pregnancy may be feasible. All the drugs in the MMV portfolio are being evaluated for their potential use during pregnancy.

**Intermittent preventive treatment in early infancy (IPTi)**

The majority of the victims of malaria are African children less than five years of age. During the first months after birth the child gradually loses maternal protection and is susceptible to severe malaria which can be fatal within 48 hours. Intermittent preventive treatment during infancy has been found to be successful in preventing severe malaria and decreasing the morbidity and mortality rate in young children, even where less effective drugs have been used. This suggests that intermittent preventive treatment, in effect a “surrogate vaccine”, can help protect children from malaria and develop their immunity. MMV will be looking carefully at drugs within the portfolio that have this potential. At present there are interesting debates and studies exploring the use of IPTi and examining the critical question of what would be the ideal drug profile for this indication.

**Treatments suitable for emergency situations**

A malaria epidemic can have dire consequences for a population with low or no natural immunity. In emergency situations (e.g. natural disasters and refugee camps where health infrastructure is poor, and the potential for an epidemic is high), a single-dose antimalarial cure can save many lives and relieve the health burden. In fact, a safe and effective single-dose cure that also blocks transmission would be the ideal drug in any situation. MMV has several drugs which have the potential for this indication, such as the new class of synthetic peroxides.

*Plasmodium vivax* malaria (including radical cure)

Although *Plasmodium vivax* does not normally cause death, it is still a significant health problem in many parts of the world. Treatment of acute blood stage *P. vivax* malaria can still be achieved with chloroquine but relapses will occur if a 14-day course of primaquine is not administrated to ensure a radical cure. Few patients complete the full course of treatment because of adverse side-effects. A new effective radical cure that is also more easily tolerated is urgently needed. The enantioselective 8-aminoquinoline project is working toward this goal. Drugs with mechanisms of action which do not include the blood stage of the parasite may be found to work against *P. vivax* liver stages. MMV is looking closer at potential drugs within its portfolio.

**Severe malaria**

Severe malaria due to *P. falciparum* is the main cause of death by malaria. Treating uncomplicated malaria early should prevent most patients from progressing to severe malaria. All too often however, patients arrive after the disease has already progressed to a stage at which they cannot take oral drugs. This is often the case when the antimalarial drugs they have taken are ineffective due to drug resistance. Severe malaria needs to be treated with intravenous or intramuscular drugs. At present there are only two drugs which can be used to treat severe malaria: intravenous quinine and quinidine. However, these are not ideal because of the potential for cardiac toxicity, and because they are relatively slow acting. Studies with intravenous artesunate have suggested that it has an advantage over...
quinine. This may be due to the artesunate's rapid clearance of the parasite. Intravenous artesunate and an intravenous form of the synthetic peroxide are the two drugs in the portfolio that are most likely to be successful in treating severe malaria.

Transmission blocking drugs
Chloroquine was an excellent antimalarial drug until resistance developed. One of the problems with chloroquine was that although it killed the parasite and made the patient recover, it did not kill the gametocytes, which remained in the blood. When a mosquito bites such an infected person, that mosquito will in turn become infected with the parasite and will be able to pass it on again to other susceptible persons. An ideal antimalarial drug will not only kill the parasite but also the gametocytes, thus blocking the transmission of the infection as well as treating the infection. Artemisinins and synthetic peroxides appear to be transmission blocking agents. All new drugs will be evaluated for this activity.

While most of the 11 discovery projects in the MMV portfolio have had successes in achieving their goals in 2003, others are struggling to meet their milestones. Based on industry averages, we expect less than 50% of discovery projects to move forward to the next level. Nine of the projects are based on new targets where chances of finding a drug candidate are much lower. The dihydrofolate reductase (DHFR), novel tetracycline derivatives, and enantioselective 8-aminoquinoline projects are less risky since they are building on classes of drugs which we know are effective. To achieve MMV's long-term goals of providing new drugs which can replace the older ones, the number of discovery projects is suboptimal. In order to have a strong portfolio and increased chances of eventual success, MMV will need to increase the number of discovery projects. There are several ways this can be done. The easiest would be to add more projects to the portfolio; however, this would be expensive and would tax the personnel resources of MMV. A better solution lies in MMV's strength: that of building partnerships. To ensure that early exploratory science is supported and focused on eventual hand-off for drug development, MMV is vigorously working on building partnerships with industry and with research funding sources.

Fourth Call for Proposals
MMV held its Fourth Call for Proposals which closed at the end of September 2004. A total of 81 Letters of Interest were received and in November they were reviewed by ESAC. Ten were selected to submit full proposals. These included two development proposals, two natural products proposals and six discovery proposals. An in-depth review by ESAC will take place in March 2005. We expect to select several new projects to replace unsuccessful ones and to expand the number of discovery projects in the portfolio.
The Phase III clinical development programme is being prepared according to International Conference on Harmonization (ICH) guidelines and has been discussed with the UK Medicines and Healthcare products Regulatory Agency (MHRA). Clinical trial site selection will start in the first quarter of 2005 and the Phase III programme is planned to start in the third quarter of 2005.

**DB289 (an improved pentamidine)**

**– accelerated project**

**Project Leader:** James Allen, Immtech International, USA

**Partners:** University of North Carolina, USA

**MMV contact:** Lise Riopel

DB289 (the pro-drug of the active diamidine DB75) has demonstrated activity against trypanosomes, *Pneumocystis jiroveci* and *Plasmodium* species in non-clinical and clinical studies. Phase II clinical trials have been conducted in African trypanosomiasis and in acute uncomplicated *P. falciparum* and *P. vivax* malaria. DB289 was shown to be safe and efficacious in the trials, thus justifying further development for these indications. DB289 has also been used for up to three weeks in patients with *Pneumocystis jiroveci* pneumonia and was well tolerated.

In the pilot Phase II malaria study conducted in 2003, DB289 was administered twice daily for five days. Recognizing that compliance to malaria therapy may be reduced with a twice daily (BID) regimen and with treatment duration of more than three days, a Phase I study was repeated to assess the safety, tolerability and pharmacokinetics of ascending dose levels of DB289 given once a day for three days. The safety and preliminary pharmacokinetic results indicate that a dose of 200 mg per day of DB289 for three consecutive days may be adequate in the treatment of acute uncomplicated malaria. A second Phase II comparing DB289 alone or in combination has been planned in consultation with the US Food and Drug Administration (FDA) and is currently being implemented in Thailand.

Important goals for 2005 include: demonstrating the safety and efficacy of a three-day regimen of DB289 alone and in combination; identifying a drug combination partner; completing required non-clinical studies prior to conducting clinical studies in small children; and manufacturing adult and paediatric formulations for the Phase II and Phase III clinical trials.

**Paediatric Coartem™ – accelerated project**

**Project Leaders:** Jens Kurth, Novartis Pharma, Switzerland

**Partners:** Novartis Pharma, Switzerland

**MMV contact:** David Ubben

The Coartem™ paediatric development programme aims to deliver to Roll Back Malaria (WHO/RBM) a paediatric dosage form suitable for infants and children as small as 5 kg in weight.

During 2004, certain milestones were achieved in the paediatric development project: The final Marketing Image (FMI) of the paediatric formulation, a powder for suspension based on the composition of the marketed tablet, was developed. The final primary packaging is a Barex Sachet.
Cherry flavour will be added to mask the bitter taste of Coartem™, as a result of a palatability study performed in Tanzania.

Based on the outcome of a pharmacokinetic bioavailability study in healthy volunteers comparing the paediatric versus the tablet formulation, a Phase IIB study is currently in preparation to evaluate the efficacy of the formulation. A multi-centre pivotal study is planned to assess the impact of artemether exposure in the treatment of uncomplicated malaria started in July 2004 and was completed in October 2004. The results for the Phase I studies were very encouraging, with good pharmacodynamics and safety. Because of the good results a Phase II pharmacodynamic study in patients with uncomplicated P. falciparum malaria was initiated in December in Thailand, at the Bangkok Tropical Medicine Hospital.

Complementing the rapid clinical development, Ranbaxy scientists have developed both an adult tablet and paediatric formulations which will be used in clinical studies. Work on an intravenous formulation is also progressing smoothly. Evaluations of potential partner drugs are going forward with several potential candidates.

**Artemifone (semi-synthetic endoperoxide)**

*Project Leader*: René Raemsch, Bayer AG, Germany

*Partners*: Hong Kong University of Science & Technology, Hong Kong

*MMV contact*: David Ubben

Artemifone provides a potentially significant improvement to the promising class of fast-acting artemisinin derivatives. This specific semi-synthetic derivate was selected based on lack of neurotoxicity using several in vitro and in vivo animal models. From this standpoint alone, the compound could overcome a worrying potential toxicological liability frequently associated with the artemisinin compounds, while its higher bioavailability and enhanced antiparasitic activity potentially makes artemifone, in all respects, an improved second-generation drug of the artemisinin class. The preclinical work required for entry into humans was completed and the Phase I programme started in December 2003 with a single-dose escalation study. Basic Phase I studies were finalized in 2004 and revealed that oral treatment of healthy male subjects with artemifone was safe and well tolerated. A Phase II dose-ranging study in uncomplicated malaria started in July 2004 and the final results of the study are expected in 2005.

**Pyronaridine-artesunate**

*Project Leader*: Larry Fleckenstein, University of Iowa, USA

*Partners*: Shk Phung Pharmaceuticals, Seoul, Korea; UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR), Switzerland

*MMV contact*: Lisa Rispel

Pyronaridine was used for nearly 20 years as monotherapy to treat malaria in the Hunan and Yunan Provinces in China, where it was discovered in the 1970s. With the introduction of artemisinins in the 1990s, the use of pyronaridine has been abandoned. In line with the current WHO recommendations concerning the treatment of malaria, a low-cost, fixed-ratio combination of pyronaridine and artemesunate is being developed for the treatment of acute uncomplicated malaria in Africa and Asia. This combination will be assessed for safety and efficacy in both adult and children patients suffering from acute uncomplicated P. falciparum malaria.

**OZ (synthetic peroxide)** RXb11160/OZ 277

*Project Leader (development)*: Yvonne Baha, Ranbaxy Laboratories, India

*Partners*: Monash University, Australia

*MMV contact*: J Carl Craft; Lisa Rispel

*Project Leader (discovery)*: Jonathan Vennerstrom, University of Nebraska Medical Center, USA

*Partners*: Swiss Tropical Institute, Switzerland; F Hoffman-La Roche, Switzerland; Monash University, Australia

*MMV contact*: Solomon Nwaka

The project objective for 2004 was to progress from preclinical development to a first time in humans Phase I clinical trial. The preclinical toxicology studies were very clean and the go ahead to start dosing in humans with a 60 mg dose was given. The team filed an Investigational Medicinal Product Dossier (IMPD) with the UK Medicines and Healthcare products Regulatory Agency (MHRA), meeting the new guidelines for clinical trials in Europe. A Phase I super protocol which included single rising dose, multiple rising dose and food effect in one study was approved both by the Ethics Committee of the clinical trial site and the MHRA. This study started in July 2004 and was completed in October 2004. It was followed by an elderly and gender study. The results for the Phase I studies were very encouraging, with good pharmacokinetics and safety. Because of the good results a Phase II pharmacodynamic study in patients with uncomplicated P. falciparum malaria was initiated in December in Thailand, at the Bangkok Tropical Medicine Hospital.

The goals for the clinical team are to choose a partner drug, start combination toxicity studies, and complete Phase II studies with RXb11160/OZ 277 during 2005. Jonathan Vennerstrom and his team have published their work in an article entitled “Identification of an antimalarial synthetic trioxolane drug development candidate”. This work has progressed well and there are now several potential back-up compounds.


**Clinical Development Projects – Phase I**

**Pyronaridine-artesunate**

*Project Leader*: Larry Fleckenstein, University of Iowa, USA

*Partners*: Shk Phung Pharmaceuticals, Seoul, Korea; UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR), Switzerland

*MMV contact*: Lisa Rispel

Pyronaridine was used for nearly 20 years as monotherapy to treat malaria in the Hunan and Yunan Provinces in China, where it was discovered in the 1970s. With the introduction of artemisinins in the 1990s, the use of pyronaridine has been abandoned. In line with the current WHO recommendations concerning the treatment of malaria, a low-cost, fixed-ratio combination of pyronaridine and artesunate is being developed for the treatment of acute uncomplicated malaria in Africa and Asia. This combination will be assessed for safety and efficacy in both adult and children patients suffering from acute uncomplicated P. falciparum malaria.
and P. vivax malaria. A paediatric formulation for children of less than 10 kg body weight will be developed and filed for registration along with the tablet formulation.

An Investigational New Drug Application (IND) was submitted to the Korean Food and Drug Administration (FDA) and the Phase I programme was initiated in August 2004. Single and repeated doses escalation, interaction and food effect are being investigated in healthy volunteers. Preliminary safety and pharmacokinetics results justify progression to a Phase II dose finding study which is scheduled to start in the second quarter of 2005. The study will be conducted in five clinical trial sites in Africa and South East Asia and will include approximately 500 patients. Parallel registration with the European Agency for Evaluation of Medicinal Products (EMEA) is envisaged.

**Preclinical Transition Projects**

**Intravenous artesunate**

*Project Leader:* Peter J Weina, Walter Reed Army Institute of Research (WRAIR), USA

*Partners:* Armed Forces Research Institute of Medical Sciences (AFRIMS), Thailand

*Drug Development and Discovery Projects*

*Drug Development and Discovery Projects*
In early 2004, the 4(1H)-pyridone derivative GW844520 progressed from discovery to development. The preclinical programme leading to the first-time study in humans is ongoing as are chemical development and pharmaceutical development programmes.

A pyridone back-up lead optimization programme was initiated in 2004 to achieve improved physico-chemical and metabolic properties while maintaining activity against atovaquone and other resistant \textit{P. falciparum} strains. A shortlist of drug candidates has already been generated.

The project objective in 2005 is to evaluate the shortlist of candidates for improved PK properties and to initiate an exploratory study to treat malaria. Its demonstrated activity in humans is a good proof of concept for the new dicaticonic molecules. Recent chemistry work from the research groups of Dr Tidwell and Dr Boykin has demonstrated that more superior compounds with good activity against malaria can be designed. The dicaticonic molecules concentrate selectively in \textit{P. 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 the haem degradation pathway, among other potential targets.

The goal of the project in 2005 is to focus on a few selected compounds, generate necessary pharmacokinetics and metabolism data, progress the best compounds in the Aotus monkey model of \textit{P. falciparum}, and identify a development candidate by the end of 2005.

\textbf{Figure 2. Structure of pentamidine}

The nature of the spacer and cationic moieties influences toxicity and antimicrobial activity

\begin{center}
\includegraphics[width=0.5\textwidth]{pentamidine.png}
\end{center}

\textbf{Manzamine alkaloids}

\textbf{Project Leader:} Mark J. Harman, University of Wisconsin, USA

\textbf{Partners:} University of Maryland Biotechnology Institute, USA; Gadjah Mada University, Indonesia

\textbf{MMV contact:} Solomon Nwaka

The goal of the manzamine alkaloid project in 2004 was to progress the lead candidate (manzamine A) to exploratory toxicology and pharmacokinetics, and to assemble data that would support progressing the drug to development. Concerns with some toxicological findings with manzamine A have created doubt regarding the continuation of this project. The project is looking at potentially more promising manzamine analogues as a way to deal with toxicity.

\textbf{Enantioselective 8-aminoquinolines}

\textbf{Project Leader:} Larry Walker, University of Mississippi, USA

\textbf{Partner:} Rice University, USA; National Institutes of Health, USA

\textbf{MMV contact:} Lisa Rispel, Ian Bathurst

To date, primaquine remains the only treatment for the radical cure (antirelapse) of \textit{P. vivax} malaria. However, its use is limited by poor compliance due to the length of treatment and the potential to cause serious haemotoxicity. As it has poor schizontocidal activity (i.e. killing blood stage parasites) it must be administered following a two-day course of chloroquine, thus adding to the complexity of the treatment. The need for a new, safe, efficacious and affordable treatment for the radical cure of \textit{P. vivax} malaria is pressing.

NPC1161B is the \textit{(-)}-enantiomer of the 8-aminoquinoline racemic mixture of NPC1161C. While it retains very potent pharmacological activities both in vivo and in vitro, it is significantly less toxic than the \textit{(+)}-enantiomer or the racemic mixture in the models tested so far. In 2004, important achievements were made to overcome major inefficiencies in the methodology used to synthesize NPC1161B. One major drawback in the method used previously was that the active enantiomer was separated from the racemate at a final stage of the synthetic process, resulting in 50% loss of the final product. The objective of the project is to develop a cost efficient and commercially feasible stereospecific route of the active enantiomer. New processes involving fewer steps and reactions that can be scaled up to industrial requirements have been developed.

Much progress has also been accomplished in the area of pharmacokinetics, metabolism and general toxicity. A study protocol to compare the blood stage and radical cure effect of NPC1161B with that of tafenoquine in primates has been developed and the study will be conducted in 2005. Other non-clinical studies to confirm the improved hemato logical safety profile of NPC1161B, as compared to tafenoquine, are underway.

Other objectives for 2005 include the production of sufficient amounts of GMP (Good Manufacturing Practice) material with the newly developed stereospecific synthetic route to initiate the non-clinical work required for an Investigational New Drug Application (IND).
**Novel tetracycline derivatives**

Project Leader: Michael Draper, Paratek Pharmaceuticals, USA

MMV contact: Ian Bathurst

Tetracyclines have been used as antimalarial drugs for over 30 years. At present, doxycycline is used for chemoprophylaxis in areas with drug-resistant *P. falciparum* malaria, and doxycycline or tetracycline are used for treatment of *P. falciparum* in combination with other drugs. As antimalarial agents, the tetracyclines have been underutilized due to concerns with phototoxicity, the potential to stain teeth when used in children, and antibacterial activity. Chemical modification of the core tetracycline nucleus has allowed for the creation of improved tetracyclines with 10-fold more potency against drug-resistant *P. falciparum* in vitro, and improved efficacy in rodent models of malaria. Thus these new tetracyclines created by Paratek Pharmaceuticals have the potential to be safer and better tolerated than present compounds, as a result of the potential for lower doses of drug needed to achieve efficacy.

**Discovery Projects – Lead Identification**

**P. falciparum protein farnesyltransferase (Pf-PFT)**

Project Leader: Wesley Van Voorhis and Michael Gelb, University of Washington, USA

Partners: Yale University, USA; Bristol-Myers Squibb, USA

MMV contact: Solomon Nwaka

In 2000, the project teams showed that farnesyltransferase inhibitors display potent anti-*P. falciparum* properties in vitro. This opened the door for “piggy-backing” on farnesyltransferase inhibitors being developed by several pharmaceutical companies.

**Figure 3. Model to predict Pf-PFT inhibitor efficacy (Modeling such as this helps to guide chemistry programme)**

Credit: O Hucke and C Verlide, University of Washington, USA

Protein farnesyltransferase (PFT) was validated as the target for *P. falciparum* with the tetrahydroquinoline (THQ) class of inhibitors from Bristol-Myers Squibb. The evidence suggests that Pf-PFT is a viable target for antimalarial drug development. Several THQs have good activity against the target as well as the parasite. The project was selected as MMV Project of the Year in 2002.

The project goal for 2004 was to focus on THQs, and assess the pharmacokinetic and toxicologic profile of the most promising molecules, and demonstrate efficacy in an animal disease model. The team was also charged to continue to pursue the acyclic series as a back-up due to the potential merits of the acyclics in terms of cost of goods. The mandate for the project in 2005 is to progress both the THQs and the acyclic series with the goal of presenting a shortlist of development candidates.

**Fatty acid biosynthesis (FASII)**

Project Leader: Jane Saltiel, Texas A&M University, USA

Partners: Albert Einstein College of Medicine, USA; Jacobus Pharmaceutical, USA; Howard Hughes Medical Institute, USA

MMV contact: Solomon Nwaka

The goal of this project in 2004 was to identify orally active compounds that could progress to lead optimization. The team focused mainly on triclosan analogues but discovered a new class of analogues based on ureas. The work on the triclosan analogues does not appear to be making much progress towards a drug candidate. The urea analogues are a potential alternative but a correlation between enzyme inhibition and whole cell activity has not been observed.
Dihydrofolate reductase (DHFR)

Project Leader: Yongyuth Pathavong, BIOTEC, Thailand

Partners: London School of Hygiene & Tropical Medicine, UK; Monash University, Australia

MMV contact: Solomon Nwaka

Drugs which inhibit the folate pathway have been widely used for treatment of malaria but their use is declining due to the emergence of drug resistance. Resistance develops through mutations in the targeted enzyme dihydrofolate reductase (DHFR). However, the folate pathway remains a good target for chemotherapy because resistant mutations depend on the structures of antifolates, and the enzyme has limitations in mutation capability. Improving technology coupled with availability of the crystal structure of both wild and mutant DHFR means that we can now design and synthesize compounds that inhibit mutant (normally resistant) enzymes. The project goal is to develop new DHFR inhibitors that are inexpensive, active against multi-drug-resistant strains of malaria, and can cure the disease within three days. The chemistry programme is being guided by the structure of the enzyme, pharmacokinetics and metabolism, as well as in vitro/in vivo activity studies.

The project goals in 2005 include: overcoming the issue of oral bioavailability, the relationships between oral bioavailability and gastrointestinal tolerance with the compound series at hand, and assessing the question of resistance. It is hoped that viable leads will be identified by end of 2005.

Drug Development and Discovery Projects

P. falciparum peptide deformylase (PDF)

Project Leader: José F García-Bustos, GlaxoSmithKline, Tres Cantos, Spain

MMV contact: Ian Bathurst

Available data show that inhibitors of bacterial peptide deformylase (PDF) also inhibit the growth of P. falciparum in vitro. This has encouraged the team to further explore the antimalarial potential of the compounds. This class of PDF inhibitors has been shown to be orally bioavailable and to have acceptable pharmacokinetics in rats. PDF is a single enzyme in P. falciparum, with an established X-ray structure. The project objectives for 2004 were to establish an enzyme expression system and to set up a target site assay. That was accomplished and existing compounds were evaluated and found to display a correlation between target inhibition and antiplasmodial activity. When assayed at 96 hours rather than the standard 48, the inhibitors displayed an approximately four-fold increase in potency, compared to a 10-fold increase for doxycycline, another inhibitor of organellar protein synthesis.

P. falciparum enoyl-ACP reductase (Fab i)

Project Leader: José F García-Bustos, GlaxoSmithKline, Tres Cantos, Spain

MMV contact: Ian Bathurst

Fab i is the only known enoyl-ACP reductase in P. 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, Fab i 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 Fab i has been shown to be inhibited by this compound. Fab i is an attractive target because it has been validated pharmacologically with triclosan.

The P. falciparum enzyme assay and the secondary assay for selectivity against FAS I are available, as is the protein X-ray structure. They are being used to guide hit-to-lead chemistry in order to progress current inhibitors to the lead declaration decision point. From the high throughput screening campaign 173 primary positives (hits) have been identified. They fall into nine different chemical families, four of them novel, plus numerous single hits. Analogue searches and IC50 determinations are in progress, with the project objective in 2005 to reach a decision point with respect to potential lead and back-up inhibitors.
The interest of GlaxoSmithKline (GSK) in 4(1H)-pyridones goes back to the 1980s when, in a programme carried out at Wellcome (one of the GSK heritage companies) on electron transport inhibitors as antiparasitic agents, a novel family of 4(1H)-pyridones, analogues of clopidol (Fig. 4), was seen to show both in vitro and in vivo antimalarial activity. This new class of compounds selectively inhibited oxygen consumption in isolated mitochondria of Plasmodium falciparum. The compounds were also potent inhibitors of erythrocyte parasitization by strains of P. falciparum having sensitivity and resistance to atovaquone, chloroquine and pyrimethamine. They were efficacious in malaria mouse models of atovaquone-sensitive and atovaquone-resistant Plasmodium yoelii.

The electron transport chain also contributes to the electrochemical proton gradient across the inner mitochondrial membrane, and this in turn provides the energy for the transport of metabolic intermediates and macromolecules.

Atovaquone blocks electron transport by inhibiting cytochrome b, a critical element in the ubiquinone:cytochrome c oxidoreductase complex, also known as respiratory complex III, or cytochrome bc1 complex (Fig. 5). The 4(1H)-pyridone derivative GW844520 was tested on isolated mitochondria side by side with atovaquone. It displayed the same pattern of inhibition of individual redox reactions, providing strong circumstantial evidence that the site of action of 4(1H)-pyridone is respiratory complex III.

Pyridones show no cross-resistance with atovaquone. Results obtained from P. falciparum mutants (having diminished sensitivity to pyridone derivative GW844520) point to cytochrome b as the molecular target for the 4(1H)-pyridones, and more specifically to the same protein domain that also contributes binding sites for atovaquone. Importantly, the binding site is probably adjacent but it is clearly not completely overlapping with that of atovaquone, as none of the four tested mutants display cross-resistance.
A chemical programme was carried out starting from the clopidol molecule. The programme explored substitutions at different positions and established structural activity relationships (SAR). One of the most successful classes of 4(1H)-pyridone derivatives is represented by the derivatives substituted at position 5 with lipophilic substituents, particularly the ary-oxoaryl substituted derivatives. Optimization of this series led to GW844520, which has been recently selected as a candidate for clinical development. GW844520 was prepared following a straightforward synthetic route involving commercially available reagents and the use of tractable and robust intermediates.

Compounds from this class of 4(1H)-pyridone derivatives, particularly candidate GW844520, exhibited excellent in vitro activity against the key pathogen, *P. falciparum*. Activity was also demonstrated against organisms resistant to marketed compounds such as atovaquone, chloroquine, pyrimethamine and mefloquine. The selectivity ratio in vitro, studied in terms of mitochondrial function and whole cell inhibition (activity against *P. falciparum* vs. cytotoxicity), was generally around 1000. In vitro data (membrane depolarization assay) against *P. yoelii*, the species used as a surrogate of *P. falciparum* in in vivo studies, correlated with those obtained with *P. falciparum*. The activity of the combination of GW844520 with most antimalarial agents in clinical use, and other antimicrobial drugs, was investigated in vitro against three strains of *P. falciparum*. All combinations investigated were additive. No antagonistic effects were observed with any of the combinations tested.

GW844520 showed a low frequency of spontaneous resistance (<10%) against *P. falciparum* tested in vitro. In addition, in vivo studies were carried out, designed to maximize the likelihood of finding resistant isolates in CD1 immunocompetent and SCID beige immunodeficient mice. No resistant isolates of *P. yoelii* were selected from animals treated with GW844520 at various doses. However, atovaquone used as positive control showed selection of resistant parasites at the same doses.

In vivo efficacy of GW844520 was demonstrated in mouse models of infection with *P. yoelii* and *P. falciparum*, including the standard 4-day dosing model and single dose, via oral administration. GW844520 was well tolerated in a 4-day mouse toxicity study at doses of up to 3000 mg/kg per day, and showed a good therapeutic window. GW844520 proved negative in bacterial and mammalian mutagenicity screening assays.

GW844520 has low total clearance (all species) and a long elimination half-life in both monkey and dog. Oral bioavailability following administration as a solution was high in all species (51–100%). Administering GW844520 with reduced particle size resulted in a considerable increase in oral exposure that is adequate for progression into safety assessment studies.

GW844520 exhibits many of the features desirable in a drug development candidate for treating uncomplicated *P. falciparum* malaria: potent antimalarial activity combined with apparently low resistance selection pressure, and, within the limitations of the studies outlined here, low toxicity. The lack of antagonism or cross-resistance with existing drugs allows some flexibility in its use in combination therapy. The synthesis of GW844520 on a multigram scale has proved relatively straightforward and the compound exhibits good solid state stability – these being important aspects in the development of an affordable antimalarial drug that is also suitable for endemic areas.

While there appear to be some similarities in the mode of action of GW844520 and atovaquone, the lack of cross-resistance and a dramatically lower propensity for the generation of resistance differentiates 4(1H)-pyridones from atovaquone. Depending on the outcome of formal toxicology studies, it is hoped that the first studies in humans will start in 2005.
MMV Board Members

The Chairperson of the MMV Board is Dame Bridget Ogilvie, former head of the Wellcome Trust, with a distinguished career in pharmaceutical research. Dame Bridget is now on the faculty of University College London.

MMV Team

from top left to bottom right:
David Ubben Director, Clinical Development
Peter Potter-Lesage Chief Financial Officer and Donor Relations
Ian Barthall Director, Drug Discovery and Technology
J Carl Craft Chief Scientific Officer
Anna Wang Communications and Advocacy Officer
Maud Courdurier Administrative Assistant
Diana Collier Human Resources and Management Services Officer
Chris Hentschel Chief Executive Officer
Marion Hutt Contracts Officer
PV Venugopal Director, International Operations
Lise Riopel Director, Clinical Development
Eric Kimball Administration and Publications Officer
Solomon Nwaka Director, Drug Discovery

MMV Expert Scientific Advisory Committee (ESAC)

The Chairperson of ESAC is Dr Win Gutteridge, former Chief, Product R&D, Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, Switzerland.

from top left to bottom right:
David Floyd Chief Scientific Officer and Executive Vice-President, Pharmacopeia Drug Discovery, USA
Alan Hudson Medicinal chemist, Chief Executive Officer, PharmaCons Ltd, UK
David Roos Professor of Biology and Director, University of Pennsylvania Genomics Institute, USA
Bob Snow Head, Malaria Epidemiology, Public Health Group, KEMRI/Wellcome Trust Programme, Nairobi, Kenya and University of Oxford, UK
George Aynilian Director of Drug Development with expertise in clinical research, international regulatory affairs and 15 years of drug development experience
Win Gutteridge Consultant and Visiting Professor, LSHTM, UK (Chairperson of ESAC)
Zulfiqarali Gulamhussien Premji Professor of Clinical Parasitology with over 25 years of experience in teaching, research and clinical work
R.A. Mashelkar Director General, Council of Scientific and Industrial Research (CSIR), India
Jack Chow Assistant Director-General, HIV/AIDS, TB and Malaria, World Health Organization, Switzerland
Win Gutteridge Chairperson, MMV Expert Scientific Advisory Committee (ESAC) (Board Observer)
Dame Bridget Ogilvie University College London, UK (Chairperson of the Board)
Leon Rosenberg Department of Molecular Biology, Princeton University, USA
Enriqueita Bond President, Burnstong Welcome Fund, USA
Chris Hentschel Chief Executive Officer, Medicines for Malaria Venture (MMV), Switzerland
Francis Mfonobah Former Director, Noguchi Memorial Institute for Medical Research, University of Ghana
Trevor Jones Former Director-General, The Association of the British Pharmaceutical Industry (ABPI), UK
Pascoal Mocumbi High Representative, European and Developing Countries Clinical Trials Partnership (EDCTP), Netherlands

The Organization

from left to right:
R.A. Mashelkar Director General, Council of Scientific and Industrial Research (CSIR), India
Jack Chow Assistant Director-General, HIV/AIDS, TB and Malaria, World Health Organization, Switzerland
Win Gutteridge Chairperson, MMV Expert Scientific Advisory Committee (ESAC) (Board Observer)
Dame Bridget Ogilvie University College London, UK (Chairperson of the Board)
Leon Rosenberg Department of Molecular Biology, Princeton University, USA
Enriqueita Bond President, Burnstong Welcome Fund, USA
Chris Hentschel Chief Executive Officer, Medicines for Malaria Venture (MMV), Switzerland
Francis Mfonobah Former Director, Noguchi Memorial Institute for Medical Research, University of Ghana
Trevor Jones Former Director-General, The Association of the British Pharmaceutical Industry (ABPI), UK
Pascoal Mocumbi High Representative, European and Developing Countries Clinical Trials Partnership (EDCTP), Netherlands

Not pictured: John A Salmon Visiting Lecturer, King’s College, London and University of Greenwich, UK
The financial year to 31 December 2004
Summary

This fifth year of operations for MMV has been a financial year characterized by considerably increased malaria drug research and development (R&D) expenditure, up by 50% on 2003 figures, as projects move through development and into clinical trials. Increased income, up by 33%, matched expenditure, thanks to successful fundraising and also in part to an early release of future pledged funding by the Bill and Melinda Gates Foundation of a supplementary USD 5 million.

In comparison with the original business plan of March 2000, MMV now has twice as many projects in its scientific portfolio, with 10 times more in the preclinical/development phase, for less than 75% of the original projected cost.

The financial infrastructure and procedures of MMV have been further improved to meet the growing needs of the organization. Furthermore, MMV underwent a successful USAID pre-award audit during the summer of 2004.

The year was characterized by a number of exceptional factors. Substantial increases were seen in both Income and Expenditure. The Foundation Capital is now 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). Non-grant income, mainly interest on investments, remained similar in 2004 to 2003, reflecting low interest rates on international money markets. Modest exchange rate gains were again placed in a Foreign Exchange Reserve to hedge against adverse fluctuations in future years.

The transition to International Financial Reporting Standards (IFRS), initiated in 2003, has moved forward and will be completed as planned by the end of 2005.

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.

The financial year to 31 December 2004
Detail

Income
Overall income increased again in 2004 by 33% to USD 28,705,652 as compared with USD 21,712,944 in 2003, USD 16,586,792 in 2002, USD 13,599,677 in 2001 and USD 7,606,949 in 2000 (these amounts do not take account of Foundation Capital of USD 4 million received between 2000 and 2003).

In comparison with the original business plan of March 2000, MMV now has twice as many projects in its scientific portfolio, with 10 times more in the preclinical/development phase, for less than 75% of the original projected cost.

Research & Development Expenditure

Financial Information

Medicines for Malaria Venture receives funding and support from government agencies, private foundations, international organizations, corporations and corporate foundations. 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 Information

Financial Modelling
Financial sustainability is essential for MMV to fulfil its mission. Financial modelling suggests that the relationship between estimated future optimal financing requirements and donations received and pledged needs to be carefully monitored. Contracts with project partners do include a 90-day cancellation clause, which could be invoked in exceptional circumstances to maintain the financial health of the organization.

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, ExxonMobil, BHP Billiton, and the Wellcome Trust.

This strategy was rewarded in 2004 by a new 4-year pledge from USAID of USD 8 million, a 5-year pledge from ExxonMobil of USD 2.5 million and a 3-year pledge from BHP Billiton of USD 750,000. The Dutch Government also made a renewed pledge for 2004 of USD 588,441 as did the World Bank with a 2004 commitment of USD 750,000.

Current forecasts for future MMV malaria drug R&D project spending are USD 40 to 45 million in 2005, rising to USD 50 to 55 million for 2006, rising to USD 60 to 70 million annually, as the developing portfolio necessitates, with projects moving through clinical trials, on to registration and to product launch and marketing.

Financial Tables
The detailed financial tables that follow – Balance Sheet, Statement of Income & Expenditure, Cash Flow, and Notes – represent MMV in its fifth full year of operation in which all of its fundamental compliance and financial components have been developed and optimized in step with the rapidly evolving scientific R&D portfolio.

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 (March 2005).

Figure 7. Actual cumulative total pledged funding against total spending and projected, as at 31 March 2005

The financial year ahead to December 2005

MMV has to operate in a complex multi-currency environment. The bulk of donations are received in US dollars. Outflows for projects are also mostly in US dollars. Many operational expenses, however, are in Swiss francs. The resulting exposure or exchange risk is hedged at budget time to provide a realistic fixed USD/CHF budget rate for the year. The accounts are kept in US dollars. Exchange movements of the US dollar against other currencies in 2004 were significant. These movements were partially counter-balanced by an exchange gain of USD 41,036 at 31 December 2004, thanks to forward buying of Swiss francs against dollars, this amount being attributed to the Foreign Exchange Reserve first established in 2003.

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 the analysis for fundraising activities aimed at financing the portfolio in line with the projections of the MMV Business Plan 2003-2007 and ongoing consultations with donors. Encouraging progress in fundraising was again made in 2004; however income was only marginally superior to expenditure.

External Evaluations & Sustainability
2005 will be a pivotal year for MMV with one external evaluation by the Donor Co-ordination Group and another by the Bill & Melinda Gates Foundation. The object of these evaluations is to assess the progress and achievements of MMV over its first five years and to assist both the organization and its multiple stakeholders in planning for future success coupled with financial sustainability over the coming years.

Foundation Capital
By 31 December 2003, the stipulated foundation capital of USD 4,000,000 was fully subscribed.

Donations & Pledges 2004
Cash received at bank amounted to USD 28,265,445 with additional deferred income from 2003 of USD 337,440 being recognized in 2004. The sums of USD 644,472 from the Wellcome Trust and USD 100,000 from ExxonMobil received in January 2004 were already recognized in last year’s accounts as income for 2003.

Staff & General Administration
The senior management team costs remained stable during 2004. Staff headcount increased by 1 to 11 while General Administration spending continued its downward trend as a percentage of total expenditure to 9.5%.

Figure 6. MMV Expenditure, 2004

Project-related R&D Expenditure 90.0%

Governance & Stakeholders 0.5%

Operations 9.5%
### MMV Balance Sheet at 31 December 2004

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<tr>
<td>Office Furniture</td>
<td></td>
<td>25 876</td>
<td>45 518</td>
</tr>
<tr>
<td>Computers &amp; Equipment</td>
<td></td>
<td>31 651</td>
<td>11 527</td>
</tr>
<tr>
<td>Total LONG-TERM ASSETS</td>
<td></td>
<td>107 657</td>
<td>102 890</td>
</tr>
<tr>
<td>TOTAL ASSETS</td>
<td></td>
<td>17 035 575</td>
<td>16 100 845</td>
</tr>
</tbody>
</table>

### Liabilities and Capital & Reserves

| CURRENT LIABILITIES         |       |          |          |
| Accrued R&D Commitments     | 2e/10 | 1 175 991| 745 892  |
| Deferred Income             | 9     | 0        | 323 440  |
| Other Creditors             |       | 74 126   | 151 056  |
| Accrued Expenses            |       | 447 523  | 376 174  |
| PROVISIONS                  |       |          |          |
| Short-term Provisions       | 2f    | 207 802  | 25 485   |
| Total CURRENT LIABILITIES   |       | 1 905 443| 1 622 048|
| CAPITALS & RESERVES         |       |          |          |
| FOUNDATION CAPITAL          | 12    | 4 000 000| 4 000 000|
| CAPITAL FUND                |       | 4 000 000| 4 000 000|
| OPERATIONS RESERVE          | 3a    | 10 679 990| 10 069 691|
| FOREIGN EXCHANGE RESERVE    | 3b    | 450 141  | 409 107  |
| Total CAPITAL & RESERVES    |       | 15 130 132| 14 478 798|
| TOTAL LIABILITIES AND CAPITAL & RESERVES | | 17 035 575 | 16 100 845 |

### MMV Statement of Income & Expenditure to 31 December 2004

<table>
<thead>
<tr>
<th>INCOME</th>
<th>Notes</th>
<th>2004 USD</th>
<th>2003 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DONATIONS RECEIVED</td>
<td>2b/9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Foundations &amp; Individual Donors</td>
<td></td>
<td>21 664 632</td>
<td>16 644 693</td>
</tr>
<tr>
<td>UN Agencies</td>
<td></td>
<td>750 000</td>
<td>750 000</td>
</tr>
<tr>
<td>Government Agencies</td>
<td></td>
<td>4 679 781</td>
<td>3 373 239</td>
</tr>
<tr>
<td>Corporates &amp; Corporate Foundations</td>
<td></td>
<td>750 000</td>
<td>100 000</td>
</tr>
<tr>
<td>DONATIONS RECEIVED</td>
<td></td>
<td>9</td>
<td>27 844 413</td>
</tr>
<tr>
<td>Interest Received</td>
<td>2k</td>
<td>128 823</td>
<td>109 092</td>
</tr>
<tr>
<td>Exchange Difference</td>
<td>2c</td>
<td>41 036</td>
<td>409 107</td>
</tr>
<tr>
<td>Project Balance Reimbursements</td>
<td>10c</td>
<td>647 466</td>
<td>310 383</td>
</tr>
<tr>
<td>Other Income</td>
<td></td>
<td>43 914</td>
<td>16 430</td>
</tr>
<tr>
<td>Total INCOME</td>
<td></td>
<td>28 705 652</td>
<td>21 712 944</td>
</tr>
<tr>
<td>EXPENDITURE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESEARCH &amp; DEVELOPMENT EXPENDITURE</td>
<td>10a/b</td>
<td>25 035 666</td>
<td>16 805 478</td>
</tr>
<tr>
<td>Expert Scientific Advisory Council Expenses</td>
<td></td>
<td>200 865</td>
<td>144 976</td>
</tr>
<tr>
<td>FOUNDATION BOARD &amp; STOCKHOLDER EXPENSES</td>
<td>11a</td>
<td>128 641</td>
<td>101 227</td>
</tr>
<tr>
<td>GENERAL ADMINISTRATION EXPENSES</td>
<td></td>
<td>1 621 297</td>
<td>1 208 671</td>
</tr>
<tr>
<td>Office Rental</td>
<td></td>
<td>259 157</td>
<td>229 124</td>
</tr>
<tr>
<td>General Insurance</td>
<td></td>
<td>3 766</td>
<td>2 659</td>
</tr>
<tr>
<td>State Emoluments</td>
<td></td>
<td>23 254</td>
<td>20 890</td>
</tr>
<tr>
<td>Supplies</td>
<td></td>
<td>1 175 991</td>
<td>745 892</td>
</tr>
<tr>
<td>Telecom, Internet &amp; Postale Charges</td>
<td>96 559</td>
<td>61 759</td>
<td></td>
</tr>
<tr>
<td>Travel Expenses</td>
<td></td>
<td>151 804</td>
<td>106 387</td>
</tr>
<tr>
<td>Fundraising</td>
<td></td>
<td>221 782</td>
<td>156 795</td>
</tr>
<tr>
<td>Professional &amp; Legal Fees</td>
<td></td>
<td>409 107</td>
<td>39 400</td>
</tr>
<tr>
<td>Training, Education &amp; Journals</td>
<td>80 734</td>
<td>44 664</td>
<td></td>
</tr>
<tr>
<td>IT Expenses</td>
<td></td>
<td>52 950</td>
<td>34 402</td>
</tr>
<tr>
<td>Web Site &amp; Advertisements</td>
<td></td>
<td>29 119</td>
<td>20 760</td>
</tr>
<tr>
<td>Printing &amp; Brochures</td>
<td></td>
<td>74 126</td>
<td>66 768</td>
</tr>
<tr>
<td>Public Relations</td>
<td></td>
<td>450 141</td>
<td>409 107</td>
</tr>
<tr>
<td>Communications</td>
<td></td>
<td>0</td>
<td>30 729</td>
</tr>
<tr>
<td>FINANCIAL CHARGES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bank Charges &amp; VISA</td>
<td></td>
<td>11 762</td>
<td>8 636</td>
</tr>
<tr>
<td>Depreciation on Fixed Assets</td>
<td></td>
<td>42 659</td>
<td>54 210</td>
</tr>
<tr>
<td>GENERAL ADMINISTRATION EXPENSES</td>
<td></td>
<td>2 792 802</td>
<td>2 176 438</td>
</tr>
<tr>
<td>TOTAL EXPENDITURE</td>
<td></td>
<td>28 157 986</td>
<td>20 228 118</td>
</tr>
<tr>
<td>ANCILLARY ACTIVITY INCOME</td>
<td>11c</td>
<td>103 669</td>
<td>109 084</td>
</tr>
<tr>
<td>RESULTS</td>
<td></td>
<td>651 335</td>
<td>2 593 910</td>
</tr>
<tr>
<td>ALLOCATIONS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRANSFER (TO) / FROM OPERATIONS RESERVE</td>
<td>3a</td>
<td>(610 299)</td>
<td>(2 184 803)</td>
</tr>
<tr>
<td>TRANSFER (TO) / FROM FOREIGN EXCHANGE RESERVE</td>
<td>3a</td>
<td>(409 107)</td>
<td>(2 593 910)</td>
</tr>
</tbody>
</table>
MMV Statement of cash flows to 31 December 2004

<table>
<thead>
<tr>
<th>Notes</th>
<th>2004 USD</th>
<th>2003 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCESS OF INCOME/(EXPENDITURE) FOR THE YEAR</td>
<td>651 335</td>
<td>2 593 910</td>
</tr>
<tr>
<td>(Decrease)/Increase in Provisions</td>
<td>182 317</td>
<td>704 707</td>
</tr>
<tr>
<td>Depreciation</td>
<td>52 659</td>
<td>54 210</td>
</tr>
</tbody>
</table>

**OPERATING RESULTS BEFORE WORKING CAPITAL CHANGES**

876 311 1 943 412

**CASH FLOWS FROM OPERATING ACTIVITY**

| (Increase)/Decrease in Donations Receivable | 9 | 744 472 | 210 192 |
| (Increase)/Decrease in Project Balance Reimbursements | 10c | (337 083) | (310 383) |
| (Increase)/Decrease in Accounts Receivable | 10c | (8 321) | (1 310) |
| (Increase)/Decrease in Recoverable Withholding Tax | 5 | (4 105) | 31 957 |
| (Increase)/Decrease in Accrued R & D Commitments | 2e/10 | 430 099 | 745 892 |
| (Increase)/Decrease in Deferred Income | 10c | (323 440) | (284 260) |
| (Increase)/Decrease in Other Creditors | 10c | (76 931) | 73 863 |
| (Increase)/Decrease in Accrued Expenses | 10c | 71 349 | 376 019 |

**CASH FLOW RESULTING FROM OPERATING ACTIVITY**

496 041 841 970

**CASH FLOWS FROM INVESTMENT ACTIVITY**

| (Increase)/Decrease in Guarantees | 4 | (4 791) | (5 026) |
| (Increase)/Decrease in Fixtures and Installations | 2d/5 | 0 | 0 |
| (Increase)/Decrease in Office Furniture | 10c | (1 776) | (5 672) |
| (Increase)/Decrease in Computers and Equipment | 10c | (40 859) | (13 235) |

**CASH FLOW RESULTING FROM INVESTMENT ACTIVITY**

(47 427) (23 933)

**CASH FLOWS FROM FINANCING ACTIVITY**

| Foundation Capital: Payment received to Capital Fund | 0 | 53 341 |
| Cash flow resulting from financing activity | 0 | 53 341 |

**NET VARIATION OF PETTY CASH, CASH & BANK DEPOSITS**

1 326 925 2 814 791

| CASH & CASH EQUIVALENTS AT THE BEGINNING OF YEAR | 14 888 729 | 12 073 917 |
| CASH & CASH EQUIVALENTS AT THE END OF YEAR | 16 213 654 | 14 888 729 |

**ANNUAL**

1 326 925 2 814 791

MMV Statement of Movement in Capital & Reserves at 31 December 2004

<table>
<thead>
<tr>
<th>Capital Fund</th>
<th>Operations Reserve</th>
<th>Foreign Exchange Reserve</th>
<th>Total Capital &amp; Reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance at 1 January 2003</td>
<td>5 946 659</td>
<td>7 866 888</td>
<td>0</td>
</tr>
<tr>
<td>Payment of capital</td>
<td>57 341</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Allocation of result for the year</td>
<td>0</td>
<td>2 186 803</td>
<td>609 107</td>
</tr>
<tr>
<td>Balance at 31 December 2003</td>
<td>4 000 000</td>
<td>10 069 691</td>
<td>609 107</td>
</tr>
<tr>
<td>Allocation of result for the year</td>
<td>0</td>
<td>610 299</td>
<td>41 036</td>
</tr>
<tr>
<td>Balance at 31 December 2004</td>
<td>4 000 000</td>
<td>10 679 990</td>
<td>450 143</td>
</tr>
</tbody>
</table>

**Notes to financial statements for the year ended 31 December 2004**

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. **Summary of significant accounting policies**

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

a) **Accounting standards**

The accounting standards followed are those of the Swiss Code of Obligations, articles 915 to 926.

b) **Recognition of donations**

Contributions from donors (both Government and philanthropic sources) are recognised in the financial statements as an accrual basis when they have been received or confirmed in writing by pledges. A reconciliation between donations received in cash and income recognized in the income and expenditure account is shown in note 9.

c) **Foreign exchange**

Transactions in Swiss francs to pay salaries and office costs are effectively hedged by selling US dollars for Swiss francs at the start of the year. Swiss franc transactions are therefore translated at this hedged rate. Transactions in currencies other than the Swiss franc are converted into US dollars at rates that approximate the actual rates ruling at the transaction date.

At the balance sheet date monetary assets and liabilities denominated in foreign currency are converted into US dollars at the rate of exchange ruling at that date. Foreign exchange differences are reported in the income and expenditure account.

d) **Fixed assets**

Fixed assets are stated at cost less accumulated depreciation. The foundation applies the straight-line method for the depreciation of these assets, using rates of 20% per annum for office furniture and 33% per annum for fixtures and installations, and computers and equipment.

e) **Research and development**

Expenditure and grants allocated for research activities undertaken with the prospect of gaining new scientific or technical knowledge and understanding are recorded on a contract or letter of understanding basis, the expense being accounted for by MMV at the moment of allocation and initial payment. In the case of any portion remaining unpaid at the year-end, it is included under current liabilities.

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

f) **Provisions**

A provision is recognised in the balance sheet where 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.

g) **Employee benefits - Pension plan**

The MMV pension plan is classified as a defined contribution plan. Contributions to the defined contribution pension plan are recognised as an expense in the statement of financial position and expenditure as incurred.

h) **Fair value**

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

i) **Cash and cash equivalents**

Cash and cash equivalents comprise cash balances and short-term deposits.

j) **Impaired**

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 an asset's recoverable amount is less than the Swiss franc are converted into US dollars at the rate of exchange ruling at that date. Foreign exchange differences are reported in the income and expenditure account.

k) **Financial income**

Interest income is recognised in the income statement as earned.

l) **Income tax**

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

m) **Use of estimates**

The preparation of the financial statements requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of income and expenditure during the period. Actual results could differ from those estimates.

3. **Reserves**

a) **Operations reserve**

The accumulated Operations Reserve represents excess of income over expenditure since the inception of MMV and is available to be utilised for future operation and project funding costs as the rapidly evolving R&D project pipeline dictates.

b) **Foreign Exchange Reserve**

Expenditure for operational costs in Geneva is denominated in Swiss francs (CHF). The Foreign Exchange Reserve represents unrealized foreign exchange gains resulting from translation of non-US$ denominated balance sheet accounts. It serves as an insurance to mitigate future adverse USD/CHF currency fluctuations.

4. **Guarantees**

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

Financial Information
5. Fixed assets

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost as at 31 December 2004</th>
<th>Accumulated Depreciation as at 31 December 2004</th>
<th>Net Book Value as at 31 December 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixtures &amp; Installations USD</td>
<td>28,643</td>
<td>28,157</td>
<td>0</td>
</tr>
<tr>
<td>Office Furniture USD</td>
<td>106,065</td>
<td>59,271</td>
<td>46,894</td>
</tr>
<tr>
<td>Computers &amp; Equipment USD</td>
<td>70,799</td>
<td>11,458</td>
<td>59,341</td>
</tr>
<tr>
<td>Total USD</td>
<td>205,006</td>
<td>268,152</td>
<td>36,854</td>
</tr>
</tbody>
</table>

6. Financial instruments

a) Foreign currency risk

MMV incurs foreign currency risk on pledged contributions that are denominated in a currency other than US dollars, and on cash and deposits that are denominated in other currencies. The currencies giving rise to this risk are principally the Swiss Franc and the Pound Sterling (GBP). MMV purchased CHF 5,800,025 at the start of the year and a further CHF 588,441 and the Pound Sterling (GBP) during the year. MMV purchased CHF 581,357 in November 2004 to cover the annual expenditure in this currency.

b) Interest rate risk

Interest rate risk is represented by the carrying amount of each financial asset in the balance sheet, principally accounts receivable, short-term deposits and cash.

c) Credit risk

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

600,000

7. Commitments

As at 31 December 2004, there were no significant capital expenditure commitments.

8. Subsequent Events

No events occurred subsequent to 31 December 2004 and prior to the approval of the financial statements that would require modification of or disclosure in the financial statements.

9. Donations received at bank

During 2004 the following donations were received:

<table>
<thead>
<tr>
<th>Donor</th>
<th>Cash received as at 31 December 2004</th>
<th>Deferred income as at 31 December 2004</th>
<th>Income deferred to following year</th>
<th>Income recognised in current year</th>
<th>Income recognised in previous year</th>
<th>Total income recognised in 2004</th>
<th>Income recognised as at 31 March 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Bill &amp; Melinda Gates Foundation</td>
<td>20,000,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rockefeller Foundation</td>
<td>1,000,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welcome Trust</td>
<td>1,309,514</td>
<td>(664,472)</td>
<td>664,452</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swiss Government (DEZAG/SC)</td>
<td>675,900</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK Government (DFID)</td>
<td>1,759,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dutch Government (NIBIO)</td>
<td>588,441</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDS Government (USAID)</td>
<td>1,500,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>World Bank via Global Forum</td>
<td>750,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Export/Import</td>
<td>600,000</td>
<td>(100,000)</td>
<td>500,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP-Boston</td>
<td>250,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total received</td>
<td>28,265,445</td>
<td>323,460</td>
<td></td>
<td></td>
<td>27,842,983</td>
<td>764,472</td>
<td>27,842,983</td>
</tr>
</tbody>
</table>

10. Project related expenditure

a) Project grants related expenditure - Grants committee

During 2004, the foundation awarded grants to the following projects:

<table>
<thead>
<tr>
<th>Project</th>
<th>Amount awarded</th>
<th>Project description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.055.639</td>
<td>3.055.639</td>
<td></td>
</tr>
<tr>
<td>850.156</td>
<td>850.156</td>
<td></td>
</tr>
<tr>
<td>1.053.758</td>
<td>1.053.758</td>
<td></td>
</tr>
<tr>
<td>681.722</td>
<td>681.722</td>
<td></td>
</tr>
<tr>
<td>2.195.550</td>
<td>2.195.550</td>
<td></td>
</tr>
<tr>
<td>889.025</td>
<td>889.025</td>
<td></td>
</tr>
<tr>
<td>722.982</td>
<td>722.982</td>
<td></td>
</tr>
<tr>
<td>3.429.000</td>
<td>3.429.000</td>
<td></td>
</tr>
<tr>
<td>671.953</td>
<td>671.953</td>
<td></td>
</tr>
<tr>
<td>1.584.164</td>
<td>1.584.164</td>
<td></td>
</tr>
<tr>
<td>1.371.954</td>
<td>1.371.954</td>
<td></td>
</tr>
<tr>
<td>439.659</td>
<td>439.659</td>
<td></td>
</tr>
<tr>
<td>2.784.413</td>
<td>2.784.413</td>
<td></td>
</tr>
</tbody>
</table>

11. Expenses

a) Governing Board and Expert Scientific Advisory Committee (EASC) expenses travel and accommodation only.

b) There were 11 full-time staff at MMV at the beginning of the year, rising to 12 as from September.

c) Ancillary activity income refers to office space and infrastructure sub-let income, which can be offset against initial rental, telecom and related operational expenses.

12. Foundation Capital

The Capital Fund is now fully subscribed at USD 1,000,000 as stipulated under the original legal statutes of MMV.

13. 2003 Comparative Figures

Some items in the 2003 comparative figures have been reclassified to ensure consistent presentation with the 2004 financial statements.
Report of the Auditors to the Board of MMV

Medicines for Malaria Venture (MMV), Geneva

As auditors, we have audited the accounting records and the financial statements (balance sheet, statement of income and expenditure, statement of cash flows, statement of movement in capital and reserves and notes) of the Medicines for Malaria Venture (MMV) for the year ended December 31, 2004.

These financial statements are the responsibility of the Foundation’s management. Our responsibility is to express an opinion on these financial statements based on our audit. We confirm that we meet the legal requirements concerning professional qualification and independence.

Our audit was conducted in accordance with auditing standards promulgated by the Swiss professional, which require that an audit be planned and performed to obtain reasonable assurance about whether the financial statements are free from material misstatement. We have examined on a test basis evidence supporting the amounts and disclosures in the financial statements. We have also assessed the accounting principles used, significant estimates made and the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the accounting records and financial statements comply with the Financial Regulations of the Foundation and the accounting principles as described in note 2 of the financial statements.

We recommend that the financial statements submitted to you be approved.

KPMG Fides Peat

David Curry
Audit in Charge

14, Quai des Bornandiers
CH-1206 Geneva

P.O. Box 849
CH-1211 Geneva 12

Telephones: +1 515.361.1919
Fax: +1 515.361.1919
Internet: www.kpmg.ch

Geneva, March 14, 2005

Exclusions:
Financial statements (balance sheet, statement of income and expenditure, statement of cash flows, statement of movement in capital and reserves and notes)