MMV: A New Model for a New Millennium

A retrospective look at MMV, 1999-2009

Prof Win Gutteridge and Dame Bridget Ogilvie
Musée de la Croix-Rouge, Geneva
November 12, 2009
Order of Proceedings

• **Win Gutteridge:**
  • 1969-1999: The challenge
  • 1997-1999: How to solve the problem?

• **Bridget Ogilvie:**
  • 1999-2004: Getting the show on the road
  • 2004-2006: Review time

• **Win Gutteridge**
  • 2006-2009: The last 3 years
The Famous Handshake
WHO, Geneva, 3 Nov 99
Driver: Few New Drugs to Treat Tropical Diseases*

Drug development output from 1975-1996: what proportion for tropical diseases? **Answer:** 13/1223 (1%)
Why Was This?

- Upfront R&D costs of discovering and developing new anti-infective agents, especially for tropical diseases, were approaching or in many cases exceeding the net revenue from the sales of such products.
- In contrast, R&D targeting non-communicable diseases of the developed world such as hypertension and diabetes were yielding massive net returns on the investments made.
Why Then?

Malaria Treatment in the 1990s

- **Treatment of uncomplicated disease:**
  - chloroquine
  - sulphadoxine + pyrimethamine (SP)
- **Treatment of severe disease:**
  - quinine
- **Prevention of relapse:**
  - primaquine

Photographs from www.who.int/tdr
Why Then?
Malaria Treatment in the 1990s

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- **Prevention of relapse:**
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Photographs from www.who.int/tdr
1997-1999
How to solve the problem?
Strategic Planning Group (SPG)
Which Established MMV*

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
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<tr>
<td>Amie Batson</td>
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<td>Louis Currat</td>
<td>GFHR</td>
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<td>Jurgen Drews</td>
<td>Roche</td>
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<td>Tim Evans</td>
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<td>Richard Feachem</td>
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<td>Win Gutteridge</td>
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<td>Bob Howells</td>
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<td>Trevor Jones</td>
<td>ABPI</td>
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<td>David Nabarro</td>
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<td>Rob Ridley</td>
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<td>Simon Sargent</td>
<td>Glaxo Wellcome</td>
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<td>Harvey Bale</td>
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<td>Carlos Morel</td>
<td>WHO/TDR</td>
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* Photograph from [www.gva.com](http://www.gva.com)
Possible New Paradigms for Re-engaging Pharma

- Options being discussed at this time:
  - **Coercion** – publicise the withdrawal and hope that the negative PR thus generated will get pharma to change their minds
  - **Artificial markets** – use public money to guarantee purchase of a certain amount of drug (pull mechanism)
  - **Public/Private R&D Partnerships (PPPs/PDPs)** – use public money to fund joint academia/industry drug discovery and development projects (push mechanism)

- All agreed options not mutually exclusive:
  - **PPPs** – the focus of the SPG’s discussions – without new R&D, there would be no effective products to purchase – ideas on how to do so already around;
  - **Artificial markets** - route adopted by WHO with the establishment of the Global Fund and the Affordable Medicines Facility;
  - **Coercion** – route followed by MSF
Initial Documents on PPP-like Organisations

- Jurgen Drews et al, Roche – the creation of a Tropical Diseases Research Institute
- John Evans et al, World Bank – public private partnership for health research
- Win Gutteridge et al, WHO TDR – the formation of a tropical diseases R&D alliance
- Trevor Jones et al, ABPI – orphan diseases: government, international institutions, pharmaceutical industry collaborations
- These 4 had many common elements
Constraints to PPP Paradigm

- Public sector and private foundations wanted **industry** involved, since they recognised therein lay the knowledge, experience and expertise of drug R&D
- Industry not prepared to shoulder the **financial burden** alone of what is clearly a public health issue
- Need for **competition** to avoid public sector concerns of nepotism and industry problems with anti-trust legislation
- Need for easy **exit** mechanisms - no one public or private sector organisation wants to sign up for ever
- All round fear of **institutionalism** – no bricks and mortar
- None judged to be a show-stopper, so agreed to develop the idea further, initially with focus on drugs for malaria
Agreed Initial Focus on Malaria Drugs

Why?

Caused by protozoa of the Genus *Plasmodium*
Transmitted by *female* mosquitoes

- Tropical disease with the highest impact on humans in terms of disease burden, deaths, clinical cases, impact on GDP
- No effective vaccines
- Current medicines losing efficacy and DDT about to be banned
- Ideal for Proof of Concept

Photographs from [www.who.int/tdr](http://www.who.int/tdr)
Solution – Create MMV - I

- Establish an independent not-for-profit foundation with the Mission of discovering and developing affordable new medicines for malaria
- Recruit a small management team to run it with operational freedom on a day to day basis:
  - Headed by a Chief Executive Officer
  - Answerable to a Board of public / private sector trustees
  - Advised on project selection by an Expert Scientific Advisory Committee
- Raise money from the public sector and private foundations to create a ‘venture capital fund’ able to donate up to USD 33 million pa
- In parallel, obtain from the private sector access to chemical libraries and key R&D facilities, gifts-in-kind and knowledge, experience and expertise of process
Solution – Create MMV - II

• Use resources raised to carry out a virtual R&D programme by:
  • Funding adequately a series of discovery research and development projects (up to several million USD pa)
  • Selecting such projects on a competitive basis through advice from an Expert Scientific Advisory Committee (ESAC)
  • Building each project around a public / private partnership
  • Having no expectation of repayment**
  • Actively pursuing any intellectual property generated

• Commercialise through private sector partner or out-licensing to pharmaceutical company

* To ensure low cost of goods
Solution – Create MMV - II

• Use resources raised to carry out a virtual* R&D programme by:
  • Funding adequately a series of discovery research and development projects (up to several millions USD per year)
  • Selecting such projects on a competitive basis through advice from an Expert Scientific Advisory Committee (ESAC)
  • Building each project around a public / private partnership
  • Having no expectation of repayment**
  • Actively pursuing all intellectual property generated
  • Commercialising through private sector partner or pharmaceutical company

* To ensure low R&D costs
** To ensure low cost of goods
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R&D priority: new medicines to treat falciparum malaria resistant to chloroquine and SP

* To ensure low R&D costs
** To ensure low cost of goods
Solution – Create MMV - III

- By end of 1999:
  - MMV constituted as an independent Foundation under Swiss law
  - Board created out of SPG with Dame Bridget Ogilvie FRS in the Chair
  - CEO (initially Rob Ridley (acting), then Chris Hentschel), Head of Operations (Diana Cotran), CFO (Peter Potter-Lesage) and CSO (Rob Ridley) all appointed
  - ESAC recruited with Simon Campbell FRS in the Chair
  - Foundation capital of USD 4 million raised from World Bank, RBM, UK DFID and Netherlands Ministry for Development Cooperation
  - Business plan prepared with BCG
  - First call for proposals, made at end 1998:
    - 101 proposals from 27 countries received, 31 from pharma
    - 6 recommended by ESAC during 1999 for the initial portfolio
1999 - 2004
Getting the Show on the Road

Bridget Ogilvie
Status of MMV by September 2004

- MMV offices established in Geneva
- Staff headcount increased to 11
- First full Board meeting held in Geneva in March 2000
- First Annual Stakeholders meeting held in Lausanne in May 2001
- Revised business plan approved by Board November 2003
- Cash pledges of around USD 107 million received by July 2004; further funding and additional stakeholders being sought
- Two further calls for projects made, amounting to nearly 300 proposals in total since MMV began
- Proposals reviewed by ESAC, resulting in a portfolio of 21 projects
- Concept of mini-portfolio developed
Revised Business Plan

• Revision commissioned to reflect fact that:
  • All senior executive positions on Board and in MMV now filled
  • Publication in 2001 of new WHO treatment guidelines for *falciparum* malaria

• Key recommendations were:
  • On-going priority focus on treatments for chloroquine- and SP-resistant *falciparum* malaria confirmed
  • Product profiles for such treatments modified to encompass need for (fixed) combinations of molecules of independent mode of action
Successful MMV Fund-raising*

MMV - Medicines for Malaria Venture
Funding: from foundation to end-2007 [as of May 2004]

(Total - received / pledged $ 107 million)

* Slide thanks to Peter Potter Lesage
Effective Expert Scientific Advisory Committee (ESAC)

- Composed initially of around 12 independent experts in the field of malaria drug discovery, development and control chosen from the global academic and industrial communities
- Chaired by Simon Campbell, then Win Gutteridge
- Prime tasks:
  - To conduct the annual review of all projects in the MMV portfolio and advise management on which projects to stop, which to continue with restricted funding and which to fund fully
  - To carry out the initial triage of projects submitted as a result of a call for new proposal, to review in detail the projects short-listed and make recommendations on which to add to the portfolio
Concept of Mini-portfolio Developed

- Concept arose from MMV’s drug discovery partnership with GSK, based at their facility in Tres Cantos, Spain
- They were working on 2 or 3 discovery projects at any one time and incubating 2 or 3 more
- Furthermore, some of the circa 50 staff costs there were paid for by MMV
- It was agreed that they should have flexibility between annual reviews to stop and start projects and to move resources between projects, subject only to agreement of a small MMV/GSK Steering Committee
- Similar model subsequently extended to the collaborations with Novartis in Singapore and Broad/Genzyme in Boston
The Sun Never Setting on the MMV Project Portfolio*

*Slide thanks to Solomon Nwaka
2004 - 2006
Review Time
INDEPENDENT REVIEW OF MEDICINES FOR MALARIA VENTURE

Commissioned jointly by the following donors:


Alan FAIRLAMB
Keith BRAGMAN
Hassan MSHINDA
Adetokunbo LUCAS – Team Leader

May 2005
2005: Independent Review - II

• Review team charged with examining the structure and function of MMV, noting its vision and goals, its context of operation and its achievements

• Main findings were that MMV:
  • “.. has made tremendous progress, clearly ahead of its predicted milestones, towards achieving its goals”
  • “.. 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 antimalarial drugs”
  • “.. must now address important downstream issues relating to the delivery of the expected products”
2005: Mission Expanded

- Initially MMV focussed on **DISCOVERY** and **DEVELOPMENT** of antimalarial medicines to regulatory approval, relying on the pharma partner to manufacture and distribute the newly registered product.
- It had been agreed by the then Director of RBM, David Nabarro, that **DELIVERY** would be overseen by the RBM partnership which would work closely with other WHO departments and pharma.
- By 2005, it was becoming clear that this demarcation was not working.
- Thus agreed MMV would become a **3D** organisation, continuing work post-registration with its existing pharma partners and with new additional partners eg RBM and appropriate WHO departments, governments, NGOs and charities.
- EVP of Access (George Jagoe) appointed and is now developing **access plans** for MMV-partnered products as they near regulatory approval.
The Third D is Proving to be Challenging*

*Slide from Chris Hentschel
2006: Personal Reflections

• The global academic community was indeed full of bright ideas for new antimalarial medicines
• The pharmaceutical industry, despite the concerns of many in the public sector to the contrary, had thus far fully delivered on its promises of partnership
• The public sector and private charities had responded to this by maintaining and, where possible even expanding, their funding
• The jewel in the crown was clearly MMV’s staff, who had used the resources provided to bridge the gap between academia and industry to facilitate a concerted effort towards the discovery and development new treatments for malaria
2006 - 2009
The Last Three Years

Win Gutteridge
Partnering Extended

- Every one of the 7 Calls for new R&D proposals over the 10 years, bar one, have yielded more than 100 applications from the global scientific community, making over 750 in total.
- MMV has partnered or is currently partnering with 132 organisations in 43 countries.
- This includes 20 (and counting) for profit pharmaceutical companies.
High Quality of Science Maintained

- Well illustrated by Project of the Year presentations given at each annual Stakeholder Meeting:

<table>
<thead>
<tr>
<th>Year</th>
<th>Topic</th>
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<tbody>
<tr>
<td>2001</td>
<td>Synthetic peroxide compounds</td>
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<td>2002</td>
<td>PFT inhibitors</td>
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<td>2003</td>
<td>4(1H)-pyridones</td>
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<td>2004</td>
<td>Falcipains</td>
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<td>2005</td>
<td>Pyramax®</td>
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<tr>
<td>2006</td>
<td>Next generation peroxides</td>
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<tr>
<td>2007</td>
<td>Queensland natural products</td>
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<td>2008</td>
<td>Coartem® D</td>
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Stakeholder’s Contributions Sustained Situation by 2009*

MMV - Medicines for Malaria Venture
funding from Foundation to 2015 (Oct 2009)
(Total Received/Pledged $470 Million)

- Bill & Melinda Gates Foundation 67.3%
- U.K. DFID 11.8%
- Rockefeller Foundation 1.2%
- Netherlands Minister Devt. Co-operation 3.6%
- Exxon Mobil Foundation 0.6%
- BHP Billiton 0.2%
- Who/RBM 0.7%
- Swiss Government S.D.C. 1.4%
- World Bank 1.0%
- Wellcome Trust 4.4%
- USAID 3.4%
- Irish Aid 2.3%
- NIH 1.6%
- Spanish Agency for International Development 1.5%

* Slide thanks to Peter Potter Lesage
Expenditure Increased
Spend to end 2009*

MMV Expenditure from Foundation to 2009 - 10 years

* Slide thanks to Peter Potter Lesage
This Matched by Pharma Partner’s In-kind Spend*

MMV Expenditure from Foundation to 2009 - 10 years

Audited figures 2000-2008 & 2009 (est.)

- R&D
- A&D
- CD&A
- Net M&A
- Board
- Business Plan

“Best guess is that pharma have invested a similar amount in the projects its partners with us” - Patrick Nef, MMV EVP BD

* Slide thanks to Peter Potter Lesage
R&D Objectives Expanded

- Urgent needs were identified for:
  - Replacement for SP for Intermittent Preventative Treatment against *falciparum* malaria
  - Better treatments for *vivax* malaria, especially a replacement for primaquine, the only drug which can achieve radical cure
  - Products that can prevent mosquito transmission of malaria from patient to patient, i.e., drugs that can kill gametocytes, sporozoites and liver stages
  - Drug combinations active against *falciparum* malaria resistant to the ACTs
- MMV’s R&D Team under CSO Tim Wells has without drama expanded the portfolio to accommodate these needs
MMV Portfolio Extended to Over 50 projects from Discovery to Delivery

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<tr>
<th>Research</th>
<th>Lead Gen</th>
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<tr>
<td>Novartis miniportfolio</td>
<td>Whole Cell Lead</td>
<td>Novartis</td>
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<td>GSK miniportfolio</td>
<td>Pyridone</td>
<td>GSK</td>
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<tr>
<td>Broad/ Genzyme miniportfolio</td>
<td>DHODH</td>
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<td>Ozonide</td>
<td>Monash/UNMC/STI</td>
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<td>Whole Cell Hits St Jude/Rutgers</td>
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<td>Other Projects 13 Projects</td>
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<td>MK 4815 (Merck)</td>
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<td>iv artesunate Quinil</td>
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<td>Tafenoquine GSK</td>
<td>Artemisone UHKST</td>
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<td>OZ 439 (Monash/UNMC/STI)</td>
<td>(+) Mefloquine Treague</td>
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<td>sigma-tau</td>
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*As at November 2009
Slide thanks to Rana Rossignol & Tim Wells

☑️ Prequalified by WHO
Ultimate Proof of Concept Provided
Registration of Novartis’ Coartem® Dispersible*

* Slide thanks to Heiner Grüninger
Ultimate Proof of Concept Provided
Registration of Novartis’ Coartem® Dispersible*

- Fixed dose Artemisinin-based Combination Therapy
- Developed specifically with infants and children in mind
- Effective against parasites resistant to chloroquine and SP
- Three days dosing; rapid parasite and fever clearance times
- Registered with stringent regulatory authority
- Costs <USD 0.50 to treat a child
The last 10 years have been challenging for MMV …

... but it is now poised to contribute essential medicines for RBM’s work to control malaria and ultimately to free the world of this disease!
A retrospective look at MMV 1999-2009

Thank you!

Thanks also to MMV’s past and present …
• Stakeholders
• Scientific partners
• Board members
• ESAC members and especially
• Staff members …
for making the SPG’s vision a reality