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INDEPENDENT REVIEW OF MEDICINES FOR MALARIA VENTURE

Commissioned jointly by the following donors:

The UK Department for International Development, The Wellcome Trust, The World Bank (through their grant to MMV), The Swiss Agency for Development and Co-operation, The Bill and Melinda Gates Foundation and The Netherlands Ministry of Foreign Affairs (DGIS).

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Title: Independent Review of Medicines for Malaria Venture

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ABBREVIATIONS OR TRADE NAMES

ACT	Artemisinin combination therapy
AIDS	Acquired Immuno-Deficiency Syndrome
Coartem	Dihydroartemisinin / lumefantrine (Novartis)
CDA	Chlorproguanil/dapsone/artesunate
CEO	Chief Executive Officer
CSO	Chief Scientific Officer
DDW	Diseases of the Developing World
EDCTP	European & Developing Countries Clinical Trials Partnership
ESAC	Expert Scientific Advisory Committee
GSK	GlaxoSmithKline
GCP	Good Clinical Practice
ICH	International Committee for Harmonization
LapDap	Chlorproguanil / Dapsone (GSK)
MDG	Millennium Development Goal
MIM	Multilateral Initiative for Malaria in Africa
MMV	Medicines for Malaria Venture
MSF	Médecins Sans Frontières
NDA	New Drug Application
PD PPP	Product development public private partnership
PPP	Public Private Partnership
R&D	Research and Development
RBM	Roll Back Malaria
TDR	Tropical Disease Research
WHO	World Health Organization

EXECUTIVE SUMMARY

The Medicines for Malaria Venture (MMV) was created to meet the urgent need for new drugs for the treatment and prevention of malaria. This new mechanism was designed by the international health community as a response to the increasing incidence of, and mortality from malaria, the declining efficacy of first and second line treatments and the limited response of the pharmaceutical industry to discover and develop new anti-malarial drugs. Market analysis showed that investment in antimalarial drugs would not be commercially viable, thereby discouraging the private pharmaceutical industry from committing large resources into developing anti-malarial drugs. This product development public private partnership (PD PPP) was designed to be a means of sharing the burden of financial investments whilst leveraging the enormous capacity and expertise of private pharmaceutical companies in drug development.

The disease

Malaria, a major cause of disease, disability and death in developing countries, constitutes a major challenge in international health. The World Health Organization estimates that 300 to 500 million cases of the infection occur globally with 1.1 to 1.3 million deaths, most severely affecting children and pregnant women. Apart from the humanitarian concern, malaria constitutes a barrier to economic development in the highly endemic countries. Currently available public health measures are failing to bring the disease under control. It is therefore, essential to develop new and improved technologies and drugs to begin to achieve the Millennium Development Goal (MDG) of halting and reversing the incidence of malaria and reducing child and maternal mortality by 2010 (see Annex 1).

At this time, the control of malaria is heavily dependent on the use of antimalarial drugs. Although encouraging progress has been made regarding our understanding of the immunology of malarial infection, there is as yet no commercially available vaccine. On the whole, vector control measures, including insecticide treated bed nets, tend to be crude, cumbersome and costly. In the past, malariologists had at their disposal a handful of cheap, well tolerated and effective anti-malarial drugs like pyrimethamine, proguanil, chloroquine and other 4-aminoquinoline compounds. The emergence and spread of drug resistant strains of the *Plasmodium falciparum* parasite has eroded the value of these drugs. Newer drugs are generally more expensive, less well tolerated and less convenient to use in practice. In the absence of a steady flow of new drugs, malaria chemotherapy has become more difficult and less effective in practice.

Medicines for Malaria Venture (MMV)

Established five years ago as an international non-profit organization, MMV is supported by grants from bilateral and multilateral donor agencies as well as private foundations. Its small administrative, managerial and scientific staff is located in Geneva with an international office in India. The Board of Directors provides policy guidance, links the programme to its numerous stakeholders both in the public and private sectors, as well as maintaining an oversight on performance. An Expert Scientific Advisory Committee (ESAC) provides technical guidance to the programme.

The Review

The review team was charged with the task of examining the structure and function of MMV, noting its vision and goals, its context of operation and its achievements. The team members have complementary scientific and professional backgrounds, ranging from biomedical scientific research, drug development in industry, to clinical, epidemiology and public health aspects of malaria in endemic countries. The team studied MMV and related documents,

interviewed key MMV staff, key members of the Board and ESAC. Two team members visited sample MMV operations in Europe and Asia.

The Mission

The mission of MMV is to bring public, private and philanthropic sector partners together to fund and manage the discovery, development and registration of new medicines for the treatment and prevention of malaria in disease-endemic countries. MMV's revised mandate extends beyond discovery and development to include issues of delivery of the new products. (Figure 1) (see para. 3.5)

Findings

The main finding of the review is that MMV has made tremendous progress, clearly ahead of its predicted milestones, towards achieving its goals. It has successfully mobilized academic institutions and pharmaceutical companies in highly productive partnerships. Within a relatively short period, MMV and its partners have established an impressive portfolio of antimalarial drug candidates, some of which are at an advanced stage of development. The most advanced drug combinations include endoperoxides, related to artemisinin but there are also some truly novel compounds at earlier stages of development. Whilst recognizing that drug development is a high risk venture and failures can occur even at advanced stages of development and clinical trials, there is reason for cautious optimism in expecting that within the next few years, several compounds in the current portfolio will successfully emerge as approved and licensed anti-malarial drugs.

The future challenge

The unexpectedly rapid progress of the MMV portfolio has created the urgent need to advance preparations for late stage development processes including clinical and field trials. MMV must now address important downstream issues relating to the delivery of the expected products. These include registration, manufacture and distribution as well as definition of the most appropriate strategic niches for the new products. MMV has recognized and accepted responsibility for all stages of the process from discovery to development and the (shared) delivery. For the discovery and early development process, MMV has successfully mobilized effective partnerships involving academia and the pharmaceutical industry. For the late stage development, clinical trials and other downstream issues, MMV would need to strengthen and utilize other partnerships.

The requirements for effective drug delivery include the early involvement of MMV's downstream partners in the drug development process. This should ensure that the final product matches the clinical need and to maximise the likelihood of the timely delivery of new antimalarials to patients. With its partners, MMV needs time to plan committed funding and personnel to ensure the large scale provision of medicines, local agreement for marketing and mechanisms for drug distribution, followed by field effectiveness studies. This is a very complex process and requires considerable operational expertise both to integrate these activities within the project team and to ensure final patient access to and distribution of medicines in the field. It should be self-evident that these downstream activities need to be planned for and initiated around the time that a decision is taken to begin large Phase III clinical trials in support of drug approval and licensure. Delaying bulk drug manufacture, plans for drug purchase and distribution, and discussion with healthcare providers (local government) will all lead to eventual delay in the provision of antimalarials to the patient.

KEY RECOMMENDATIONS

The following is a synopsis of the main recommendations arising from the review. Specific details may be found elsewhere in the report.

1. The Mission
 - a. We support the extension of the initial mandate from *discover, develop and register* to *discover, develop and deliver*. To what extent MMV's activities will extend into delivery will depend upon funding, the respective roles of the partners and local and national malaria treatment policies. (see para. 3.5)
2. Composition of Board and ESAC (see para. 3.2)
 - a. Both the Board and ESAC should continue to include the best qualified individuals but should be mindful of the need for appropriate gender and geographical representation.
3. ESAC (see para. 3.2.3)
 - a. ESAC could sub-divide its committee to separately consider discovery and development projects. This would allow for a broader and more considered approach to the projects. More time should be given to the assessment of clinical projects as they now represent the greatest financial commitment. Some ESAC members should attend both sessions to ensure continuity.
 - b. We recommend strengthening the expertise of ESAC in the areas of design and execution of clinical trials and statistical methodology.
 - c. The ESAC review process should be standardised with the aid of project and portfolio management tools that track operational activities, map the critical path to the delivery of an approvable New Drug Application (NDA) dossier to the competent regulatory authority, manufacturing/marketing/distribution activities, and model the capital requirements with expected return on investment.
 - d. Considerable demands are made upon the time of certain ESAC members. We recommend that honoraria be paid in recognition of their contribution.
 - e. ESAC should seek confirmation that either MMV or its partners are planning sufficiently far ahead with regard to the eventual provision of new antimalarials in the field. (Figure A)
 - f. The World Health Organisation (WHO) has a long history of working with government in disease endemic countries and the support of WHO will be critical to MMV obtaining prequalification and testing of new antimalarials under field conditions. It would seem especially advantageous to include senior representation from WHO / Tropical Disease Research (TDR) / Roll Back Malaria (RBM) at the relevant ESAC sessions.
4. MMV Staff (see para. 3.2.2)
 - a. The MMV team should be strengthened and expanded to ensure effective management of its increasingly diverse portfolio. This would include additional expertise in drug development and malaria.
 - b. Project management of the clinical projects should be strengthened and standardised with appropriate tools, critical path analysis and development plans.
5. Discovery, Development and the Portfolio (see para.3.3)
 - a. Selection of the appropriate molecular targets for high throughput screening is critical for the downstream drug discovery process. ESAC should be strengthened by additional scientific expertise in biochemistry and molecular biology to avoid subsequent costly failure at a later stage.
 - b. The portfolio should be strengthened and include more early stage projects to adequately fuel the drug pipeline.
 - c. The Chief Scientific Officer has a particularly heavy burden at the present time and should not have day to day project management responsibility. Additional staffs are required to address this.

6. The Downstream Partners (see para. 3.5)
 - a. MMV and its downstream partners need to review and strengthen their mechanisms of collaboration, and clearly define roles and responsibilities to ensure the timely delivery of new and affordable drugs to disease endemic countries.
 - b. Because TDR, RBM and some other WHO departments can play key roles in some of the downstream functions, a special effort is required to establish effective collaborative mechanisms between MMV and its WHO partners. The team strongly recommends a high level independent review of MMV's interaction with TDR and RBM. The aim of the proposed review is to ensure that whatever arrangements are agreed at the programme level, will receive explicit guaranteed support at the highest management level of both MMV and WHO.
7. The Donors
 - a. Donors should be prepared for sustained and increased financial commitment over the next five years to assure the success of MMV. Although we anticipate important new antimalarials coming out of MMV, not everything will succeed and donors should be mindful of the risks in determining their future funding strategy.

Table 1 summarizes key observations and recommendations.

Table 1
Key observations and recommendations of the MMV review team
Each cell contains an observation and a key recommendation; the latter is bulleted and in italics

	Scientific	Managerial/operational	Financial
Strengths	Strong technical guidance from ESAC. <ul style="list-style-type: none"> <i>Provide honoraria</i> 	Strong, effective Governing Board & small dedicated Management team <ul style="list-style-type: none"> <i>Expand and strengthen the Management team</i> 	Generous support especially from private sector donors. <ul style="list-style-type: none"> <i>All donors continue to give high priority to MMV</i>
Weaknesses	Gaps in expertise – statistics, clinical science -- in ESAC & the Science team; limited expertise in clinical trials & field work <ul style="list-style-type: none"> <i>Strengthen ESAC & Science team</i> 	Science team heavily dependent on complementary expertise in ESAC <ul style="list-style-type: none"> <i>Expand Science team to fill identified gaps in expertise</i> 	Present financial arrangements do not ensure a steady flow of funds <ul style="list-style-type: none"> <i>Donors should ensure steady flow of resources to maintain steady progress of MMV projects</i>
Opportunities	Innovative ideas and leads from academia <ul style="list-style-type: none"> <i>Maintain MMV's capacity to follow up on useful leads</i> 	Potential new partners identified for downstream functions <ul style="list-style-type: none"> <i>Develop & strengthen partnerships with WHO & other partners</i> 	MMV's rapid progress on discovery and early development provides opportunities for fast progress towards its goals. <ul style="list-style-type: none"> <i>Donor group should respond positively to MMV's needs</i>
Risks/Threats	Failure to take up promising leads may undermine morale in academia <ul style="list-style-type: none"> <i>Ensure that MMV has enough resources to maintain its momentum;</i> 	Difficulties in developing effective partnerships for the downstream work. <ul style="list-style-type: none"> <i>Careful task analysis of downstream issues, identification of potential partners and matching capacity to needs.</i> 	Stalling of progress in managing a very promising portfolio <ul style="list-style-type: none"> <i>Donors should consider using a replenishment model similar to that adopted by the Global Fund to Fight AIDS, Tuberculosis and Malaria</i>

1 TERMS OF REFERENCE AND THE REVIEW PROCESS

1.1 Donor Co-ordination Process

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Annex 2 contains the detailed Terms of Reference for the review. The four members of the review team were:

1.2 The review team

Keith Bragman MD (Lond), FRCP, FRCPath, FFPM, Consultant in Pharmaceutical Development and Healthcare, Non-executive Director of BruCells SA. Specialist in drug development for infectious diseases

Alan Fairlamb, MB,ChB, PhD, FRSE – Wellcome Principal Fellow and Head of Division of Biological Chemistry & Molecular Biology, University of Dundee. Research scientist, drug development with special reference to parasitic infections

Hassan Mshinda, PhD, Director, Ifakara Health Research and Development Centre, Expert in epidemiology and malariology

Adetokunbo O. LUCAS MD, DSc, FRCP, FFPH, FRCOG Adjunct Professor, Harvard University. Public Health Specialist

Annex 3 contains more detailed biodata of the team members

1.3 Work plan

The team tackled its task by reviewing relevant documents, interviewing key members of the MMV team, selected members of the Board and ESAC, officials of WHO and other partner organizations. Two members of the Review team, KB and AF attended a meeting of ESAC and also went on site visits to MMV projects in India, Thailand and Spain. Face to face interviews were supplemented with teleconference interviews (see Annex 4 for list of persons interviewed). The team met in Geneva twice, in February and in March spending 3-4 days on each occasion.

2 BACKGROUND ON MALARIA

The work of MMV and this review are best examined against the background of the epidemiology of the disease and the current status of global effort to control it. The main points can be briefly summarised:

- The malaria problem is massive and growing. Over 2 billion persons are at risk of infection with *Plasmodium falciparum* malaria; more than a million deaths occur among about half a billion cases each year;
- Chemotherapy, the main control tool, is of declining efficacy because of the emergence of drug resistant strains of *P. falciparum*. Current therapy is largely based on combinations of artemisinin based compounds with other anti-malarial drugs. There is an urgent need for new drugs that can be effectively used for treatment and prophylaxis
- Commercial considerations limit the response of the private pharmaceutical industry from investing resources in developing new anti-malarial drugs;
- The international health community has responded to the challenge of malaria by creating the Roll Back Malaria alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and specifically to fill the gap of drug development, the Medicines for Malaria Venture.

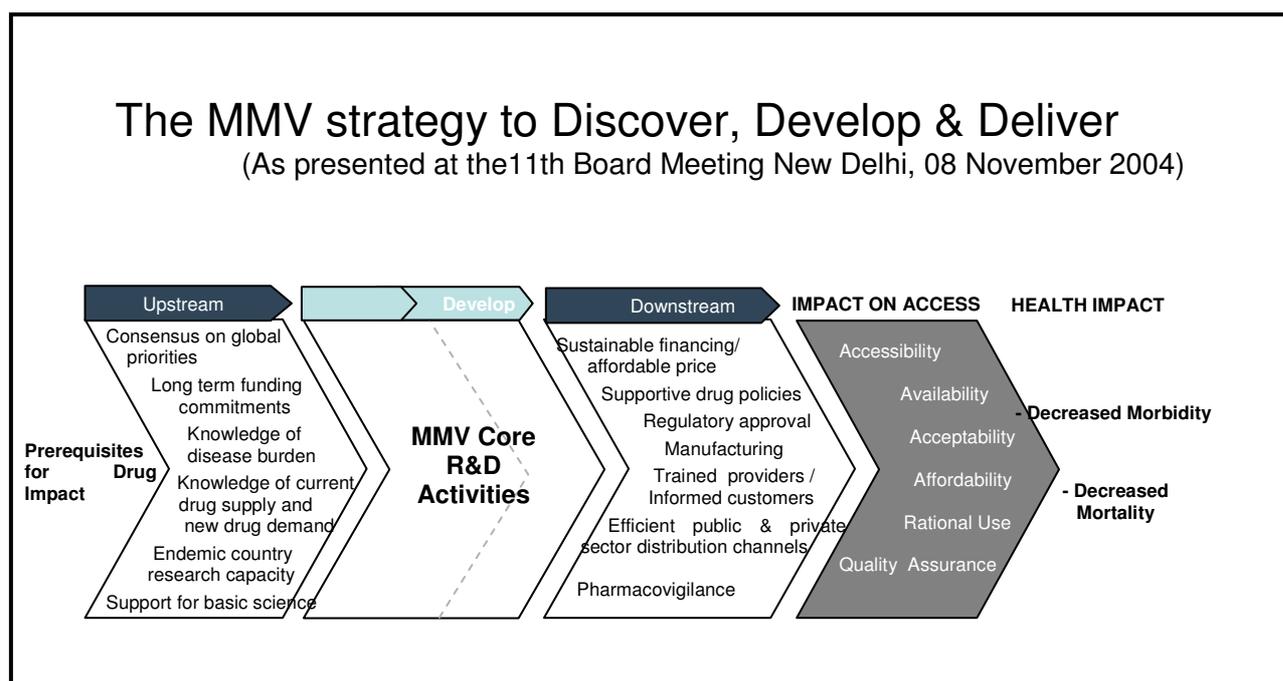
Annex 5 contains a more detailed review of the background of malaria.

3 REVIEW OF MMV OPERATIONS

3.1 MMV's Mission

The mission of MMV is to bring public, private and philanthropic sector partners together to fund and manage the discovery, development and registration of new medicines for the treatment and prevention of malaria in disease-endemic countries. Initially, MMV's mission was to discover and develop new antimalarial drugs but more recently, it has realised the need to be involved in the downstream issues of ensuring the delivery of affordable drugs to the target populations. Its new mission statement embraces the three objectives: DISCOVER, DEVELOP & DELIVER. (See Figure 1)

Figure 1



MMV has made rapid progress in discovery and early development -- its upstream tasks (See Figure 1). It is now making plans to tackle the downstream tasks which eventually should lead to the ultimate goal of the programme in making available new, effective anti-malarial drugs that are accessible and affordable to the target populations in developing countries. Paragraph 3.5 contains the review team's analysis of MMV's role beyond discovery and development to include delivery.

3.2 Governance of MMV

3.2.1 Board of Directors

The Board of Directors is the highest policy and decision-making body of the MMV programme. Under the leadership of its chair, Dame Bridget Ogilvie, the Board is responsible for the overall policy and it provides a general oversight of the programme. Dame Bridget, a Fellow of the Royal Society and a former head of the Wellcome Trust, currently serves on the faculty of University College, London. Each member of the Board serves in a personal capacity but brings knowledge, expertise and experience from involvement with other organizations and programmes. Annex 6 shows the present composition of the Board. Several committees carry out some of the detailed work of the Board (Annex 7). The Board interacts closely with ESAC, the body that provides scientific and technical advice to the programme.

3.2.1.1 Comments on the Board

- a. The Board of MMV has developed an efficient working relationship with the MMV team and with ESAC. The Board is anxious that donors and other stakeholders should have realistic expectations about the outputs from the MMV programme. Even though at this stage, MMV has accumulated and is managing an impressive portfolio of promising compounds, one must always be conscious about the

- known risk that some of the compounds may fail in the course of development and clinical evaluation.
- b. MMV and its Board have developed strong relationships with many partners and stakeholders.
 - c. Women are under-represented in both the Board and on ESAC.

3.2.1.2 *Recommendation on the composition of the MMV Board and ESAC*

- a. The Board and ESAC should continue to ensure that the most qualified and experienced individuals are included within their respective groups.
- b. Every effort should be made to achieve a better gender balance by recruiting female members to serve on both bodies.

3.2.2 *MMV Team*

The MMV team is responsible for all day-to-day operations of the organization. Under the leadership of Dr. Christopher Hentschel, the Chief Executive Officer, the MMV management team includes a Chief Scientific Officer, a Chief Financial Officer and a Human Resources and Administration Manager. The Director of International Operations, four Scientific Officers, a Communications and Advocacy Officer as well as administrative support staff complete the MMV team. (see Annex 6 for details of management structure and an evaluation of the International Office of MMV).

This relatively small team, with major support from ESAC, achieved remarkable progress in establishing and managing MMV's portfolio. The senior management team costs and staff headcount remained stable during 2003 while General Administration spending continued its downward trend as a percentage of total expenditure to 11%.

The MMV management team provides valuable information for the guidance of donors and other stakeholders. The official website, www.mmv.org contains annual reports, news of scientific progress and other up to date information about the programme. MMV maintains close relationship with its financial donors and meets their various requirements for progress reports and other information. With the large number of donors contributing to MMV, the reporting requirements of individual donors could become unnecessarily burdensome to a small organization. It would reduce the administrative burden on the management team if all stakeholders would agree on a standard reporting form.

3.2.2.1 *Recommendations on strengthening the MMV Team*

- a. The MMV team needs to be expanded and strengthened in order to maintain the momentum generated in the first five years of operations.
- b. The team needs to acquire additional expertise in drug development and malaria to ensure the effective management of its portfolio.
- c. As more projects enter clinical trials, more expertise in the clinical and epidemiological aspects of malaria is needed to complement the biomedical and drug development skills.

3.2.3 *Expert Scientific Advisory Committee (ESAC)*

3.2.3.1 *Introduction*

The Expert Scientific Advisory Committee (ESAC) is the scientific advisory board to MMV. Two members of the review team attended two days of ESAC business and observed ESAC's monitoring of MMV's preclinical and clinical development projects and portfolio management. Overall ESAC and MMV have achieved impressive progress in their drug development activities over the last five years.

The recommendations set out below reflect the current balance of the portfolio, now heavily weighted towards clinical development, and ESAC and MMV's anticipated future needs.

3.2.3.2 *Role of ESAC*

ESAC has a broad remit in evaluating the portfolio of projects covering the entire drug discovery process from early phase discovery through to Phase III clinical trials. Also ESAC makes recommendations on the inclusion or discontinuation of projects within the portfolio. MMV issues calls for new proposals usually on an annual basis and receives about 80 to 100 brief letters of interest. These are reviewed by all members of ESAC by email and assigned a priority score, which are then averaged and used to invite the most promising (~10) applicants to submit a full proposal for detailed review by the committee. In addition, ESAC reviews progress of funded projects at its annual meeting in March. Depending on the nature of the project, these include: project plans, results of studies, development issues (pre-clinical and clinical, manufacturing etc., etc.), planned studies and regulatory strategy.

3.2.3.3 *Composition of ESAC*

Until 2004 the committee was chaired by Dr Simon Campbell, former Senior Vice-President, Worldwide Discovery and Medicinal Research and Development (R&D), Europe, Pfizer and subsequently by Dr. Win Gutteridge, former Chief, Product R&D, TDR, WHO. Dr Gutteridge is an effective leader and chairperson. ESAC members are all internationally recognized experts in their fields and include representation from Europe, USA, Africa and Asia (see Annex 5). In 2004, the size of ESAC was increased from eight to twelve members to broaden and strengthen the expertise on the committee. Overall this would appear to be a mature and well organized team and should be complimented for their achievements to date. ESAC is central to the strategic and, at this time, operational direction of MMV. This has resulted in an excessive workload for ESAC.

3.2.3.4 *Scientific review process*

Principal investigators present a progress report to ESAC followed by a review led by two designated members of ESAC. Other members of the project team are present along with invited observers from other agencies and donors. Members of other project teams can also attend provided they have signed a confidentiality agreement. This makes the scientific review process as transparent possible while protecting intellectual property. ESAC then deliberates in private for 30 min. Projects were reviewed in an efficient and business-like fashion with key issues identified and discussed. Pragmatic decisions were taken regarding the therapeutic value of individual projects, the continuation of projects and whether these projects should be retained in the MMV portfolio and clear recommendations made. These were summarised and recorded by the Chairperson and approved by ESAC.

3.2.3.5 *Management of the Portfolio*

Discussions and recommendations on the composition of the MMV portfolio were made in a closed session. This followed on from the individual project reviews and did not include a rigorous evaluation or ranking of programmes by either scientific merit or relevance to MMV's strategic goals. This meeting was part of a more extended process of portfolio evaluation which took place in March 2005. At that time further recommendations for the addition of new projects were made.

This subject is further discussed under “MMV’s Drug Discovery and Development Portfolio”.

3.2.3.6 Comments on ESAC:

- a. The scientific activities covered by the ESAC range from early stage discovery to late stage clinical trials. Figure 2 in Annex 8 illustrates the composition of the portfolio in January 2005. This is a broad remit for such a small committee and heavily reliant on the recommendations of one or two individuals with specific expertise in a particular topic.
- b. Careful consideration of issues relating to clinical trials is vital, since costs dramatically increase as compounds enter late stage clinical development. Under the present structure, there is insufficient time to adequately review the clinical programmes, which represent the largest investment for MMV.

3.2.3.7 Recommendations on ESAC:

- a. Membership of ESAC must always strive to achieve the highest possible scientific expertise, but should be mindful of the need to ensure appropriate geographical and gender balance.
- b. MMV should consider honoraria for the ESAC membership in recognition of the current and excessive demands made upon the group.
- c. ESAC should consider introducing a more structured assessment of projects by the separate evaluation of “discovery” and “late stage pre-clinical and clinical projects” with some ESAC members attending both sessions to ensure continuity.
- d. A detailed understanding of the physical, chemical, structural and mechanistic properties of potential drug targets, including genetic or chemical evidence that they are essential for parasite survival (the “target identification, selection and characterisation” stage of discovery) is critical for the downstream drug discovery process. “Fail early, fail cheaply” should be the motto. An additional scientist with expertise in parasite biology, biochemistry and structural biology would strengthen this critical initial step.
- e. The addition of one or more clinical scientists with expertise in the design and execution of clinical trials in malaria endemic countries would be advisable on ESAC. This could include an expert statistician to ensure that clinical trials have sufficient statistical power to provide meaningful outcomes.
- f. The ESAC mandate appears to relate only to the technical issues of drug development. Drug development does not end with the completion of the clinical studies required to obtain approval from a competent regulatory authority. Even if ESAC has no responsibility beyond oversight of development programmes, ESAC should seek confirmation that either MMV or its partners are planning sufficiently far ahead to ensure patient access and the timely distribution of new drugs.
- g. Drug development in the field of malaria is extremely complex and must include and take account of the specific needs of individual countries burdened by this disease. WHO has a long history of working with government in disease endemic countries and the support of WHO will be critical to MMV obtaining prequalification and testing of new antimalarials under field conditions. It would seem especially advantageous to include senior representation from WHO/TDR/RBM at the relevant ESAC sessions.

3.3 Discovery and Development Portfolio

3.3.1 Introduction

MMV is a non-profit foundation dedicated to reducing the burden of malaria in disease endemic countries by discovering, developing and delivering new affordable antimalarials through effective public-private partnerships. Over the last five years MMV has achieved considerable success in establishing a comprehensive portfolio of antimalarial drug candidates. Neither the public nor the private sector could have achieved these objectives alone and MMV is to be congratulated for forging such productive partnerships. MMV's development budget has been modest to date and exceptional value has been created within the portfolio.

Academia and industry have made significant contribution to the partnership. Industry has provided access to diverse expertise, including drug discovery platforms, development and manufacturing capabilities. Academia has provided scientific knowledge ranging from the application of basic research to an understanding of the biology of the disease and its application to the drug discovery process. It is difficult to quantify the precise value of these contributions in financial terms. However the input from industry and academia has been critical to containing costs and the success to date of MMV's portfolio.

A detailed review of two flagship programmes has been made to assess MMV's partnership model with two different pharmaceutical companies. First the GlaxoSmithKline (GSK) drug discovery mini-portfolio (see Annex 9) represents the interaction with a large global partner with considerable expertise in all stages of drug development. The second is with Ranbaxy, a mid-sized company with expertise in the development and manufacture of generic medicines, but with limited capabilities in developing a new drug (see Annex 10). Both examples are representative of how a partnership between industry, academia and the public sector can be mutually beneficial to all concerned and highly productive.

3.3.2 Portfolio overview

MMV's approach to drug development follows the conventional industry pathway and is described schematically in Figure 2. MMV has focused on developing antimalarials in combination chemotherapy because of concern that single agent therapy is more likely to promote drug resistance. Also combining drugs with differing mechanisms of action may be more efficacious and further reduce the chances of the parasite acquiring resistance to treatment. Theoretically, a new drug with a novel mechanism of action should protect and prevent the parasite acquiring resistance to older and commercially available drugs. However the recent report of selection for drug resistance to the lumifantrine component of the artemisinin combination therapy (ACT), Coartem, in human subjects suggests that this rationale may be flawed and requires further investigation (JID 2005; 191:1014-1017). Figure 3 shows the evolution and growth of the portfolio. The development strategy spans drug discovery to late stage clinical development. In 2001 there were six projects in discovery, rising to a steady state of approximately twenty projects from 2003 onwards. The portfolio covers a range of different therapeutic needs. As can be seen the portfolio contains examples of drug development covering the needs of both adults and children for severe and uncomplicated malaria.

Figure 2: MMV Development Pathway

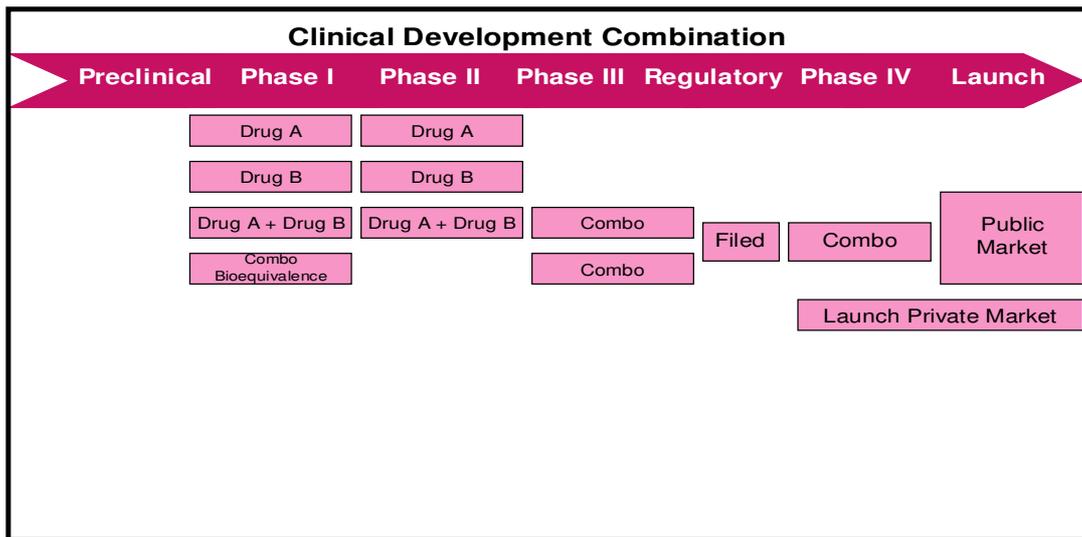


Figure 3: Evolution of the MMV Portfolio

Colour code: Red = ongoing, Grey = under consideration, Black border = GSK mini-portfolio drug discovery, Black = discontinued, Yellow = new project addition, Pink = subject to contract negotiation
 PANDA = Pyronaridine Artesunate , Coartem = Lumefantrine/Artesunate
 ARTEKIN Dihydroartemesinin/Piperaquine, DB289 = Diamidine,
 OZ = OZ 277/RBx 11160, CDA = Chlorproguanil/Dapsone/Artesunate

MMV Portfolio May 2001

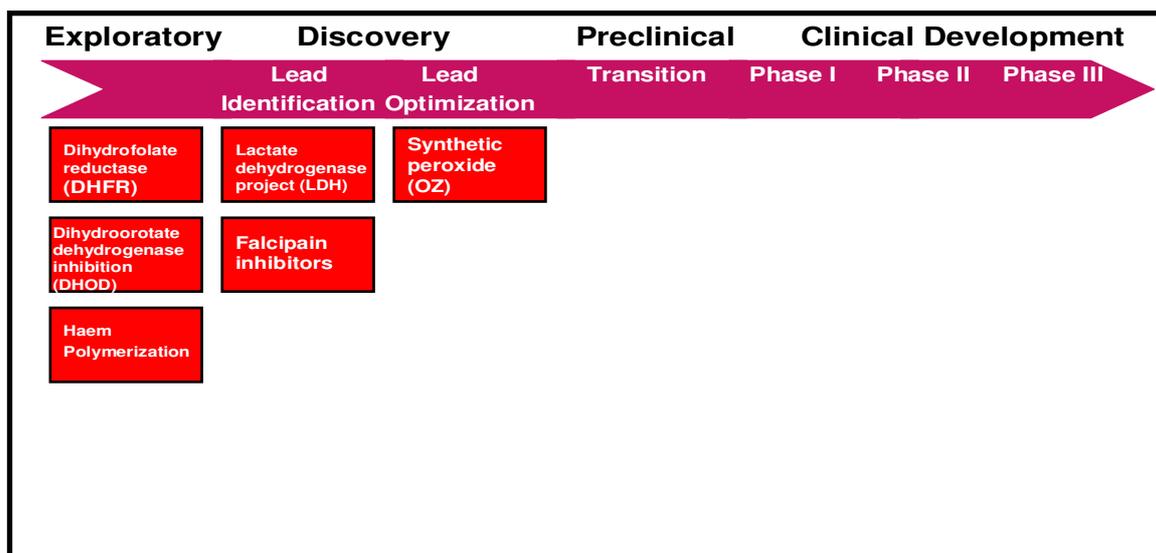
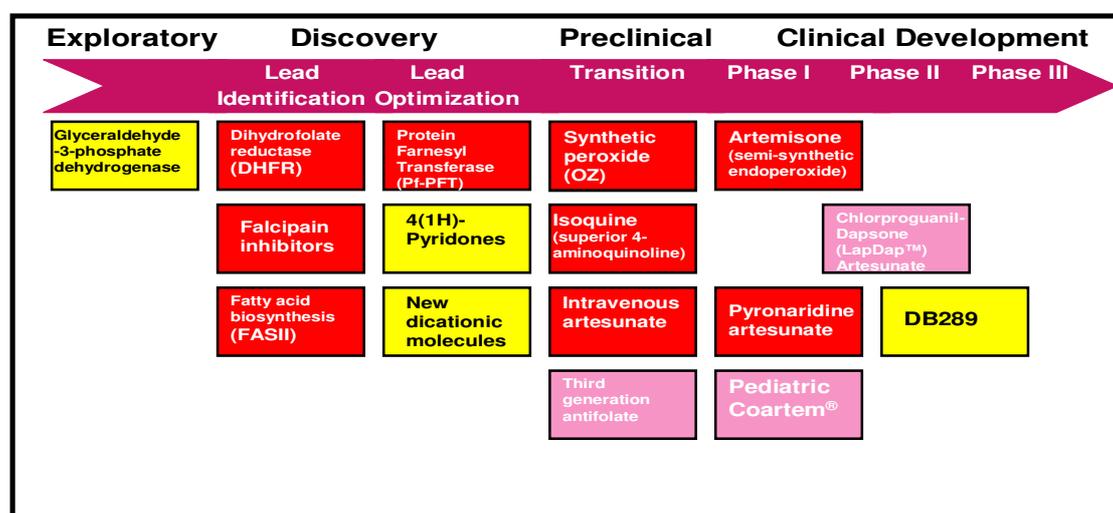
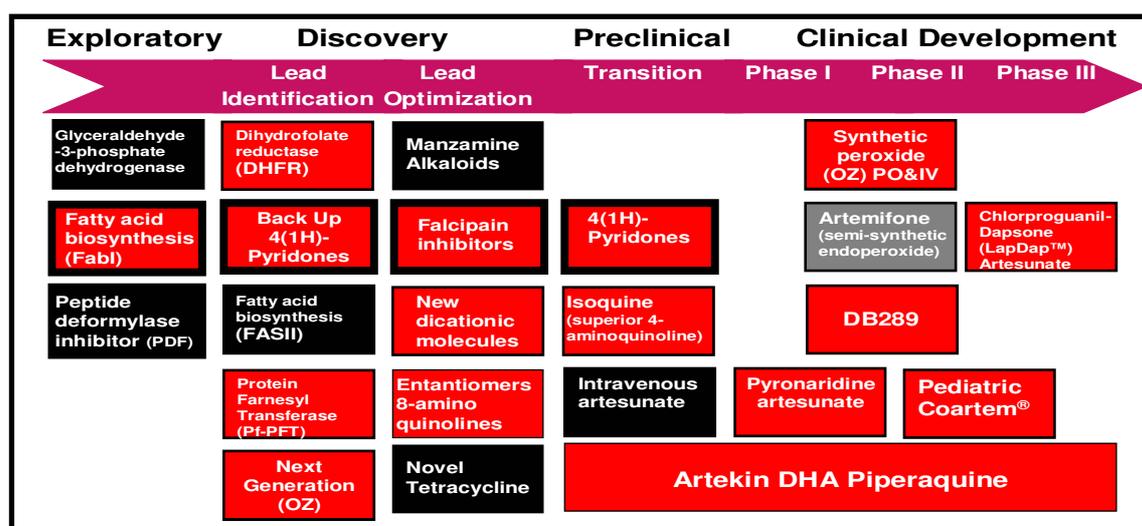


Figure 3 Contd.

MMV Portfolio May 2003



MMV Portfolio Jan. 2005



The portfolio contains several examples of artemisinin-based combination therapy (ACT). (Figure 4). Artemisinin, an endoperoxide, is a natural product derived from the plant (*Artemisia annua*). Limited plant cultivation is threatening supplies and increasing the production costs of the drug. This represents an increasingly serious problem at this time. Artemisinin and its derivatives in combination therapy (ACTs) are particularly prominent in the portfolio because of their ability to reduce the parasite burden rapidly, thereby reducing the potential for the selection of resistance to the partner drug. Fortunately, resistance to artemisinin has not yet been documented in the field. The development of resistance to artemisinin would seriously compromise the ACT strategy. Consequently it is prudent that the portfolio should contain new compounds with entirely novel modes of action (e.g. DB 289 and the 4(1H)-pyridones).

Figure 5: Artemisinin Based Projects

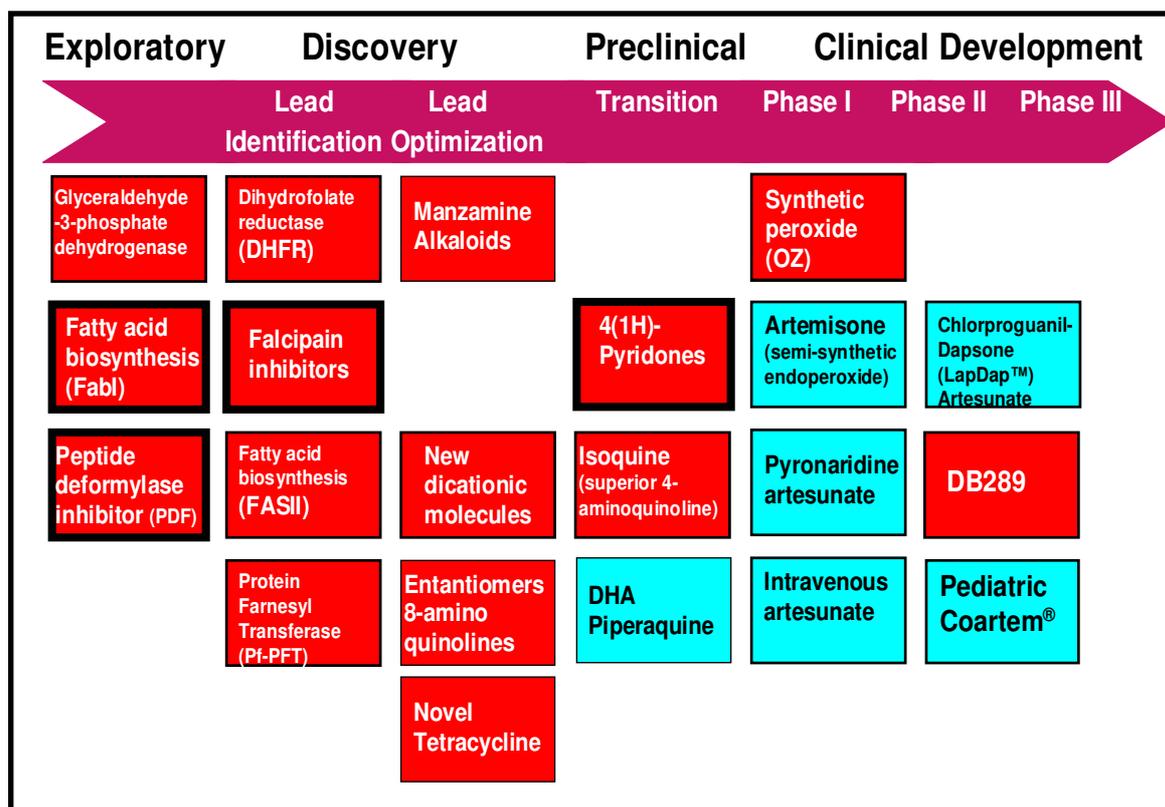
Colour code: Red = ongoing, Black border = GSK mini-portfolio drug discovery,

Blue = artemisinin based project

PANDA = Pyronaridine Artesunate, Coartem = Lumefantrine/Artesunate

ARTEKIN = Dihydroartemesinin/Piperavaquine, DB289 = Diamidine,

OZ = OZ 277/RBx 11160, CDA = Chloroguanil/Dapsone/Artesunate

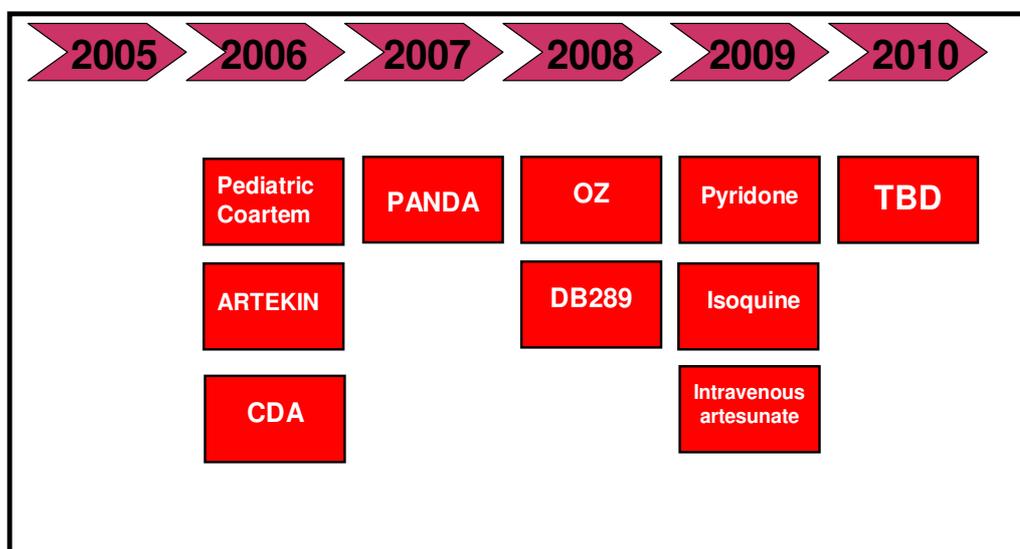


The synthetic endoperoxide, OZ 277/RBx 11160 is now in Phase II clinical development. This project has major public health significance because of anticipated efficacy in combination therapy against *P. falciparum*, ease of manufacture and low cost. OZ 277/ RBx 11160 would potentially substitute for the artemesinins and solve the present supply problem. (See Annex 10)

The CDA (chloroguanil/dapsone/artesunate) project will be the first to enter Phase III clinical development later in 2005, assuming that the current safety concerns highlighted by RBM with LapDap (chloroguanil/dapsone) are resolved in a satisfactory manner. The CDA project could be completed in 2006 with regulatory approval of a fixed dose combination of the constituent drugs by 2007. However, WHO has not yet recommended the addition of LapDap to national formularies for the treatment of malaria. This continuing uncertainty regarding the safety of LapDap could conceivably lead to the discontinuation of the CDA project at this late stage, with ensuing loss of the total investment in the project to date, approximately \$5.7 M USD. This highlights a major deficiency in communication between MMV and its downstream partners.

MMV should be able to begin filing NDA's for regulatory approval from 2006, (see Figure 4).

Figure 4: Potential regulatory filings by year



**PANDA = Pyronaridine Artesunate , Coartem = Lumefantrine/Artesunate
 ARTEKIN = Dihydroartemesinin/Piperaquine, DB289 = Diamidine,
 OZ = OZ 277/RBx 11160, CDA = Chlorproguanil/Dapsone/Artesunate**

3.3.3 Management of the Portfolio

Discussions and recommendations on the composition of the MMV portfolio were made in a closed session of ESAC and separate to project review. The development of a totally synthetic endoperoxide (OZ227/RbBx11160) is particularly exciting as it has progressed much more rapidly than anticipated. However, success is not without problems, as more products have been advanced into pre-clinical and clinical development than was anticipated in the 2000 and 2003 business plans. If all projects are to be advanced, this will inevitably place unanticipated and increased demands on financial resources.

3.3.4 Probability of Success in Drug Development

The data in Table 2 below is derived from estimates in MMV's original business plan (2000). The phase transition probabilities for development are in general agreement with industry standards. The probability to successful registration of a new drug at each stage is calculated by multiplying together all of the individual probabilities for each downstream step. The reciprocal of this value indicates the number of projects required at any single stage in development to achieve a single NDA (e.g. $1/0.216 = 5$ projects in Phase I to account for attrition in subsequent stages). This column indicates why larger numbers of projects in the discovery phase are required to keep the discovery pipeline full. The probability to NDA multiplied by the number of projects in the portfolio gives the potential NDAs at any stage of development and the sum of each column predicts the total potential value in the portfolio. For example, in 2005 this is approaching 3 NDAs.

Conclusions to draw from this Table are as follows:

- Each year that a product progresses successfully in the portfolio leads to an increase in the probability of success, and an increase in the portfolio's value

- As of 2005 (current), it is probable that MMV will produce 2.9 NDAs; this is a higher figure than had been anticipated at MMV's origination
- MMV's pipeline is currently out-of-balance; whilst the clinical development phases are doing very well (well ahead of expectations) the early stage disease research phases are rather thin

Table 2

Phase	Probability	Prob to NDA	Projects for 1 NDA	Projects						Potential NDA						
				2000	###	###	###	###	###	2000	2001	2002	2003	2004	2005	
Discovery																
Early	0.3	0.013	78	3	3	1	3	3	1	0.04	0.04	0.01	0.04	0.04	0.01	0.01
Lead identification	0.65	0.042	24	1	2	3	3	4	3	0.04	0.08	0.13	0.13	0.17	0.13	0.13
Lead optimization	0.55	0.065	15	2	2	1	5	4	3	0.13	0.13	0.07	0.33	0.26	0.20	0.20
Preclinical	0.55	0.119	8		2	3	3	3	5	0.00	0.24	0.36	0.36	0.36	0.59	0.59
Clinical development																
Phase I	0.7	0.216	5			3	3	4	2	0.00	0.00	0.65	0.65	0.86	0.43	0.43
Phase II	0.5	0.309	3				3	3	5	0.00	0.00	0.00	0.93	0.93	1.54	1.54
Phase III	0.65	0.618	2							0.00	0.00	0.00	0.00	0.00	0.00	0.00
Registration	0.95	0.950	1							0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total portfolio "value"		1.000		6	9	11	20	21	19	0.21	0.49	1.21	2.42	2.62	2.91	2.91

At this time MMV does not have its own project management systems and is dependent upon management tools provided by its pharmaceutical partners. Also drug development plans are at various stages of completion. This has led to a lack of uniformity in how projects are managed. As the portfolio grows, it will become increasingly difficult for MMV to both manage projects and take management decisions across the portfolio.

3.3.5 Portfolio Management Recommendations:

- MMV should standardise its processes and procedures and ensure that its development partners present information according to an agreed format. This should aid portfolio management, provide greater transparency where projects are benchmarked against the original timelines and planned milestones with an analysis of the critical issues at hand. In addition, critical (development) path analysis with decision trees that capture alternative development scenarios, should further strengthen decision making and streamline MMV and ESAC activities, respectively.
- ESAC and MMV are already aware that there are insufficient projects in preclinical development to optimally fuel the drug pipeline. To take account of the increased likelihood of failure in early development, the portfolio should have many more early stage projects. MMV's decision to emphasise and again focus on funding discovery and early development stage projects is supported by this review.
- MMV is in the fortunate position of being able to review the project and portfolio management tools used by its pharmaceutical partners. MMV could pick and choose tools appropriate to its needs and rapidly implement the chosen systems and processes. MMV has been extremely successful to date and the above recommendations are made on the assumption that MMV will need additional support and infrastructure to manage an increasingly diverse and complex portfolio.

3.3.6 Management of Individual Projects

The MMV organisation has approximately ten staff including a Chief Scientific Officer supported by three Scientific Officers. This is a small number of individuals relative to the size of the portfolio and reflects MMV's philosophy of a lean organisation whilst outsourcing their needs to external groups. Due to limited expertise in the biology and clinical aspects of drug development for malaria within the organisation, MMV is highly dependent upon ESAC and other external advisors.

The Chief Scientific Officer (CSO) has a particularly heavy burden at this time and is also the Chair and Scientific Officer for the OZ 277/RBx 11160 and CDA projects, respectively. This could be construed as a conflict of interests. Ideally the CSO should overview the activities of other scientific officers and provide scientific direction on individual projects as required.

3.3.6.1 Recommendation—project management:

MMV should strengthen the drug development capabilities and clinical expertise in malaria within the Science team. This would be in addition to the suggested expansion of ESAC to also include greater clinical expertise.

3.3.7 Conclusions

MMV is addressing major treatment and public health needs. However it is apparent that beyond the initial registration of new drugs and combination chemotherapy, there are many more therapeutic needs to be covered.

Other treatment indications of interest include:

- Intermittent treatment in pregnancy
- Intermittent treatment in early infancy
- Severe malaria
- Treatments suitable for emergency situations e.g. single dose treatment for refugee camps
- *P. vivax* malaria (including radical cure)
- Chemoprophylaxis

MMV is working in an area of drug development which in addition to being technically difficult has unique challenges. The countries most affected by malaria are the same countries that are least equipped to conduct clinical research to international Good Clinical Practice (GCP) and regulatory standards. Whilst MMV has picked experienced clinical investigators, there will still be a need to train and support investigators and clinical sites to be eventually assured of success. TDR could play an important role here through its activities in research capacity strengthening in disease endemic countries. MMV is supported by experienced providers of clinical trial services in the target countries which should reduce the risk of failure.

Beyond 2005, how will MMV manage and fund a portfolio which is increasingly slanted towards late phase clinical development projects which represent the greatest need for capital investment. The price of treatment has been a critical question in determining whether a project should remain in the portfolio or be discontinued. The strategic direction (content) and longer term funding of the portfolio will be a critical point of discussion between MMV and the donors.

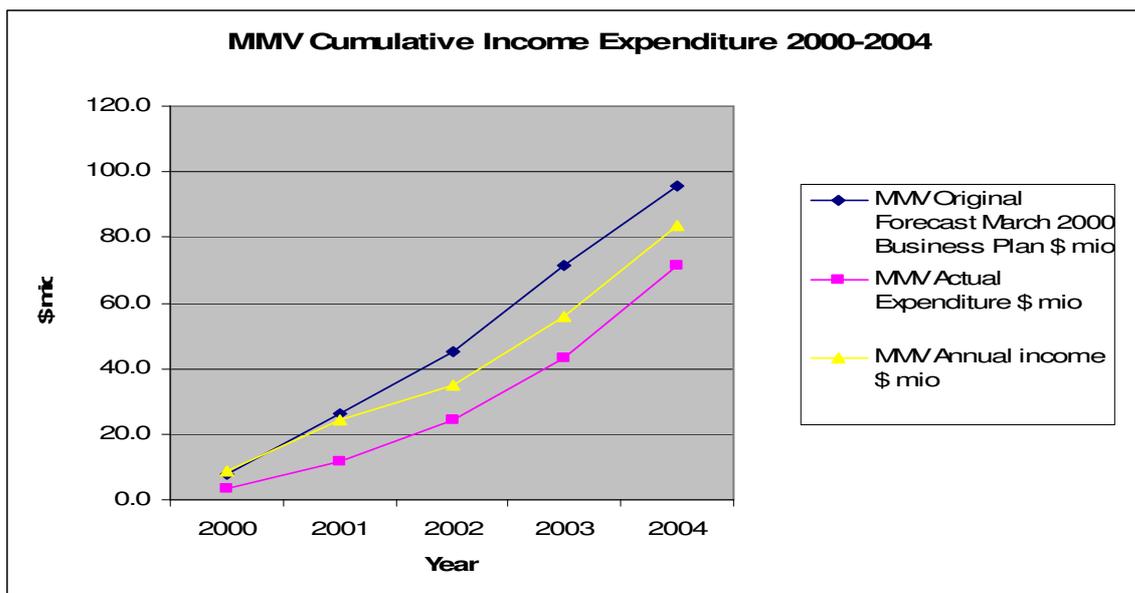
3.4 Finance

MMV's cumulative development costs have been less than was originally planned in their business plan, see Figure 5. MMV has successfully advanced their development programme at an accelerated pace whilst exercising prudent fiscal control. Project related costs are shown in Figure 6.

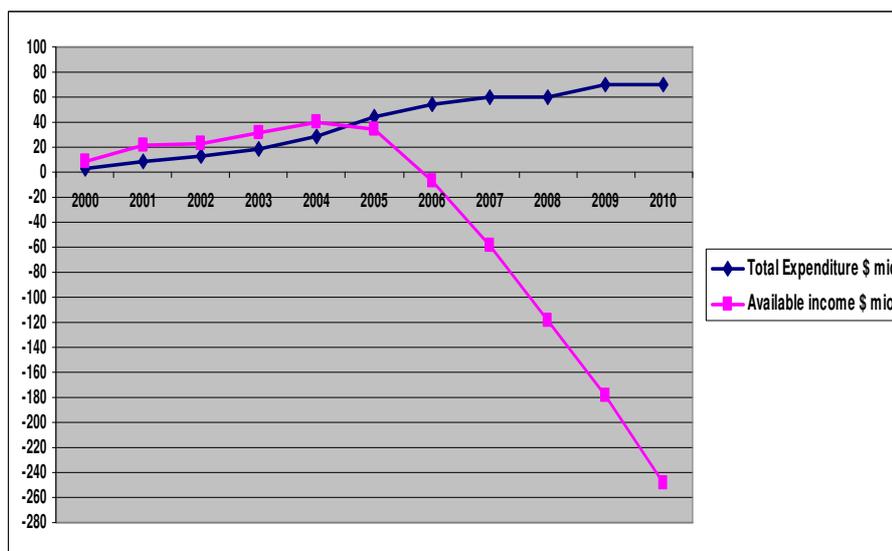
As can be seen in Figure 5, if funding continues at the present rate there will be an increasing deficit, reflecting the high cost of late phase clinical development: Phase III

clinical trials, Phase IV efficacy/field studies and scaling up manufacturing capabilities. By 2010 the funding deficit will approach \$300 M USD without including all of the costs associated with scaling up the manufacture of bulk drug supplies and distribution. This is the inevitable price of success and reflects fruitful collaborations with MMV's numerous pharmaceutical partners and academic institutions around the world. Table 2 shows the cumulative probability for success in delivering an approvable NDA according to the stage of development and the number of compounds in each stage of development. Beyond 2002, the likelihood of an approvable product increases in line with the increased number of compounds entering late stage clinical development.

Figure 6: Development Costs and Funding Needs

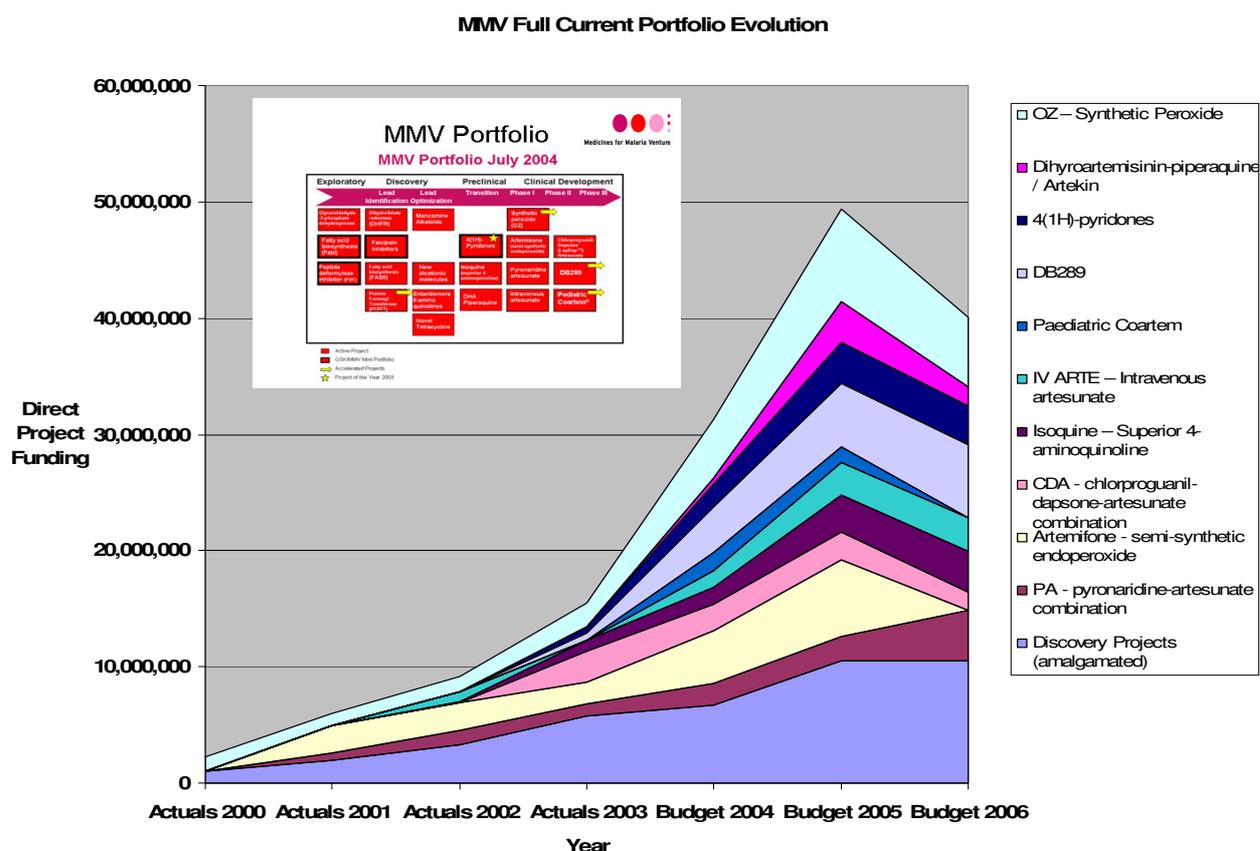


Current Estimated Funding Needs to 2010*



*Excluding costs of manufacture/scale up, post registration surveillance, and Phase IV

Figure 7: Relative Project Funding



In 2005 the portfolio includes at least two projects with the potential to lead to an approvable NDA. Therefore, MMV is considerably ahead of its initial goal to deliver one new product in the first ten years of its existence. However, it should be noted that the number of projects in either discovery or preclinical development has progressively diminished and with expected attrition rates, this is now insufficient to maintain the drug development pipeline much beyond 2005.

MMV's cash flow already shows the increasing divergence between donor funding and expected outgoings at the beginning of the year (Figure 6). Figure 7 shows relative and individual project related costs. Cumulative expenditure to the end of the year 2004 has been approximately US\$ 70M and represents excellent value in consideration of the portfolio size and stages of product development. It should also be noted that this figure does not include or attempt to value the contribution of academia and pharmaceutical partners.

Thus far, MMV's donors have provided additional funds to cover operational expenses in the latter part of the year. This pattern of funding is not consistent with managing a portfolio of this size, where clinical trial costs can be expected to ramp up over the next year or so. Also, there are likely to be regular and intermittent delays in project activities with increased uncertainty and impaired decision making.

Drug development is frequently expensive and success is not assured even for products in late stage development. The portfolio is now heavily weighted towards clinical development which will place increasing demands on project management. Drug manufacturing, late stage preclinical activities and the clinical trials will likely take place in disparate regions of the world, all adding to the complexity of drug development.

Of the 28 projects recommended for funding from 2000-2004, nine have been terminated and one project failed to commence due to an inability to finalise a contract. Thus, one third of projects have been terminated at a cost of \$8.4 M, i.e. 12% of the total spend on projects (\$69.8 M). The reasons for termination can be roughly characterised as: lack of progress towards identifying an optimised lead (30%); toxicity issues (20%); failure to identify a suitable partner (20%); issues relating to resistance potential and cost of goods (10%); difficulty in identifying a development candidate (10%); and inability to agree a contract (10%). However, the two most expensive projects which have been terminated are the FAS II (fatty acid biosynthesis) and the LDH (lactate dehydrogenase) inhibition at a cost of \$2.5 M and \$2.0 M, respectively. With the benefit of hindsight, or stronger scientific direction within MMV, these projects could have been terminated earlier.

3.4.1 Comment on financing:

Donors need to be prepared for the failure of some projects as well as success. The present project failures have occurred in the discovery phase and are relatively inexpensive compared to failure during clinical development. However, it should be noted that unexpected failure may still occur in late stage clinical development.

3.4.2 Finance Recommendation:

A realistic level of funding should be set at the beginning of the year. This should adequately cover planned operational expenses over twelve months. The donors should be aware of the financial implications of beginning Phase III clinical trials which may straddle more than one financial year and the costs of scaling up drug manufacturing to support these programmes. Whilst the latter costs might be borne by a pharmaceutical partner, MMV needs to be assured of continuing support beyond a twelve month period for advanced projects. For a portfolio of the current size and stage of development, this requires forward budget planning over a minimum period of 2 years. Ideally portfolio management should be over an even longer time frame of the order of 5 years.

3.5 Delivery

Access to malaria treatment depends on household and health system factors. Household factors may include recognition of disease and perception of its cause, treatment seeking behaviour, decision making process, availability of financial resources, season, distance from health facility, availability of transport, etc. Health system factors include geographical location of health facilities, interaction with other alternative facilities such as shops or drug retailers, traditional healers, availability of quality care, presence of user fee or other mode of payments, availability of essential drugs. Throughout the whole process, from discovery to development, in order to meet the needs of the poorest segments of population in malaria endemic countries, the issue of the cost and affordability of the product must remain of paramount importance. It is not possible for MMV to address all of these issues by itself, nor would it be appropriate for it to attempt to do so. MMV's original business plan focused on drug discovery and development. Later on, its stakeholders encouraged MMV to move beyond the core functions of drug discovery and development to include delivery as a means of ensuring that people in endemic countries have access to the new products and can thereby achieve public health goal of reducing the morbidity and mortality from malaria.

The new business plan of MMV covering a period of 2003 to 2007 includes a delivery component. As with the discovery and early development component of the programme in which MMV worked closely with academia and the pharmaceutical industry, MMV will

collaborate with relevant partners in tackling the delivery component of its mandate. This will include late stage clinical and field trials, fast tracking regulatory approval, mission driven manufacturing, efficient distribution mechanisms as well as definition of the most appropriate strategic niche for the new products. (Figure A)

It is highly likely that at least one new treatment will emerge from the portfolio over the next five years. In tackling these downstream tasks, MMV had three broad options (Figure A):

- MMV could go it alone and attempt to cover all the downstream tasks on its own;
- MMV could end its involvement with the clinical trials and registration of effective drugs but leave the other issues – policy making, manufacture, distribution etc. to other interested agencies like WHO, bilateral agencies and the pharmaceutical industry; or
- MMV could work with appropriate partners in tackling the downstream issues.

The review team commends MMV's decision to select the third option of working with partners in achieving the delivery component of their extended mandate. MMV has proven expertise in drug development but must also collaborate effectively with its downstream partners. MMV must continue to engage with its partners to ensure that new treatments will be made available to those most in need..

MMV has already started to develop new partnerships for its delivery function – a process involving two stages (Table 3):

- First, a careful analysis of the tasks that need to be performed leading to the identification of relevant partners; and
- Developing mechanisms for collaboration with each new partner.

Table 3

Partnerships for downstream issues – illustrative model

Item	Tasks	Candidate Partners	Comment
Phase 3 clinical, field trials	<ul style="list-style-type: none"> • Identify suitable centres • Strengthening capacity as required • Supervise & monitor progress 	<ul style="list-style-type: none"> • WHO/TDR • EDCTP • DNDi 	<p>TDR Track record – work with industry: mefloquine, ivermectin, miltefosine, etc. EDCTP: new entity DNDi: new entity;</p>
Registration	Countries of manufacture and distribution	• RBM alliance	
Manufacture	Large scale production	Industry	<ul style="list-style-type: none"> • Large pharma • Manufacturers of generics
Policy	Identify niche for new drug	<ul style="list-style-type: none"> • RBM dept. • MIM 	Continuing review of best policy for suing the new drug
Distribution	Ensure access in endemic countries	<ul style="list-style-type: none"> • RBM alliance • RBM dept. • MSH • NGOs (eg MSF) • Public sector • Private sector/industry 	Involve a broad coalition of stakeholders

Thus, for example, for clinical trials in developing countries, MMV could work with WHO/TDR which has a track record for working with industry in clinical evaluation of drugs for tropical diseases. Other potential partners for clinical trials are the European & Developing Countries Clinical Trials Partnership (EDCTP) and Drugs for Neglected Diseases Initiative (DNDi); these new entities have recently been created. Médecins Sans Frontières (MSF) the sponsor of DNDi, has been very active in advocating access to essential drugs but its initiative to produce generic azithromycin has apparently foundered.

Another potential partner is WHO's RBM department which provides technical advice globally to endemic countries about malaria control. It is vital for MMV to work closely with the department that will ultimately guide global policy on the use of new antimalarial drugs. For example, whilst MMV is moving swiftly with its flagship CDA project, expert review by RBM department is assessing the safety of a key component, LapDap. The success of CDA will depend on the final decision about the policy recommendations about LapDap. Furthermore, TDR has recently put out a request for applications for ***“The pharmacokinetics, efficacy and safety of chlorproguanil-dapsone (Lapdap) versus sulphadoxine-pyrimethamine (SP) in the treatment of uncomplicated falciparum malaria in pregnancy”***. With such common interests, it is vital that MMV should work closely with these WHO departments and other partners. For drug manufacture and distribution, MMV would need to work with partners in the pharmaceutical industry, international NGO's and other agencies.

3.5.1 Recommendations on Delivery

- a. MMV needs to establish effective communication and coordination with its downstream partners.
- b. Several departments of WHO, specifically TDR and RBM, can and should play valuable roles in helping to achieve MMV's goals but it would be important to establish effective mechanisms that can help reconcile the working patterns of WHO and MMV. Specifically, in order to ensure smooth dovetailing of the cooperative activities of both WHO and MMV, it would be necessary to set up clear mechanisms that are clearly supported at the highest level of each organization. For example, with the authority of the top management of WHO, MMV related projects could be granted a fast track for bureaucratic processes such as legal clearance and ethical review, thereby ensuring that there is no unnecessary delay.
- c. The team recommends the establishment of an independent review of MMV's interaction with TDR and RBM to advise on how these groups should best work together responsibilities as well as clear endorsement of the modus operandi at the highest level of the management of both organizations.

4. MMV – A MODEL PD PPP

This section addresses the issues raised about MMV's performance as a PD PPP and the lessons that can be learnt from the experience.

4.1 Strategic direction

MMV is filling a clear niche. Until it was established, a major crisis confronted the world with the steady loss of the efficacy of available anti-malarial drugs without significant effort on the part of the pharmaceutical industry to develop new drugs. WHO/TDR's effort at promoting drug development were hampered by the limited resources that were not sufficient to encourage the industry to continue to invest in the field. Since MMV was founded, the

Médecins Sans Frontières has established a promising, new programme, Drugs for Neglected Diseases initiative (DNDi). MSF, the parent organization has been a powerful advocate for promoting access to essential drugs. However, MSF project for producing generic supplies of azithromycin apparently foundered. Thus MMV represents the critical hope for bringing new anti-malarial drugs to the market in the near future.

Some of the questions about the role of MMV such as its contribution to the achievement of MDG goals are somewhat premature. Although MMV has made tremendous progress in the discovery and early development phase of its operations, there is much work to be done before the first product is registered for use. If present progress is maintained, MMV promises to deliver a steady stream of effective antimalarial drugs which help to turn around the malaria problem and thus contribute to the achievement of MDG goals.

4.2 What factors have contributed to MMV's success?

A realistic assessment of MMV is of a programme that has made more rapid progress than predicted on its establishment but it will take more time and more investments before it achieves its ultimate goal of delivering effective anti-malarial drugs. Favourable factors that have contributed to MMV's progress are:

- A sound structure with well-defined relationship among its main elements;
- Strong leadership in the three major bodies: the Board, the MMV team and ESAC which all include highly qualified persons;
- Access to high quality technical and professional guidance often provided on a *pro bono* basis;
- MMV's achieved credibility with its academic and industrial partners by using transparent and objective processes for selecting and managing projects;
- Enthusiastic response of academia and industrial partners;
- Generous financial support from donors that enabled MMV to take up its most promising leads

4.3 MMV in comparison with other options

MMV was created because there is little incentive for the private for-profit pharmaceutical sector to invest in the development of anti-malarial drugs. The public sector through grants to research institutes and academia but lacks the capacity of industry to develop these ideas into usable products. It was this consideration that led to the creation of MMV and other PD PPPs. So far, MMV has fulfilled the promise in building up a credible portfolio of potential drugs. Currently, it is reckoned that it takes on an average US\$ 800 million to bring a new product to the market. MMV's performance so far indicates that it may register its new products at much lower cost. Thus, MMV is proving to be a cost-effective PD PPP but will require a steady flow of funds to maintain the momentum that it has generated.

4.4 The role of donors

The generous contributions of donors represent MMV's lifeline. But beyond financial input, the donors need to be involved in the programme:

- Donors must reconfirm their long-term commitment to MMV right through to the achievement of the ultimate goal of making new effective and affordable anti-malarial drugs available to people in endemic countries – ***“As much as is required for as long as it takes”***. This would encourage MMV partners, especially the private pharmaceutical industry to maintain and expand their involvement in this venture;

- As key stakeholders, donors must continue to monitor MMV's progress and responding flexibly to its needs and requests;
- Donors should use their influence in motivating relevant partners and stakeholders in support of MMV.

5 APPLICATION OF THE PATHWAYS MODEL TO MALARIA

This is an interesting tool which illustrates the complex process of drug development from basic science through to the delivery of a new treatment of malaria and post marketing activities. The potential barriers or difficult processes are highlighted with a red border. The user may add or delete boxes (processes) or change the order of events depending upon the choice of scenario.

This is a strategic tool that can not substitute for project or portfolio management tools. The Pathways Model has application as an advocacy and communication tool and to enable interested parties (stakeholders) to analyse and consider their relative positions in either upstream (discovery) or downstream (delivery) activities.. The process of drug development is usually a reiterative process rather than the linear pathway as suggested by the model. Also, the model does not address critical path analysis, milestones and timelines. MMV has so far, not used this model. (See Annex 8)

6 TEMPLATE FOR FUTURE REVIEWS OF PD PPP EVALUATIONS

Future reviews of PD PPP should be developed within the following framework:

a Mission / Goals

- Has the mission of the programmes been clearly defined?
- Do the goals clearly focus on the needs of the target population?

b Structure and mechanisms

- Is the structure appropriate and will it enhance the probability of success:
 - Policy making, scientific and technical support, management
- Has the programme developed effective mechanisms for its operations?
 - Are the procedures transparent and are decisions based on objective analyses?

c Time lines and milestones

- Has the programme set time lines and milestones?
- How is the programme performing in relation to its targets?

d Budget and finance

- Is the budget realistic?
- Are resource flows adequate to sustain progress?

e Monitoring and Evaluation

- Are monitoring mechanisms in place both for individual projects and for the portfolio?
- Are lessons learnt from successes and failures used to guide future directions?

On the basis of lessons learnt from the current review, the team members propose some practical guidelines for future studies. (Annex 11)

7 CONCLUSIONS AND RECOMMENDATIONS

This independent review of the Medicines for Malaria Venture (MMV) led to a clear conclusion that the programme is well led and efficiently managed. MMV has successfully mobilised creativity and innovation from academia in partnership with the pharmaceutical industry which contributes expertise and effective tools for drug development. The programme has achieved and surpassed its goals as it now has an impressive portfolio of promising compounds, some of which are at an advanced stage of development. If present trends continue, MMV is poised to deliver a steady stream of new anti-malarial drugs in the coming years.

Detailed recommendations are outlined in the Executive Summary but three points deserve emphasis:

- In order to cope with the increasing workload and the late development processes, both the Science team and ESAC need to be strengthened
- Donors should ensure a steady flow of funds to enable MMV maintain the tremendous momentum generated in the first five years of its operation
- So as to attain a seamless transition from the discovery and early development phase to the late development and other downstream processes, MMV should strengthen the collaborative mechanisms with relevant partners, notably, TDR and RBM.

ANNEXES

- ANNEX 1: Millennium Development Goal (MDG)
- ANNEX 2: Terms of Reference
- ANNEX 3: Resumes of team members
- ANNEX 4: List of persons interviewed
- ANNEX 5: Background on malaria
- ANNEX 6: MMV Board and Expert Scientific Advisory Committee
- ANNEX 7: Governance of MMV
- ANNEX 8: Pathways Model
- ANNEX 9: Glaxo Smith Kline (GSK) collaboration with MMV
- ANNEX 10: The development of OZ 277
- ANNEX 11: Practical guidelines for future reviews of PD PPP