

PUBLIC-PRIVATE-PARTNERSHIPS: NEW WAYS TO DISCOVER, DEVELOP AND DELIVER DRUGS FOR TROPICAL DISEASES

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INTRODUCTION

Topical diseases, except where they are coincidentally also diseases of the developed world, are often characterized as neglected diseases because of the relative paucity of global investment directed at them and the consequent relative lack of new products and services developed to treat them (Anonymous, 2001; Touiller *et al*, 2002). This lecture will explore some of the facts behind this characterization and the potential of a relatively new group of organizations, the product development Public-Private-Partnerships to help remedy the neglect.

A previous Chamlong-Tranakchit Harinasuta Lecture, the 7th by Dr Carlos Morel skillfully reviewed the fundamental need to balance current investments in disease control efforts with those in R&D for new products or so called disease-control 'tools' (Morel, 2001). I therefore do not need to make the case again here; I am assuming that most scientists and even a good majority of the broader public health community would concur with his conclusions.

THE NEED FOR CONTINUOUS R&D

Given the need for continuous R&D, there are five elements that I will develop in this lecture:

1) I will explore where, why and by whom health research is done globally.

In fact about half of all 'health research' is done in the public and half in the private sectors – but whether private or public, overwhelmingly by and for diseases linked to the rich or transition countries (like Russia or those joining the EC) (Global Forum for Health Research, 2001). One relatively new trend in global health research, however, is the emergence of significant levels of private not-for-profit research funding. Already this source of funding (prime

examples today being the Gates Foundation and the Wellcome Trust) represents about 8% of the world total. It is this sector that largely supports MMV and the other Public-Private-Partnerships (PPPs). Low income countries account for only about 3% of global health research expenditure and their percentage is if anything going downwards.

- R&D spending is not surprisingly correlated closely with where innovation occurs, for example, where new drug registrations are occurring. In the period 1975-1994, 45% of all new drug registrations were in the USA and 41% in Europe and 7% in Japan (Barral, 2003). Since 1994, the dominance of the USA as the center for bio-pharmaceutical innovation has grown. However, it is important to point out here that one could describe these data as only partial in that they only deal with where new medicines have been registered and also only medicines that have been registered under the ICH guidelines - ICH Medicines for short. These represent the medicines that should have a strong scientific basis to their discovery and development, and which incorporate the highest regulatory and manufacturing standards ensuring safety and efficacy before they can be registered and marketed.

- Although such ICH medicines are the only ones now being registered in the US, Europe and Japan it is as well the case that these territories represent by far the largest territories for global drug sales and profits, representing greater than 90% of the global total. Excepting Japan, the whole of Asia and Africa, which contain the majority of the world's populations, have ICH medicine sales roughly comparable to the UK alone, or to a few percent of the US market (IMS, 2003).

- Despite this we should not forget that countries in Africa, Asia and Latin America use traditional medicine (TM) more or less effectively to help meet some of their primary health care needs. In Africa, up to 80% of the population uses traditional medicine for primary health care. It would be wrong to conclude that TMs can have no innovation in them or evidence to support their use. In fact, it is obvious that many of today's successful ICH medicines have origins as traditional medicine (WHO 2003).

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- Another point worth making when discussing innovation is that it would be wrong to conclude that the very successful generics industries that have developed in Asia (particularly in India) have no innovation in them. In fact, chemistry innovation is what has enabled them and keeps them competitive. Some are now beginning to do genuine drug discovery.

2) In the second element I will review the nature of the so-called 10/90 gap as it pertains to drugs.

- The facts I have just outlined are sometimes described as the problem of the “10/90 gap” - the huge disequilibrium in health research between the magnitude of global disease burden and the allocation and focus of research funding. The phrase relates to the assertion that 90% of health R&D and health R&D outputs are focused on just 10% of the world’s population (Global Forum for Health Research, 2001-2002).

- The gap, whatever its true size, is increasingly recognized as having consequences for not only global public health but also economic development and security.

- Hindered innovation for tropical infectious diseases is a prime example of the effects of the gap. Of the 1,393 total new drugs approved between 1975 and 1999, only 1% (13 drugs) were specifically indicated for a tropical disease, and often these were spin-offs from R&D motivated by military or even animal health needs. However, even amongst tropical neglected diseases, some are more neglected than others. MSF (Doctors without Borders) in its campaigns for access to essential medicines has, therefore, developed the concept of the “most neglected” diseases – those in the developing world where there is no overlap to the interests (medical, military, or otherwise) of the developed world (Anonymous, 2001; Touiller *et al.*, 2002).

- Malaria by this definition is therefore not a “most neglected” disease. Antimalarial drug sales are an admittedly small but potentially profitable \$300-350m, most of which is derived from travelers to Africa and Asia from Europe and the US. There is, of course, in addition a largely unregulated non-prescription informal market which operates on very low margins and which cannot easily be quantified. Irrespective of the real market sizes for malaria drugs, genuine commercial innovation for new classes of these drugs has been well below what is needed given the disease burden and the development on parasite resistance (MMV, 2000).

- Historically, the business of adding value to a

concept for a new drug has been referred to as a ‘value chain’. Both public and private sectors are typically involved. The starting scientific concept is seen as the low value starting link which can be enhanced by adding new links by a series of complex, scientific, regulatory, and manufacturing steps, which, if successful, end as a registered drug. Importantly, from a public health perspective, these drugs can eventually become low cost generics or even so-called public goods (Commission on Macroeconomics and Health, 2001). The process will be illustrated by the example of mepfloquine.

- The value chain concept - implying a linear series of linked steps is an oversimplification of what typically happens with drug R&D – the truth is more complex. The path to a new ICH-type medicine is perhaps better described as a long and winding road or perhaps even a maze. Many R&D programs have to be stopped because the maze is never solved. The result is a high attrition of programs, which has to be built into all financial models of drug development. The cost of a success has to also carry the cost of failures. Furthermore, for a commercial entity the fact that money is spent many years before any returns are possible -the so-called opportunity cost-must also be added. All of these ‘costs’ together are accounted for in the \$800 million price the pharmaceutical industry typically pays per successful proprietary drug registration (DiMasi *et al.*, 2003).

- Given this fact and the relatively small market for proprietary antimalarial drugs it is not surprising that there has been a substantial pharmaceutical industry withdrawal over several decades from doing malaria drug R&D, at least as a commercial activity. These negative trends occurred despite the fact that, as has been well documented by the WHO and other public health agencies, anti-malarial drugs have been one of humanity’s most precious and cost-effective public health resources – resources that can only continue to be kept effective by sustained innovation to keep ahead of encroaching drug resistance (MMV, 2000).

3) The changing nature of drug R&D

- All of the foregoing may seem rather depressing when set against the urgent need to get more innovation to occur and more products to be developed for tropical disease. Indeed this would be the case were it not for some important positive trends, one being the changing nature of drug R&D.

- ‘Big Pharma’ R&D was once described (in the 70’s and 80’s) as an NIH process. This was not a

reference to the US National Institutes of Health but to the phrase “Not Invented Here”. The implication was that ‘Big Pharma’ could more or less do everything needed in-house and that they shunned anything not invented or controlled internally. In the intervening decades, this way of thinking has slowly but surely broken down. In fact, it runs counter to most ‘best practice’ today since no company, however large, can master all of the rapidly evolving enabling technologies needed for modern drug R&D. The emergence of the ‘virtual R&D’ methods pioneered in the biotechnology industry and the fact that drug R&D has over time become increasingly modular and outsourceable means that small organizations with sufficient management know-how and experience can do much of what was once almost entirely the exclusive preserve of the large companies. Everybody benefits from this, including the large companies who can now change R&D direction and access novel technologies without having to restructure departments and hire new people.

- The modular nature of modern drug R&D has another element to it that is particularly important to small organizations without large R&D budgets – it eases planning and allows one to ‘ring fence’ project costs module by module. For public-private partnerships, this is critical.

- Lastly, when considering the rapidly changing nature of drug R&D, we need to appreciate that low-cost development and particularly manufacturing is increasingly possible by contract – another module that can either be purchased or negotiated as a joint venture or co-development agreement.

- These R&D trends are continuing, allowing smaller organizations, with appropriate know-how and management capacity to participate in drug discovery and development in a way not previously possible. For tropical disease drug R&D, they herald a major new start – particularly when executed with the pharmaceutical industry as public-private partnerships (PPPs).

4) In the fourth element of this lecture I will review the emerging role of public-private partnerships (PPPs) (IPPPh).

- It is clear from much of that, that the pharmaceutical industry, while at core a commercial sector like any other, is also connected with, and regulated by, the public sector in ways that are both complex and widespread. This has always been true, but the nature of the relationship has never been the focus of so much interest and commentary as today. The balance of powers and interests is under intense scrutiny in every way, from the rules governing IPRs

globally to issues of ethics and informed consent in clinical trials (IFPMA).

- Though aspects of this complex relationship are beyond the scope of this lecture, an understanding that pressures exist and are growing to bring global public health interests more to the fore in the way global drug R&D options are prioritized and executed, is important to understanding PPPs.

- The public-private partnerships are a reflection of this, in that they have been created mainly to reverse some aspects of the ‘neglect’ of the neglected diseases. They are thus part of a broader phenomenon that seeks to bring innovation to areas not currently well served by strictly commercial R&D and includes other initiatives, such as the Orphan drug legislation enacted in the USA and Europe.

- PPPs’ exact missions and modes of operation vary considerably, but about 35 are described as Product Development partnerships. They share a central objective, to shorten timelines and increase throughput of products for the disease they represent. In some cases where product R&D was not occurring at all, their goal is to initiate product innovation – *ie* for the most neglected diseases. New money to finance this new R&D has come from a number of philanthropic and public sources – a total of about \$700 million has been invested so far.

- Although PPPs are a relatively recent phenomenon we know they can work. For example the most recently registered antimalarial Lapdap (Chlorproguanil/ Dapsone) was developed by a PPP.

5) In the fifth and last element I will discuss the experience thus far of the Medicines for Malaria Venture (MMV).

- MMV was launched on Nov 3rd, 1999, at the Geneva Headquarters of the WHO. The symbolic handshake between the public and private sectors was given by Dr Gro Harlem Brundtland (for WHO) and Sir Richard Sykes, then President of the IFPMA (for the Pharmaceutical Industry).

- MMV has a highly-focused mission – which largely distinguishes it from other R&D organizations involved with antimalarial drug R&D: “Medicines for Malaria Venture is a not-for-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.”

- It is important to note that MMV’s mission relates specifically to health impact as an ultimate goal and there

are no intermediary goals, such as research capacity strengthening in disease-endemic countries. In this sense, MMV is entirely complementary to the work of other existing research organizations, like TDR described in the 7th Chamlong-Tranakchit Harinasuta Lecture.

- MMV's goal is thus to achieve early and sustainable registration of innovative antimalarial drugs. The detailed way it goes about this goal with its many partners was developed in 1999 and 2000 as a "business plan", albeit one that is constantly being refined from experience (MMV, 2001, 2003). The elements of MMV's operations are not in fact very different from those of a number of other PPPs:

- We identify new antimalarial drug opportunities competitively, following a public 'call for proposals' using an expert scientific advisory committee (ESAC) to help us.

- We try to achieve rapid Win-Win partnering agreements with the partners.

- We manage these against agreed milestones.

- and crucially, MMV exercises control of the portfolio as a whole (portfolio management).

- Using these principles, MMV already manages the world's largest portfolio of anti-malarial R&D projects with a total of 25 partners. I'm very glad to say that Mahidol University is one of them. From the pharmaceutical industry we have several global giants like Roche, Bayer, Novartis and GSK, as well as some smaller players like Shin Poong of Korea and Ranbaxy of India.

- As is clear from the geographical spread of the work being done in the MMV portfolio, distance is no barrier to the kind of 'virtual R&D' it is engaged in. In fact, one of MMV's most rapidly advancing projects, the new generation of synthetic peroxide antimalarials has had research or management elements (modules) being done in Nebraska, London, Geneva, Basel, Delhi and Melbourne, contemporaneously.

- The MMV portfolio expects and has experienced attrition. The rates used in developing our portfolio model are derived from industry figures but adapted specifically for malaria drug R&D. We have also chosen phase transition durations which we believe are realistic.

- Today, there are 21 active projects in the portfolio, spanning exploratory research to clinical development. There is a growing sense of confidence that the portfolio will start delivering new drugs (including new formulations and combinations) well before the date promised when MMV was launched – 2010.

CONCLUSION

MMV is working. It will continue to focus on its core R&D activities but will also actively interface with other global players to ensure that its goal of health impact can occur as quickly as possible (Hentschel and Itoh, 2003; MMV, 2003).

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