Medicines for Malaria Venture (MMV) very much welcomes the opportunity to contribute to the consultation on the Green Paper on a common strategic framework for EU research and innovation funding. MMV’s mission is to discover, develop and deliver new effective antimalarial drugs. MMV’s vision is a world in which innovative medicines will cure and protect the vulnerable and under-served populations at risk of malaria, and help to ultimately eradicate this terrible disease.

MMV is a non-profit Product Development Partnership (PDP) charged with developing a pipeline of anti-malaria medications for the developing world. PDPs such as MMV use public and philanthropic funds to engage the pharmaceutical industry and academic research institutions in undertaking R&D for diseases of the developing world that they would normally be unable or unwilling to pursue independently, without additional incentives. MMV is funded in large part by the Bill and Melinda Gates Foundation, the Wellcome Trust, UK DFID, Spain, and USAID among others.

To date, MMV has been successful in supporting the development and registration of the first paediatric artemisinin combination treatment (ACT) globally for malaria and an intravenous drug for the treatment of severe malaria. Over the last 20 months, 54 million courses of this paediatric medicine developed in partnership with MMV’s expert support have been delivered to Africa. In addition, MMV has developed a strong pipeline of follow up drug candidates, focusing on drugs to also address the vivax strain of malaria which is prevalent in Asia Pacific where malaria drug resistance has now been confirmed, drugs with better pharmacokinetic and safety profiles and drugs which have the potential to be active against the strains of parasite recently identified in South-East Asia which show reduced susceptibility to current standard of care.

Two new medicines are currently awaiting regulatory approval and MMV has 14 innovative novel molecules in the pipeline with the potential to tackle drug resistance. Moreover, 50 projects are specifically targeting malaria eradication.

Together we CAN defeat malaria.
MALARIA - A burden at all levels
Despite great gains in the fight against malaria over the past decade, the diseases still infects 225 million people every year and causes almost 800,000 deaths, mostly young children under 5 years and pregnant women in Africa. In malaria-endemic regions, all layers of society are affected. For countries it slows economic growth by 1.3% per year, translating to a loss of annual GDP across sub-Saharan Africa of US$12 billion. For communities malaria is the reason why children miss school or why crops are not harvested. For families malaria means the death and disability of young children, and increased risks in pregnancy for both mother and baby. The sad truth is that many African communities simply accept malaria as part of everyday life, trapped in a vicious cycle in which malaria is both the cause and consequence of grinding poverty.

African children hardest hit
The malaria statistics are stark: More than 1 million deaths every year. A child dies every 45 seconds. Globally, 85% of all malaria deaths are in pre-school children. Over 40% of African national health budgets are soaked up by the disease. Africa, where the climate, mosquito vector, malaria parasite and poverty all combine, continues to bear the brunt with more than 90% of all cases worldwide.

A preventable disease
Malaria is preventable using the tools we already have: insecticides, mosquito nets, preventative drugs and effective treatments. Malaria has already been eradicated from many regions of the globe, including parts of Europe and North America. Control and eventual eradication will be difficult in the remaining areas, but the situation is far from hopeless.

A global will
There is now real international will to bear down on malaria, reduce the burden so that no-one dies for want of health interventions, and ultimately wipe the disease from the face of the earth. The past decade has seen unprecedented international cooperation to defeat malaria. With effective tools at hand, the resources are at last being made available to deliver on the promises. Effective, safe and high-quality antimalarial drugs of the kind developed by MMV are at the forefront of this re-energized approach.
Focus on Antimalarial Drugs

The current generation of antimalarial drugs, artemisinin-based combination therapies or ACTs, are highly effective at curing malaria, even the most lethal falciparum form which is increasingly resistant to other drugs. This is because ACTs use a combination of drugs to combat the parasite, one of which is artemisinin, a potent antimalarial extracted from a Chinese herb – *Artemisia Annua*.

There is, however, no room for complacency. The wily *Plasmodium falciparum* malaria parasite has a tendency to become resistant to medicines. This means that, even as we are using ACTs to cure millions of people worldwide and working to deliver ACTs to many millions more, we do not know how long these medicines will remain effective. We will always need something new in the medicine cabinet.

But malaria drug resistance now emerging along the Thai-Cambodia border threatens all recent gains. Totally new classes of medicines are needed with a different way of attacking the parasite. To prepare for this MMV’s focus has been on building a world-class and diverse portfolio of antimalarial projects, so that new compounds are already well ahead in the R&D process and are closer to emerging from the pipeline as an effective drug.

Continuous and increased investment into Research & Development of new effective medicines is urgently needed including drugs to treat severe malaria and treatments for specific patient groups including pediatric formulations for children and preventative treatments for infants and pregnant women as well as drugs with transmission-blocking capability.

Current medicines available to treat falciparum malaria require a 3-day treatment course. We urgently need a drug that requires just one administration to ensure that treatment can be directly observed by the healthcare worker. This is especially important when treatment follow-up is difficult, as is the case in many malaria-endemic countries. A long-sought one-dose cure developed by MMV and its partners is now entering Phase II trials. Blocking the transmission of the parasite from patient to patient is key if we are to achieve our goal of malaria eradication. In an infected patient some of the parasites continue to replicate asexually resulting in the clinical symptoms of malaria, while others form gametocytes or the sexual form of the parasite.

At each stage along the continuum from malaria control to elimination and ultimately eradication, R&D investments are critical to ensure that new tools are developed. There is another pressing reason for the discovery and development of new drugs. The global agenda has recently changed from just controlling malaria to eventually eradicating it: wiping the parasite off the face of the planet. This ambitious vision has driven a change in MMV’s approach. We will continue to develop drugs to treat uncomplicated falciparum malaria as outlined above, but we will also develop new drugs to different ends.

One new goal, driven by the eradication agenda, is to research and develop drugs which block transmission of malaria between people, and so help protect those at risk but not yet infected.
Malaria is transmitted by the blood-feeding *Anopheles* mosquito, which acts as a ‘flying syringe’ to carry parasite from one person to another. MMV is developing drugs which will kill these sexual parasite stages and block transmission.

Another area of innovation is medicines to kill the parasite in the second most common form of malaria, *Plasmodium vivax*, when the parasite hides, dormant, in a person’s liver. Without an effective ‘radical cure’ for these dormant parasites – and the two current drugs are very far from ideal – patients can be cured of the blood parasites but suffer repeated malaria relapses months after the initial infection when the dormant liver forms reawaken. MMV has a new drug, Tafenoquine, in advanced clinical development to meet this need.

**Investment into R&D for malaria**

In total, full funding of artemisinin resistance containment and prevention would be upwards of US$ 175million per year globally, with just over US$ 100 million for programme support and about US$ 65 million for research and development. These estimates are based on the assumption that tier I and II areas are limited to those in and around the currently suspected foci in Cambodia, Myanmar, Thailand and Vietnam. When the funding requirements for managing artemisinin resistance are added to the estimates for malaria control and elimination described in the *Global Malaria Action Plan* (US$ 6.9 billion in 2010, including US$ 6.2 billion for control and elimination and US$ 0.7 billion for research), the total cost of controlling malaria and containing artemisinin resistance is estimated to be US$ 6–7 billion annually through 2015.

Figures as stated in 2011 GPARC: The *Global Plan for Artemisinin Resistance Containment* (GPARC) developed in consultation with members of each of the constituencies of the Roll Back Malaria Partnership including MMV. The work was coordinated by the World Health Organization (WHO) Global Malaria Programme, with the direct support of The Boston Consulting Group and funding from the Bill & Melinda Gates Foundation.

Today progress in both malaria control and elimination is happening, however increasing investment in R&D today for these crucial new tools will save lives tomorrow. If we are to eradicate this serial killer we need to significantly invest into R&D of new medicines now or we will risk losing all past investments. Therefore, within the context of the FP8, we urge the EC to enhance their support for applicants which cover the full innovation cycle from research to market, such as PDP’s. MMV has proven their effectiveness to bring innovative products for neglected diseases to market whilst incorporating consumer & market access into their core strategies getting to the most vulnerable populations affected by malaria: women and children.

**MMV’s recommendations for the framework programme for research and innovation (FP8):**

- **Sustainability:** Continue FP malaria funding to successful global partners and strategies including EDCTP. Continue financial and expert support for R&D of new and effective malaria drugs – medicines are the tip of the spear to eradicate malaria

- **Structure:** Current EU FP funding mechanisms are not accommodating MMV’s portfolio management strategy, but a fast moving product pipeline built to industry standards is essential for successful product development. The portfolio approach constantly reprioritizes the best product candidates and has the flexibility to terminate if a product candidate is not evolving as planned. Risk of failure and ineffective use of donor investment is hereby mitigated.
• Scale-up: MMV suggests a substantial increase of funding for R&D into neglected and poverty related diseases including malaria drug R&D. Currently, only 4% of the overall EC contribution to health R&D under FP7, or €250 million, is dedicated to research into AIDS, TB and malaria.

• Flexibility: R&D investments will increase in the future and to conquer malaria we will need long-term, flexible and non-project based funding to successfully bring new medicines from the laboratory bench to the bedside.

**Further foster coordination of antimalarial drug discovery and development**

In order to meet the treatment objectives in the timescale of the Global Malaria Action Plan (GMAP), there is a need for the R&D being undertaken to be more coordinated and focused on key objectives. This will also help with establishing priorities for funding and resourcing. The CRIMALDDI Consortium funded under FP7 is a great example of a joint coordination effort set up by its members to develop and publicize an integrated and prioritized roadmap for antimalarial drug R&D to complement GMAP.

Currently there are a number of European and international organizations and initiatives that are committed to antimalarial drug discovery, development, and deployment. In Europe these include WHO/TDR, The Medicines for Malaria Venture (MMV), AntiMal, EDCTP, the Wellcome Trust, and many academic groups and pharmaceutical companies (such as GlaxoSmithKline, Novartis, and sanofiaventis).

There is an urgent need for coordination, rationalisation and integration between activities so that funders can prioritize their support in a systematic and transparent way. Engagement with small and large industrial partners and endemic country scientists, all of whom could contribute significantly to these initiatives is weak, as are dissemination efforts. This coordination effort aims to address these deficiencies, maximize the potential effectiveness of existing activities, and gain synergies through this coordination effort. (www.crimalddi.eu)

The CRIMALDDI Consortium members are engaged in a structured process to:

1. Identify the work needed to meet the GMAP objectives for drug treatment in both the Control & Elimination phases of the Plan;
2. Identify the work currently being undertaken around the world and where there are gaps with the work needed;
3. Prioritize the R&D efforts needed to fill the gaps, especially drug discovery and the development of platform technologies;
4. Work with other experts to develop detailed action plans to fill the priority gaps.

We hereby encourage the EU to further enable, support and engage initiatives such as CRIMALDDI for the coming years as they are a crucial coordinating instrument to further accelerate the malaria drug R&D agenda.
Annex 1: External Reviews MMV – a PDP leader

PDPs, which are currently funded by the UK DFID, USAID, the Bill and Melinda Gates Foundation, The Wellcome Trust, Spain and others can effectively use funds that are directed by Australia, and can do so in concert with other donor monies as well.

In malaria-endemic Africa, PDP networks are particularly wide-reaching, strong, and efficient. These networks have strong relationships with doctors, hospitals, and community health structures at grassroots level, as well as health ministries at government level. PDPs manage over 40% of global grant funding for neglected disease research and development. Very low administrative overheads of these organizations, many of which conduct “virtual” product development also mean that they are an efficient use of taxpayer money. PDPs were created from a need to generate innovative approaches to alleviate the global burden of neglected diseases by taking the expertise and knowledge of both the private and public sectors, and exploiting each of their strengths to find the most efficient and effective solutions.

PDPs address the lack of commercial incentive to undertake the cost of development for vaccines, diagnostics, and drugs for neglected diseases of the developing world. They use public and philanthropic funds to engage academic research institutions and the pharmaceutical industry in undertaking development of solutions for diseases of the developing world that these institutions would normally be unable or unwilling to pursue independently, without additional incentives. The specific objectives of individual PDPs vary, but the basic mission is the same: to develop products for use as a public good to address the health needs of vulnerable populations in the developing world.

The sections below provide insights on PDPs from the World Health Organization, UK DFID and the Sydney-based Policy Cures Institute.

The World Health Organization (WHO) states:

> Overall, product development partnerships score very highly on developing country impact because of their focus on developing affordable suitable products for developing country use; their routine practice of working with developing country researchers and developers; and, to varying degrees, their capacity building efforts in developing countries. Donors are increasingly favouring product development partnerships as their vehicle of choice to disburse neglected-disease funding, while smaller donors may disburse virtually all their funding in this manner (likely reflecting the ability of product development partnerships to minimize donor management needs). The product development partnership route offers high developing-country health impact and operational efficiency, and is the only mechanism that successfully stimulates early and ongoing involvement of multinational corporations. The PDP acts as a facilitator and catalyst, bringing dedicated sources of funding and know-how to committed professionals so they can collaborate on the right projects to fulfill the objectives of the PDP’s mission.

Public health, innovation and intellectual property:
World Health Organization, Sixty-third World Health Assembly
8 April 2010

UK DFID in its framework review regarding malaria also found a positive impact of PDPs:
Malaria product innovation, particularly for drugs, has evolved significantly in recent years. Product development partnerships (PDPs), such as the Medicines for Malaria Venture and Drugs for Neglected Diseases Initiative, have brought together pharmaceutical industry expertise with public financing and a focus on the needs of developing countries. This has resulted in an accelerated development and the approval of new ACT formulations, including child-friendly products. Product development partnerships have also been established to accelerate the development of malaria vaccines (Malaria Vaccines Initiative) and new insecticides for vector control (Innovative Vector Control Consortium).

The product development partnership (PDP) model has provided an important means to incentivize and accelerate technology development for product markets that may not otherwise be commercial priorities. Other approaches, such as market based incentives to encourage greater private sector investment in malaria product development and to strengthen R&D in malaria endemic countries, should be explored to complement investments in PDPs.

Breaking the Cycle: Saving Lives and Protecting the Future
The UK’s Framework for Results for malaria in the developing world, December 2010

The independent Sydney-based Policy Cures Institute did an analysis in 2010 of the role PDPs in research and development for neglected diseases. PC's published report stated the following:

Despite their relatively young history, PDPs now occupy an important place in the global R&D landscape for neglected diseases. In 2007, they collectively attracted 42.0% (US$465 251 887) of global external funding for neglected diseases (excluding NIH funding) and nearly a quarter (23.1% or US$469 392 952) if NIH is included. This success can be explained by various factors. The PDP business model can be very attractive to funders, in particular small to medium size funders. In general, PDPs select, manage and terminate projects and partners within the overall product portfolio, rather than requiring funders to make these choices. This reduces the management load on smaller funders. For instance, Irish Aid explicitly mentioned the low management responsibilities associated with PDPs as a reason for choosing this channel for future increases in aid flows. It also greatly mitigates the risks they are exposed to as highly technical scientific decisions are made by PDPs in consultation with their Scientific Advisory Committees, who advise on the selection and scientific merit of projects to be funded and progressed, rather than by funders who maybe less familiar with the complex, multi-million dollar scientific choices involved.

Financial risk is also greatly reduced since, under the PDP model, investments are made by multiple funders into portfolios of multiple projects. This means that failure of one lead or product does not mean a funder’s investment is wasted, since funds can be rapidly shifted to other more promising projects within the portfolio. The portfolio approach is also more resilient, since a sudden decrease or withdrawal of funding by one donor does not necessarily have a fatal impact on the R&D programme, thus also protecting the investment of other funders. By contrast, the model under which funders choose individual projects to invest in (sometimes called ‘picking winners’) has a higher risk for both the funder and the science: the former, if the project fails; the latter if the funder withdraws their
support for the project, at which point it dies or goes on the backburner, no matter how promising it might be.

Effective PDPs – we note that not all PDPs are equally effective – also offer excellent health returns on investment, since they have lower R&D costs than the private sector model. This is due partly to their lower cost of capital (PDP funds come mainly from the public and philanthropic sectors rather than the stock market) but also their ability to leverage in-kind contributions, and to build partnerships that maximise efficiency by using each R&D player in their area of comparative advantage (e.g. industry groups working on medicinal chemistry; academic groups providing disease expertise in clinical trial design; developing country manufacturers providing lower-cost scale-up and manufacturing expertise).

M. Moran, J. Guzman, A.L. Ropars, A. Illmer,
“The role of Product Development Partnerships in research and development for neglected diseases”
International Health 2 (2010) 114–122
Annex 2: PDP Quick facts: Medicines for Malaria Venture (MMV)

**Mission**: Discover, develop and deliver safe, effective and affordable antimalarial drug products to treat and protect people most at risk of malaria infection. Also, influence, innovate and integrate to provide public health community most appropriate tools to achieve maximum public health impact and malaria drug uptake effectiveness.

**Impact**: To date, MMV has registered two medicines—an intravenous form of artesunate for treatment of severe malaria, and Coartem® Dispersible, a pediatric formulation developed in partnership with Novartis. Since this formulation was made available in late 2009, 64 million doses have been delivered for children in 35 countries.

**History**: Founded in 1999 by WHO/TDR, IFPMA, World Bank, donor governments, research partners and philanthropic foundations. MMV is a Swiss not-for-profit operating as public-private partnership.

**Business Model**: MMV partners with a broad range of research entities and pharmaceutical firms spending 80% of its typical USD 55 million annual budget on product development. These funds typically attract an approximately 1:1 matching “in-kind” contributions by its research and pharmaceutical partners. From 1999 to 2010 MMV mobilized over $US480 million in support of its research, management and access work.

**Governance Model**: Comprises a set of integrated mechanisms including Board of independent non-executive Directors (Expert Science Advisory Committee, Safety Advisory Committee, Access and Delivery Advisory Board, annual audited financial reports and published *ad hoc*, periodic reviews by external, independent NGOs and major funders).

**Global Partnerships**: Over 140 partnerships in 48 countries including Africa, Asia Pacific, US, Europe) - **Africa**: Clinical trials conducted in 15 African countries (Benin, Burkina Faso, Gabon, Gambia, Ghana, Ivory Coast, Kenya, Malawi, Mali, Nigeria, Mozambique, Senegal, Tanzania, Uganda, Zambia) **Asia**: Over USD $9m invested 2000 – 2010 funding R&D projects at eight institutions (Monash University, QIMR, Australian Army Malaria Institute, Eskitis Research Institute Griffiths University, Alfred Hospital, Royal Adelaide Hospital, Darwin University, Melbourne University), APPMEN – Asia Pacific Elimination Network, Research and clinical trial partners in 13 Asia Pacific countries Cambodia, China, Hong Kong, India, Indonesia, Laos, New Zealand, Philippines, PNG, Singapore, South Korea, Thailand, Vietnam

**Drug Development Costs and Comparison**: MMV built the largest malaria drug pipeline in history comprising almost 60 projects. All this has been accomplished in 11 years. MMV is extremely cost-effective when compared to conservative industry estimates of $800 million to develop one new chemical entity through clinical trials and market launch.