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# Regulatory Strategies and Challenges for Neglected Infectious Diseases of High Medical Impact, but Low Commercial Value: the Case of the *Medicines for Malaria Venture*

The Medicines for Malaria Venture (www.mmv.org) is a public private partnership that was established in November 1999 following an incubatory period in the Tropical Disease Research Unit of WHO (www.who.int/tdr). Its mission is the discovery, development and internationally recognised regulatory approval of one new antimalarial drug every five years to meet the challenges of medical need and drug resistance posed by malaria. As we enter the third millennium, malaria is a disease that still results in 1 to 2 million deaths per year worldwide, most of which are young children in sub-Saharan Africa.

In its approach MMV relies on experience gained in industrial collaborations over the past 25 years through WHO/TDR for a number of significant tropical diseases. It will also soon be sharing experiences with the newly formed Global Alliance for TB Drug Development (www.tballiance.org), which has a similar mission to address the need for new and improved anti-tuberculosis drugs.

The establishment of MMV as an independent entity fills a gap left by the withdrawal of pharmaceutical companies from antimalarial drug discovery and development over the last two decades due to an escalation in R&D costs and low market expectations. MMV meets R&D needs by funding, to significant levels, collaborative ventures between academic and pharmaceutical companies. These utilise both scientific knowledge of malaria, increasingly being generated by genomic and cell biology research, and the enhanced capabilities of industry to bring together associated technologies and expertise in discovery, development and regulatory issues. The result so far is a portfolio of 11 projects that will cost approximately $15 million to maintain in 2002 and which needs to grow to about 20 projects by 2004, at a cost of $30 million per year, to meet MMV's target of one new registered drug every five years. These projects are carried out under contracts that will ensure low pricing of final products to the public sector in developing countries, where the disease is most prevalent and where regulatory approvals ultimately need to be attained.

## Regulatory strategy

This well defined mission has caused MMV to reflect on its approach to project management and to devise appropriate regulatory strategies to bring about rapid global approval of innovative products. To ensure that appropriate regulatory strategies are considered and put in place, a regulatory expert has recently been brought into MMV's management team. Before discussing these issues in more detail, it must first be made clear that MMV will not be attempting to register new drugs in its own name. MMV operates in partnership with pharmaceutical companies, large and small, to achieve its goals and the drugs will be registered in the name of the partner companies taking responsibility, and risk, for production and commercialisation. MMV is now building capacity that will enable it to effectively drive projects through the R&D process, but it only envisages initiating phase III studies once it has secured a commercial partner.

The regulatory strategies and challenges for MMV's projects, several of which are on the verge of entering clinical studies, are dependent on the types of companies partnering its projects and on their location. For example, when working with a large multinational company, such a partner has the capacity and know-how to take full responsibility for the organisation of the regulatory process. This will include appropriate monitoring and quality assurance of non-clinical and clinical studies, quality assurance of process of production and manufacture, and appropriate archiving of material and dossier preparation. According to normal practice, the company would obtain regulatory approval and marketing authorisation in its own country (or perhaps its own region in the case of Europe) and then use this as a basis for gaining regulatory approval in targeted countries where malaria is endemic. It should be stressed that all regulatory submissions for MMV projects will meet global standards. Registration, obtained through orphan drug legislation where appropriate, will be valid for marketing in developed countries as well as serving as a regulatory reference for developing countries.

Several pharmaceutical companies have used this strategy for the registration of antimalarial drugs over the past 20 years. Mefloquine (Lariam®) from Roche and halofantrine (Halfan®) from Smith Kline Beecham (now GSK) were both initially registered through the orphan drug legislation of the US FDA in the mid 1980's. Atovaquone - proguanil (Malarone®) from Glaxo Wellcome (now also GSK) was registered through the UK and the EU mutual recognition procedure in 1997. Lumefantrine - artemether (Riamet®) from Novartis was registered first in Switzerland in 1999, followed by registration in the UK and the EU mutual recognition procedure in 2000.

## Differing levels of regulatory practice

Potentially the situation becomes more complex when a partner company operates from a country where drug regulatory procedures are still evolving and where authorities are more used to registering generics rather than dealing first hand with New Chemical Entities. The

 

need to engage in such registration may increasingly be required for MMV projects as the market size for new antimalarial products is more likely to appeal to small companies used to operating off generic margins than to companies used to operating off margins resulting from marketing exclusivity as a result of holding appropriate intellectual property rights. As highlighted in the report of the third IFPMA Asian Regulatory Conference[1] the number of countries with the capacity to deal with NCE initial registration is limited.

Where smaller companies operating in developing countries are taking on the registration, production and marketing of products, a key issue is the development and establishment of appropriate capabilities to ensure a high quality registered product. The capabilities may often need to be developed and established both at the level of the company and the regulatory agency itself, as well as within the MMV organisation. A strategy being considered by MMV that would ensure a high quality product as well as promote good practices in the partner company and the regulatory authorities of the country in which it is established, would be to carry out studies with a view to a parallel initial filing in both the country of manufacture and with a major regulatory agency e.g. US FDA or centralised European agency. This would ensure best practice was followed, and would enable MMV to unify its project management strategies around common high standards based on ICH guidelines. In addition it would enable MMV to access the resources and expertise of the major regulatory agencies, whose input and advice could be used to inform all parties of appropriate approaches. An added advantage of this strategy is that if there is a need to change a partner during the course of development then one is not unnecessarily tied into the processes of one particular regulatory agency.

## Global approach to registration

Although this approach may appear to present high technical hurdles for a project early on, and many may say that this approach might limit the speed of the first registration, we believe that in the long term it ensures a more rapid and efficient global registration of products in a wide variety of countries. From a financial perspective it is also cost-effective as there is less likelihood of having to repeat studies or revise reports at the request of different authorities, if the initial studies are carried out to a globally recognised regulatory standard.

In the past regulatory authorities in many developing countries have lacked sufficient capacity to manage or implement efficient regulatory reviews and control of new products. This appears to be changing. Issues of drug quality and counterfeits are bringing increased demands on regulatory agencies and there are growing pressures for globally acceptable standards and regional collaboration to assist in their development[1]. In addition, with the impending implementation of TRIPS in 2005, many countries that have previously concentrated on generics production may find that several of their more developed companies become research-based, bringing challenges to their regulatory procedures as they attempt to introduce NCEs for their home markets. It is our perception that the global regulatory environment will be much more professionally managed and harmonised in five years' time, when MMV's most advanced projects will likely be filing submissions. Our strategy is to enable our project teams and partners to meet this challenge with professional dossiers of high quality in all cases and to all national regulatory agencies with whom we deal.

## Virtual project management

Having settled on our broad strategy as outlined above, the next challenge relates to the appropriate management of our development projects. Our projects require virtual management through teams that network with pharmaceutical companies, universities, and national and international organisations. A clear definition of the product profile and regulatory requirements, together with an outline of the package insert are established with our partners at the outset of MMV sponsored projects. In addition a regulatory strategy with provisional time lines and costs is agreed. Great care is also taken to ensure that an appropriately qualified project development team is established, with access to all the necessary technical expertise to bring the project to fruition (or to an appropriate halt if necessary). Managing the outsourcing of elements of the work to appropriate contract research organisations is a key component of this effort. An MMV scientific officer is in regular liaison with the project team and all projects are regularly assessed on their performance with the assistance of an Expert Scientific Advisory Committee headed by Dr Simon Campbell FRS, formerly World Wide Head of Drug Discovery and European Research and Development with Pfizer.

## Costs of reaching regulatory approval

We estimate that the cost to MMV of obtaining regulatory approval of one new product every five years, including the cost of failures, will be approximately $150 million per drug. Taking into account opportunity costs at a discount rate of 8% would increase this cost to approximately $186 million. This cost compares favourably with the oft-quoted industry figure for R&D costs of approx $500 million per new drug. This is attributable to the nature of the indication, partner contributions, low clinical costs due to the services of dedicated clinicians, and access to a lot of inexpensive advice from talented and experienced individuals who wish to contribute to helping address the malaria problem. Similar assistance with costs and advice from regulatory agencies would also be welcome in this regard and an expansion of the concept of orphan drug legislation in more countries to include neglected diseases such as malaria would be very useful.

## Role of orphan drug legislation

Following the introduction of orphan drug legislation in the USA in 1983, under which two antimalarial drugs

have already achieved registration, Singapore (1991), Japan (1993), Australia (1998) and EU (1999) have all introduced orphan drug legislation. The EU in its pronunciations has frequently linked this legislation to its applicability for neglected diseases. Australia also makes specific reference to 'essential drugs' in its legislation, defined as drugs for use in relatively large numbers of patients with serious illnesses for which no other drug treatments are available, and whose supply may have stopped for commercial reasons. The importance of these registration paths for diseases such as malaria in terms of developmental advice, fast tracking of decisions, financial subsidies and the waiving of fees cannot be stressed enough. As more ventures such as MMV and the Global Alliance for TB Drug Development become established it is to be hoped that this legislation will be utilised more and more and tested in the area of neglected diseases through high quality drug development projects. As national regulatory agencies develop their capabilities, especially the target countries most afflicted by the disease, it is to be hoped that a similar focus on providing assistance for neglected diseases will be encouraged. The pooling of regional regulatory resources and information for such drugs, which lack significant commercial lobbying, could greatly facilitate the appropriate introduction of badly needed medicines.

## Challenges and prospects

Beyond initial registration of the products, other related challenges remain to be addressed by MMV and its partners. These include undertaking appropriate phase IV studies and ensuring adequate post-marketing surveillance. This will be critical for obtaining information that can inform, help modify and improve national essential drugs lists for antimalarials, which will in turn guide public sector purchases and reimbursement. Such vital data also assists the development of a strong evidence base on products that can inform national drug policy and positively impact on the control of priority diseases.

Another area of growing debate for which best practice may need to be further developed is that of ethical considerations around clinical trials for neglected diseases conducted in endemic areas, most recently highlighted by the revisions to the Helsinki Declaration[2].

This is an exciting time for those involved in research into neglected diseases. New biological information and technical advances are enabling many new solutions to be contemplated. There is also an increased provision of funds being made available to appropriate research and development through organisations such as MMV. There is a greater political will being developed to meet disease needs more broadly, as manifested by Dr Kofi Annan's recent call for the establishment of a Global Fund to facilitate access to medicines and treatment for HIV/AIDS, malaria and tuberculosis[3]. Greater harmonisation of regulatory approaches to these diseases and, particularly in the case of diseases unique to developing countries such as malaria, an improved awareness of their global significance by regulatory agencies, will be of extreme practical importance in the years to come.

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