

**Product Development Public Private Partnerships for Diseases of Poverty.
Are there more efficient alternatives? Are there limitations?**

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A brief analysis of the alternatives to public private partnerships for product research and development (R&D) for diseases of poverty is presented. At their extremes these consist of private sector driven and managed R&D and public sector driven and managed R&D. It is concluded that the private sector will not collectively / competitively fully finance and manage product R&D unless the public sector injects many billions of dollars into creating a competitive market for such products. Similarly, the public sector cannot endeavour to fully take on the full role of innovators and providers of new products unless it is prepared to invest much more heavily, not just in financing R&D, but also in the sustainable generation of a capital intensive product R&D infrastructure. Such an infrastructure is necessary to provide a chance of sustained success in what is generally recognised to be a high-risk endeavour and this infrastructure currently resides in the private industrial sector. It is concluded that public private partnerships, despite the challenges of managing activities across the cultures of the public and private sectors, offer many advantages over product R&D undertaken solely by the private sector or solely by the public sector. This is especially the case when they are managed virtually with little need for additional capital investment. Furthermore there is limited evidence that the products generated through public private partnerships are efficiently generated and highly relevant to public health needs. Thus, public private partnership should be further promoted and supported.

The current environment and landscape in which Product R&D PPP's operate is assessed. It is noted that there has been a significant increase in product R&D activity but that this has been diverse and multi-organisational in nature. The total product R&D activity for diseases of poverty currently ranks at the level of a small pharmaceutical company, but there is a likely doubling of size in the coming five years resulting in many thousands more individuals being engaged in product R&D for diseases of poverty. There are several areas that warrant future discussion, support and oversight. These include: a) that the partnerships are neither over-competitive with each other, nor monopolistic; b) that there is a sense of common purpose and direction and that cross-linkages and synergies are facilitated; c) that the product profiles being sought by PPP's are in line with global health needs; d) that exploratory research, and early product R&D - translational research - is supported to ensure that pipelines are maintained; e) that appropriate mechanisms are in place to ensure the continued and sustainable production of useful new products once they reach the market; f) that there is appropriate downstream research - transitional and implementation research - undertaken to optimise the use of the products and provide evidence for policy and implementation; g) that conflicts of interest are minimised; (h) that capacity building and capacity utilisation in developing countries is integrated into product R&D activities; (i) that there should be strong stakeholdership from developing countries within the context of product R&D, product use and product delivery.

1. Introduction

The last several years has seen an explosion of product R&D based not for profit organisations dedicated to develop new drugs, vaccines and diagnostics for diseases of poverty. Many of these classify themselves as Public Private Partnerships, though some engage more readily with the private sector than others. Examples include: IAVI for HIV vaccines; MMV for malaria drugs; MVI and EMVI for malaria vaccines; GATB for TB drugs; Aeras for TB vaccines; IOWH for multiple diseases of poverty; DNDi also for multiple diseases of poverty; Microbicides Initiative; FIND for TB diagnostics, with possible expansion beyond TB. The vast majority of these organisations owe their existence to funding from a limited number of foundations and government donors. By far the largest of these is the Gates Foundation, though the Rockefeller Foundation has also been instrumental in many partnerships. In addition there are a variety of single PPP activities initiated such as the development of a diamidine for African Trypanosomiasis, funded by Gates Foundation, or the development of Lapdap for malaria, funded by U.K. DFID. For the purposes of this article I may sometimes include Foundations such as the Gates Foundation within the 'public sector', in that they are not for profit and are providing resources solely for the public good.

The PPP organisations have added to several public sector and philanthropy based organisations and programmes that have long been active in this field and also partner with industry to deliver new products. Such organisations include WHO/TDR (Tropical Disease Research); WHO/HRP (Human Reproductive Programme); PATH, Walter Reed Army Institute for Research, NIH Small Business Research Grants; other national *ad hoc* programmes and projects. Special mention should be reserved here for the Chinese government sponsored discovery and development of the artemisinin derivatives. These organisations have also added to the activities of several pharmaceutical companies that have been active in this field over the years, such as Merck, Roche, Aventis, GSK and Novartis, as well as numerous smaller companies. It is worth noting in passing that many additional companies also have programmes related to improving access to specific products, ranging from vitamin A to anti-retrovirals. In connection with product R&D the establishment of multi-million dollar drug discovery facilities by GSK (Madrid - malaria and TB), Astra Zeneca (Bangalore - TB) and Novartis (Singapore - TB and Dengue) should also be highlighted, as well as other industry initiatives such as Sanofi's malaria drug R&D programme.

With this background in mind, this paper will address two key issues.

- First, what are the alternatives to public private partnership? Are we correct to move down the road of public private partnership? Should we instead, as some people have argued, focus on providing financial and market (pull) incentives for industry to competitively engage in product R&D? Should we focus on developing public sector capacity to discover and develop, and hence own, products and thus bypass pharmaceutical companies altogether?
- Second, are there limitations, or gaps, in the landscape of the multiple organisations working to develop new products? If so, what are they and how can they be addressed?

2. Assessment of alternative options to, and unique characteristics of, PPP's

For the purposes of this discussion I will define a public private partnership as a project, or portfolio of projects, in which public or philanthropic funds and resources are combined with pharmaceutical company resources, in a functional partnership that is co-managed by both parties under an agreement that stipulates the terms of that arrangement and defines the product that is to be discovered / developed to meet a public health need.

By definition, this does not include products for which pharmaceutical companies identify a market opportunity, or a strategic objective, that justifies independent competitive activity. Currently antibiotics and anti-retrovirals for HIV/AIDS fall into this non-PPP category.

The two extreme alternatives to public private partnership are: private sector financed and controlled product R&D and public sector financed and controlled product R&D. I will deal with each of these in turn and finally assess the attributes of product R&D public private partnerships before stating my conclusion.

2.1 Private sector R&D: I can classify two types of case where private sector owned R&D could operate for diseases of poverty.

First, if a company recognises a commercial and / or strategic and / or philanthropic motive in developing a product by itself. Past examples of this include the development of coartem for malaria by Novartis and previous cases of antimalarial drug development during the 80's and 90's. It also applies to many diagnostics, of which I will say more below.

Second, if a (perhaps legislative) system is put in place that offers sufficient (financial) incentive for companies to invest by themselves in developing and producing new products for specific indications. Examples of this are not yet found in the area of diseases of poverty, but can be found in the market exclusivity granted through orphan drug legislation for rare diseases of the North and in U.S. legislation to promote the development of paediatric formulations. One might also classify the concept of the Global Fund for AIDS, TB and malaria as a potential non-legislative financial pull mechanism if the funds were adequate in size. At the moment they are self-evidently insufficient to have such an impact

Taking the first case, history has shown that even if a few companies do take on the praiseworthy task of developing such products for limited financial gain, or for strategic / philanthropic reasons, the collective output does not result in a sustainable pipeline of innovative new products, especially in the case of drugs and vaccines. Excluding HIV/AIDS, the closest example we have over the past 50 years of industry working independently in this manner is for malaria, and that has obviously left us with an inadequate situation. I would also go further and add that the antimalarial products historically produced by such pharmaceutical companies have either not always been primarily directed at the poorest of the poor, or even if they have, the

lack of public sector / academic engagement in their development may have contributed to some of the limitations of those products.

Thus, malarone was developed for malaria primarily as a prophylactic agent. This is not to belittle the accomplishment or the medical need for this product, but it shows that not all products for the target diseases are automatically going to be of use to poor populations suffering the disease. In the case of Coartem, the product is a good product, but its development solely through the private sector route perhaps contributed to its slow introduction into widespread use. In addition, certain initial limitations on its label and use probably would have been averted if there had been stronger earlier public sector engagement. Coartem introduction was slow as the company needed, after marketing approval, to discuss with the public sector (in this case WHO), on the need, cost and other aspects of its introduction. In addition, due to its (label) use as either a 4-dose or 6-dose treatment and its limitation to children above 10kg, further public-private partnership research with TDR has had to be carried out to validate a 6 dose regimen in Africa and to demonstrate safety and efficacy in children down to 5 kg. This information is now about to be submitted to the Swiss regulatory agency.

No product, including one developed in public private partnership, should automatically find its way into public sector use. This can only occur if it demonstrates 'in real life' its superiority and value over other products and, in the case of drugs, justifies inclusion on national essential drugs lists. However, if a public private developed product has the relevant qualities, it often has the potential to be more readily transitioned into use. For example, the recently marketed products of Lapdap (GSK - TDR) for malaria and miltefosine (Zentaris - TDR) for visceral leishmaniasis are now already undergoing extensive post-regulatory investigation to provide evidence to inform policy makers on their appropriate use.

For vaccines, where the technical hurdles are much greater than for drugs and diagnostics, the economic situation relating to private sector engagement for diseases of poverty is similar to that of drugs. In many cases we have been fortunate that advances in vaccine technology directed at the North has had benefit for the South (e.g. Hemophilus Influenzae type B vaccine; hepatitis vaccines, multi-component childhood vaccines). However, there are cases of vaccines being developed for diseases that had potential for use in the developing world, but for economic reasons, they have not been developed for such use within the private sector. A good example of this is meningitis. The meningitis belt across sub-Saharan Africa is not covered by the standard vaccine of the North because it results from a different strain of meningitis. A special public private partnership initiated by WHO and funded by Gates and involving several other partners is now moving this development forward.

In the case of diagnostics, companies have invested in products for diseases of poverty, but due to small market size small diagnostics companies predominate. In addition, due to a lack of regulatory oversight a vast array of products may exist with little advice being available to the consumer, or purchasing organisation, on their relative value. Once again, public sector engagement with companies after product approval is often necessary to enable the public sector to assess which products meet approved standards for public sector procurement. Examples of this approach have recently been undertaken by TDR in collaboration with WHO's Western Pacific

Regional Office to establish criteria for the identification of malarial diagnostics that justify public sector procurement. Similar studies are being completed to establish which of the marketed syphilis diagnostics justify public sector procurement. It is noteworthy that so far in similar studies, none of the gonorrhoea or chlamydia diagnostics tests have been declared valid for public sector procurement. This can be contrasted, for example, with a current PPP project for the development of a patch test diagnostic for onchocerciasis by TDR in collaboration with a German company, where extensive preclinical and clinical testing will be done to provide evidence of value, prior to a decision by control programmes on its utilisation. Other tests, including some for TB with TDR and FIND, are at late stages of development and once again extensive evidence will be generated to inform the public sector whether or not they justify procurement.

A final word needs to be made on Biotech engagement in product R&D on drugs and vaccines for diseases of poverty. Biotech companies are indeed engines of innovation and due to their small size they can move very rapidly in areas where they have speciality. This has led many to believe that Biotechs are an answer to our problem if only we can appropriately employ diligent use of venture capital for investment. Evidence to date has not borne out this simplistic scenario, with several small 'profit venture capital' driven initiatives failing to take off. There are two main reasons for this. Firstly, small biotech companies, even more acutely than large companies, have to cover the full costs, especially if they are publicly listed and owned. Secondly, their future, just like large companies is dependent upon making people believe that they have one or two products that will earn a significant financial return. Although they can write off some costs of R&D by 'demonstrating' that their technology can produce a particular result or product in the 'diseases of poverty area', and thus gain credibility and further investment, ultimately such an investment is always a poor second to their core business. Although there are plenty of examples where biotech companies have 'tested the water' of such product R&D through limited initial investment, there are few if any cases where they have continued to go ahead on their own, without significant public sector support. In a few instances I am aware of where this was attempted the companies are no longer in business.

Taking the second case of developing financial incentives, including through legislation, there are no cases where this has been achieved for diseases of poverty. The bottom line is that market sales of circa \$200M a year for a product are needed to justify a company investing by itself in a portfolio of drug R&D projects. Assuming multiple products are already on the market, creating an element of competition, plus the fact that several of those are, or will in the future become, generic, thus putting pressure on prices, then one probably needs a total market size approaching \$1 billion. In addition, due to the political nature of the diseases in question there is intense pressure on companies to keep their prices low once a product comes on to the market, further limiting profitability and incentive for investment.

Many ideas have been put forward to mitigate this situation, such as orphan drug legislation providing enhanced market exclusivity; tax breaks for both R&D and for provision of final product; transferable credits for extending patent life and / or market exclusivity on other profitable products. However, all of these require intense lobbying for legislative intervention and this legislative intervention may differ from

country to country. Once one looks into the details of these proposals they become increasingly complex and potentially difficult to manage.

The idea of a grand prize for the development of an innovative tool such as a vaccine that meets pre-defined specifications has also been proposed. This seems simplistically straightforward. However, once again when one looks at the detail, problems arise. For example, what if a second, superior, product is developed soon after the first? Which product is put into use? Who gets the prize? Is some sort of sharing undertaken that devalues the reward? These are interesting questions but of course the whole idea is currently hypothetical because nobody has yet put up the money to back the idea.

I believe the bottom line is that companies will only be incentivised to competitively engage in product R&D if they see, and hence believe, that the public sector is investing funds in the purchase of existing tools. If they see the billions of dollars going into the purchase of tools that public health needs demand, and they see that there is substance behind the rhetoric of providing increased resources, then they will invest. However, given that it takes many years to develop a drug or a vaccine they will also have to be convinced that public sector purchase will be sustained over the long term. It is also likely that companies will be very focused in their response. A huge increase in funds for ARV's will only elicit a response for ARV's, not for other diseases of poverty.

Even the large funds moving into public sector purchase of antiretrovirals, TB and malaria have not generated any sign of increased competitive private sector R&D. The increase in funds has however stimulated further competition for increased private sector investment in production and manufacture and improved formulations in these diseases, particularly in the generics sector, suggesting that if sufficient funds were provided then independent private sector R&D might be stimulated.

In conclusion, many additional companies have become engaged in product R&D over the past 5 years. My belief is that this is only minimally due to increased public sector purchasing power, or the belief that there will in the future be such an increase. Although this has helped, the expansion is mainly due to an increased availability of funds and resources available through public private product R&D partnerships to 'push' R&D, coupled with an increased political awareness by companies of the need to demonstrate good corporate citizenship.

2.2 Public Sector R&D

It is stated by some individuals and organisations that there should be no reliance on the private sector for the generation of products and that the public sector should take a stronger lead and fully resource product R&D. In such cases it is often left open how the production, manufacture, distribution (and sale?) of these products should be managed.

There are several issues that need to be assessed in addressing this argument, over and above the philosophical / political arguments of the relative merits of the case. Philosophical and political positions equally impact on both free market proponents,

as well as anti free market proponents, opposing public private partnership. As there is often little that can be said to impact on these opinions, no further discussion of this issue is warranted in this article.

With this caveat I would state the issues as follows: can public sector dominated approaches produce tools of the quality and standards that we need?; can public sector dominated approaches produce tools in a time efficient and cost-effective manner?

There are case histories demonstrating that public sector managed programmes can deliver new tools that justify clinical use. Perhaps the best historical example is the case of the early vaccine industry, which was built largely on public sector research leading to public sector owned institutes producing and manufacturing vaccines. However, it is notable that over recent years, this approach has become unsustainable, and the need for private investment to improve on existing technologies has resulted in R&D based vaccine activities moving largely into the private sector. The other example that springs to mind is the R&D, production and manufacture of agents related to war and national security. Thus antidotes and vaccines against biological and chemical warfare agents are often developed and manufactured within the infrastructure of the public sector.

So, public sector R&D, manufacture and production is certainly achievable. However, globally, the experience is that private sector managed innovation has resulted in more improved products. Most areas involving product R&D have therefore moved into the private sector. This has resulted in an extremely limited public sector infrastructure available to support product R&D. Where such infrastructure exists it is also less likely to be as modern and up to date as in the private sector.

This lack of infrastructure and manpower in the public sector means that any public / philanthropic sector approach would require the provision of this infrastructure and would result in the need for extensive capital investment. In order to recruit the high quality human expertise needed there would be a need to offer incentives for scientists and technicians on a par with the private sector, further increasing costs. Furthermore, the availability of expertise which projects could draw upon, would be significantly less than in the private sector. Choice of people to undertake research, choice of projects that could be undertaken, choice of location where research was undertaken, would all be substantially reduced..

In conclusion, a public sector driven approach is do-able, but would be extremely costly and capital intensive, due to the need to generate and sustain an extremely complex infrastructure. It would also result in less choice and reduced access to available expertise. Finally , there is always the added concern that once such a capital intensive organisation was placed entirely within the public sector, where there is also limited experience of governing such institutions, that additional restrictions might slow down progress.

2.3 Public Private R&D

Much has been written about public private partnerships and there is no need to repeat that in detail in this paper. However, I would draw out the main argumentation as to

their added value over private or public sector programmes and present some limitations.

The claimed added value of such partnerships comes from:

- a) the utilisation of both private sector expertise in product R&D and product specification, and public sector expertise in the diseases and populations of interest and an understanding of the environments in which the products will have to be tested and ultimately used;
- b) the sharing of resources for an activity thus limiting the risk to both the private sector and the public sector partners
- c) the sharing of existing infrastructure, limiting the need for capital outlay
- d) the use and combination of best practices of management, selection and review of projects from both sectors, and to secure avoidance of conflict of interest
- e) the potential ease of transition of new products into public sector use, based on a more detailed understanding by the public sector of the relevant merits and faults of any given product.

The potential negative elements of public private partnership include:

- a) the need to develop and operate a partnership under legal agreements that may involve different operational cultures
- b) complex virtual managerial structures for individual projects

My belief is that the positive elements outweigh the negative elements, though it needs to be recognised that public private partnerships are not a panacea. In some cases mistakes will be made and projects and organisations will fail, not just due to science but due to inherent organisational and partnership reasons.

In summary, my personal conclusion is that unless the public sector is prepared to invest far more funds (many billions of dollars), either to ensure sufficient commercial 'pull' to get the private sector to competitively invest in R&D, or to ensure that there is a viable capital intensive infrastructure for public sector R&D, that public private sector partnerships remain the only viable alternative for the foreseeable future. I would go further and state that even if the options were available to go the private sector route or the public sector route, that on balance public private partnerships have the capacity to deliver better products more suited to public health needs and to produce them more cost-effectively into use.

3. Assessment of the current operating environment of PPP's.

The expansion of organisations engaging in public private partnerships has had the net effect of bringing in more public sector and philanthropic resources into product R&D for diseases of poverty. In the next paragraphs I will be referring to some financial estimates. I should stress that these figures have not been closely researched, but represent 'ballpark' estimates based on my current understanding of what is happening in product R&D PPP's and in related activities. They need to be further researched and validated before further quoting in the public domain. However, I believe that they are useful in transmitting to you an idea of the scale of investment that we are talking about.

Back of envelope calculations suggest that focused product R&D funding from traditional organisations such as TDR, HRP, PATH, NIH, USAID, WRAIR, Wellcome Trust, EU and others, including various nationally supported projects probably stands at around \$50M. The increased expenditure due to new organisations probably adds around \$100M per year, with potential to grow to around \$200M per year over the next five years as these organisations further scale up. This does not count a lot of 'overhead' input from the public sector in terms of university and organisational infrastructure that is also committed to these activities. It is difficult to calculate the in kind commitment obtained from the private sector in partnership projects. However, it is likely that PPP institutional funding has leveraged at least an equivalent amount of resources from the private sector as they contribute in kind resources into projects, and particularly if one counts investment in production and manufacturing. At an extreme, in the case of TDR partnership with Zentaris to develop miltefosine we have calculated that the ratio of company to public sector investment was greater than 10 to 1. If one takes into account the specific industry initiatives of GSK, Astra Zeneca, Novartis and Sanofi, mentioned in the introduction, then the collective total will probably easily match that of the public sector. Thus we are talking of a total increase in resources of around \$200M per year since the late 90's, with the amount possibly rising to around \$400M in the coming five years if current trends continue. By 2010 we might be talking of total product R&D levels for diseases of poverty, excluding HIV/AIDS drug R&D, of around \$500M.

It is critically important to realise that these funds represent the input of additional personnel, people whose intellect, expertise and dedication would not be channelled into these endeavours unless these funds were available. If one assumes an average full time equivalent cost of around \$100,000 (this is a conservatively high guesstimate based on the fact that it includes the high FTE costs of industry and well paid public sector individuals, combined with the lower costs of scientists, technologists, post-doctoral fellows, graduates and technicians performing much of the work, and the increasing numbers of people engaged in developing countries, where personnel costs are low) then we are talking of the equivalent of 5,000 or more additional full time equivalents of people working on product R&D for neglected diseases by 2010.

As stated at the beginning of this section, these figures are extremely approximate and need further verification, but they give some idea of the scale and magnitude that we are discussing. To put this further into perspective R&D expenditure of \$500M is about 10% of that found in the largest pharmaceutical companies and 5,000 people equates to about 25% of R&D personnel found in large pharmaceutical companies.

This represents a significant body of activity that is characterised by its diversity and its multiplicity of activity. Whereas output from a single pharmaceutical company is coordinated and directed, the activity described above comprises of many individual partnerships each with their own goals, sometimes as part of a broader portfolio of activities and sometimes not. This multiplicity of activity brings to it an element of confusion amongst the donor community, those involved in health policy, governments of countries in which the products are to be utilised and the general public. This confusion can be further exacerbated as the general public and many of those overseeing the financing of health research in general often find it difficult to clearly distinguish between product R&D and research in general, and often even between drugs and vaccines.

I list below several areas where I feel specific attention needs to be paid as we move forward with expanding product R&D public private partnerships and providing the institutional and governance background support to ensure their success.

a) Partnerships should be neither over-competitive with each other, nor monopolistic;

There is increasing competition for funds to finance public private partnerships and other forms of health research. This is healthy, especially if it results in a net increase of funds coming into the area, but given the relatively small level of investment going into product R&D for diseases of poverty, we also need to have an environment of mutual support and interaction between organisations. There has been an explosion of improved and more professional 'advocacy and communication' activities, which again has been helpful in promoting the entire area. However, we have to be careful as a community that we distinguish between 'delivery' and 'promise' and between 'reality' and 'soundbite'. While recognising the value of economies of scale and the need to avoid too much duplication of effort; indeed, while recognising that downstream we may even be merging of small organisations into larger organisations, there is also a need to ensure that no one organisation creates an absolute monopoly in a given area. In any sphere of life, to put all ones hopes in one single organisation can result in disappointment. The nature of innovation demands that there be a multiplicity of routes by which promising science can be converted into new tools and that no one person, organisation or committee has complete global responsibility for one particular area.

b) A sense of common purpose and direction is needed that facilitates cross-linkages and synergies where appropriate

As mentioned above, the product R&D activities we are discussing represent a relatively small collective effort compared to the pharmaceutical industry. Just as for a pharmaceutical company, there is a need for us to focus on and generate new products, but as a community interested in product R&D for diseases of poverty we are very diverse, compared to the cohesion of a single company. Recognising that there are many players in R&D, that there are many stakeholders in the basic science from which product R&D is derived, and that many more stakeholders are involved in the end use of the products, there is a need to generate a common purpose and direction. Such common purpose does not mean that there should be micromanagement, but that there is discussion and consensus around the key elements of the types of product that we need (product profiles) and an understanding of the environments and healthcare systems in which they will be used. Such 'common purpose' then makes it easier to link between organisations and generate synergies

c) The product profiles being sought by PPP's should be in line with global health need

It is absolutely critical that the profiles of the products being sought are in line with medical needs and the limitations imposed on their use by human nature and social environments, i.e. that the products we produce are relevant for the populations for whom they are intended. This sounds straightforward, but it is a factor that can often be lost within the complex technical environment in which the products are generated, and where there is often a temptation to 'go early with what we have got', rather than to wait a little and 'go later with an optimal product'. In the past, with

minimal R&D investment we in the public sector have had to take the former philosophy. With increased resources we can now afford the luxury of moving toward the second philosophy. Once again, as intimated above, there is immense value in generating a broad consensus on product profiles and it is an area that justifies further discussion. By generating and publicising such consensus we can ensure that multiple organisations are essentially 'pulling in the same direction'.

d) Exploratory research, and early product R&D - translational research - needs to be supported to ensure that product R&D pipelines are maintained;

The focus on product R&D should not detract from the need to invest in the early stage research that is necessary to ensure a full pipeline of activities and so enhance the chances of success in delivering new products. Particularly important is the need to focus more investment in the area of 'translational research', research that moves an interesting scientific observation to a stage where it justifies significant investment to optimise it and develop it into a product for testing and clinical evaluation. In the area of drug discovery this requires the conversion of genomic information into robust biochemical assays and the availability of high throughput screening and other secondary activities to generate lead molecules worthy of optimisation. For vaccines it may be that a particular promising antigen requires further optimisation, scale up of manufacture and detailed animal testing and process development. For diagnostics it may be that an early stage assay needs to be further optimised prior to its development into a format that is robust, quality assured and ready for evaluation.

e) Appropriate mechanisms need to be in place to ensure the continued and sustainable production and distribution of useful new products

In addition to the lack of engagement by major pharmaceutical companies in product R&D for diseases of poverty there is a danger that a similar lack of engagement occurs in the production, manufacturing, marketing and distribution of products. As we move forward with an expanded agenda, this is particularly of concern for diagnostics and for drugs and other products for the smaller diseases. If a major R&D based company or a major generic company is the private sector partner then they can utilise their vast networks of affiliates to ensure marketing and distribution. If smaller companies are involved this might limit distribution and availability. Some interesting and innovative examples are around about how such issues can be addressed. For example the creation of a special not for profit organisation, the Concept Foundation, was initiated to handle IPR and licensing issues associated with a new contraceptive developed through the Human Reproductive Health Programme at WHO. This initiative, created with Rockefeller Foundation support has been highly successful in engaging with local manufacturers and distributors to ensure widespread availability of affordable product. Even with the engagement of major pharmaceutical companies, there is an urgent need for complementary activity to be undertaken to enhance the number and quality of dispensing (pharmacy) capacities in developing countries. In many cases products are being made available through local shops and markets. This is better than no distribution at all, but given the need for appropriate use of drugs to ensure cure and to limit drug resistance, more effort needs to be directed towards distribution mechanisms, dispensing capacity and regulatory oversight.

f) Appropriate downstream research - implementation research - needs to be undertaken to optimise product use and provide evidence for policy

As well as ensuring there is adequate research to feed into product R&D, there is equally a need to ensure that there is adequate research done on products as they become registered so that evidence is generated for optimal use and policy. This requires a different skill set to product R&D and requires a deeper understanding of health care systems. As new products come through public private partnership we need to learn from past experiences in this area; for example ivermectin for onchocerciasis, praziquantel for schistosomiasis, and more recently Lapdap for malaria and miltefosine for visceral leishmaniasis. Each of these cases is slightly different, but what was common was a fairly smooth transition from development to regulatory approval into exploration of optimal use and the provision of evidence for policy.

g) Conflicts of interest should be minimised;

With the increased sums of funding involved there is a need to ensure that selection, monitoring and review of projects is carried out as objectively as possible and that those undertaking the projects are not involved in anyway in the selection and review of their own work. In order to minimise any perceived and real financial and other conflicts, strict rules should be enforced about declarations of interest.

(h) Capacity building and capacity utilisation in developing countries should be integrated into product R&D activities

In order to develop a truly sustainable system whereby new products are effectively discovered, developed and implemented, it is important that appropriate capacities in developing countries are both developed and utilised. A sense of local ownership of data and products greatly assists and improves the ability of countries to implement new tools, methodologies and policies. In addition, the expansion of research capabilities and the generation of an appropriate research based culture in countries results in far better understanding of the options available for policy and hence better decisions on how and what to implement. For example, for product R&D projects, the utilisation of developing country investigators, especially for clinical studies, can be extremely useful in ensuring that expertise in best practices are built into country capacities in a sustainable manner. TDR and others have placed great emphasis in recent years on enhancing GCP training and facilitating the development of capacity for ethical review within the context of all their product development activities.

(i) There should be strong stakeholderhood from developing countries within the context of product R&D, product use and product delivery

Product R&D is often about speed and technical excellence. This is sometimes interpreted to mean that utilisation of developing country expertise or the 'building of research capacity on the job' is a 'nice to have' add-on that can be ignored in the interest of getting a rapid regulatory approval. This is further exacerbated by the fact that almost all donor organisations are from the North and many of the initial recipients of their funds are based in technical, university and industrial institutions in the North. These individuals, even if they have experience of developing country environments, may fail to understand the long term value and indeed the social responsibility to engage equally with southern partners and to work to ensure that once a project is completed that there is a sustained residual capacity left behind that

can undertake similar work in the future. Part of this omission occurs, I think, because those involved in the projects view regulatory approval as the end goal. That may be the limit of their responsibility, but it is not why the funding has been given, nor the true goal of the projects. That goal is reached when the products are used and understood by the consumers and are put into use within national health systems, whether within the private or public sector. To ensure this occurs rapidly and effectively, developing country scientist and developing country institution participation as equal partners in development teams is essential. There are thankfully many examples within current portfolios where developing country scientists and institutions are playing the lead role. However, there is a long way to go to bring any real semblance of parity in this area. If developing countries genuinely believe they are true stakeholders then they may also be inclined to contribute more themselves to product R&D projects and organisations, both through financial and in-kind resources.

4. Concluding Remarks

We have come a long way very quickly in the area of product R&D for diseases of poverty and this progress deserves to be recognised. It should also be recognised that this is due to the financial contributions of a limited number of public sector and philanthropic donor organisations and in kind contributions from a limited number of pharmaceutical companies. Both of these contributions and the human capital and personal commitment of many individuals engaged in public private partnerships at the scientific and technical level should be equally valued.

Much of this paper has presented the big picture and has looked at product R&D for diseases of poverty as a whole. However, within the indications that are of interest we should recognise that there remains a great disparity between areas of major expenditure and global impact (HIV/AIDS, TB, malaria, reproductive health) and others of lesser expenditure and more regional impact (e.g. dengue, schistosomiasis, filariasis, kinetoplastid diseases). A person infected with one of these latter diseases is just as important as one infected with the major diseases and from a human rights and equity perspective, and as a social imperative, these diseases should not be left out of the PPP equation and deserve further prominence.

Finally, we are operating in a new environment with many new players on the stage of product R&D for diseases of poverty. As a community we need to work closely together to ensure that we obtain maximum benefit from this increased array of activities. We need to ensure that pipelines are maintained through enhanced translational research and that new products, once registered, are optimally evaluated and used. As an integral part of a successful strategy we need to ensure we work on the diseases of interest in a manner that is sustainable and builds and utilises research and other capacities in developing countries.