THE BROOKINGS INSTITUTION

# THE NEW LANDSCAPE:

# DRUG DEVELOPMENT FOR NEGLECTED DISEASES

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MILLER REPORTING CO., INC.
735 8th STREET, S.E.
WASHINGTON, D.C. 20003-2802
(202) 546-6666

P R O C E E D I N G S

MS. BRAINARD: [in progress] in the development field, which is that all of the innovations or the vast majority of them, for many years, have been targeted at diseases that Mary calls in her report commercial diseases, which is a terrible term but it does capture that essence that there's a commercial return on being able to actually develop therapeutics and diagnostics around those diseases, and there is no commercial return for the diseases that kill so many more people in poor countries.

There are a variety of proposals that have been out in this domain over the last year or two, some of which Brookings has been very closely associated with, in partnership with people at Harvard and at the Center for Global Development.

Mary Moran's news today I think is very positive news, which is that even in the absence of big new government framework, things are happening in the field of public/private partnerships that are very exciting.

So just by way of brief introduction, Dr. Moran is a medical doctor who switched, after many years of practice, and became, I think, devoted to the area of development and of addressing the problems of global poverty.

In the last few years, she's been running this project at LSC, which I think has now moved to Australia; is that correct? And when she is done with her presentation, we will also invite other members of the panel to come up and we'll have a discussion.

And I'll just introduce them briefly right now.

Amanda Glassman is the deputy director of the Health Financing Task Force, which is a joint between the United Nations Foundation and Brookings.

Lynn Marks is senior vice president for GSK Medicine Development Center.

Chris Hentschel is the president and CEO of the Medicines for Malaria Venture, and Jerry Sadoff is the president and CEO for the AERAS Global Tuberculosis Vaccine Foundation.

So these panelists all represent a different piece of this puzzle and I think Mary's remarks will make clear why all the pieces need to be put together to make this work.

Mary.

DR. MORAN: Good morning, everyone.

Thanks for those introductory comments.

I think that captured our understanding of neglected diseases, what people have generally been thinking, which is that not much is happening.

The problem is that there's limited commercial return, and what we've mostly been focusing on is trying to get something happening, probably by increasing the commercial returns, or making a market, or

getting some kind of bigger financial reward per company, and that was certainly our understanding when we started this project.

But our findings were very surprising to us and I think you might find them surprising here today as well.

I'm going to run through, first of all, what we found, how much work's happening and who's doing it, and why, and then we'll look at how effective is it. Is it really working? Based on that information, what kind of policy approaches might help move forward drugs in this area?

So first of all, despite the lack of government policies or new policies, what we found was a lot of activity in this field. There was over 60 projects, half being done by large firms on a not-for-profit basis, and half being done by small firms on a purely commercial basis.

When we looked at large companies—now these companies are big multinational firms that have over 30 projects now. The key point was that this was completely unrelated to a return on investment in the neglected disease market.

So these firms aren't doing this research or making their decisions based on a profit in that market, and their drivers were very clear. There was eight multinationals involved but they all shared the same motivations. Managing reputational risk was a very big driver for them.

Strategic issues. Some firms were looking at getting into these emerging markets, lower cost R&D centers, and corporate social

responsibility. That wasn't a huge driver for some firms but for a company like GSK, actually, I have to say that came up again and again as something to drive them.

The reputational risk was the front runner and that was the case for all the companies involved in this field.

Then we looked at small companies. This was the other half of activity. This was interesting too because they didn't say there's not a market. They said this makes good commercial sense for us, for a number of reasons.

For some people it was slow on gains where they have a shared target, or between a commercial market and a neglected disease market. The neglected disease work could give them shared data or proof of principle; support their business model to move forward to a commercial market.

Cash contracts with public/private partnerships were very big, and some of the biggest CROs said to us that they say this is a really potential growing niche market for them.

And surprisingly, for a small number of firms, they say this market actually is attractive for us. 120 million a year is not bad for a small company. And there was one company that produced the last drug for that. There are some companies working on TB drugs on that premise.

The next thing that surprised us was that three-quarters of these projects were being run through public-private partnerships. That was including with small and large companies.

So the predominant activity in the field was partnerships, which again we hadn't realized, and that turn to partner is increasing. More large companies are moving, plus to sign more contracts in the neglected disease field with PPP's.

And when we looked at all this, the motivations, and looked at how people were doing this, in theory, this is impossible. If there's not a market return, it's impossible that this should be cost-effective for a company. So we had to look at how is this working.

And what we came up with, the eight companies that do this work, now four have dedicated and neglected disease portfolios. That's over 200 scientists, mostly working in dedicated facilities. That's all they do.

This is exactly the kind of activity that we've been saying hasn't happening, and, you know, it's not happening and how can we get it. But we discovered it actually was happening and they were already there busily working around new products.

Now all the really active companies—this is these firms with dedicated portfolios—have moved to a very different business model, a new business model, and that let them increase their R&D activity at very

reduced cost and risk, and some of them actually called this the "no profit, no loss" model.

Companies who hadn't moved to that model can afford to do, and in fact did do, when we looked at it, much less R&D, and much less innovative R&D.

And I'm going to talk in a little bit of detail about that model now, and the key point is that it completely reverses our traditional public policy approaches in this area. It completely overturned our understanding, certainly, and I think the general understanding of how you should get this process happening.

So this is the traditional approach. This is the drug pipeline that you see here, starting at discovery and bringing a product through to registration.

Now normal policy settings say the public will work on a compound early, discover a drug late, they'll bring it along to maybe Phase 1 or Phase 2, and then they'll hand it over and the private sector will commercialize it or do the large-scale clinical trialing, registration, manufacture. I think that's been all of our understanding.

But when you actually look at it, the private sector, their area of maximum expertise in neglected disease field, is finding drugs. Where their expertise decreases—and the companies were very clear with us about this—where they're less interested and less expert is doing large-scale trials with

pregnant women, and children, in remote, developing countries, in diseases that they don't know about.

So they said, you know, I actually don't want to trial a drug in infants, in Nigeria, on a disease that I don't do.

The public sector, on the other hand, very limited experience in bringing drugs to market. I mean, there are none, no public drugs have been brought. Private funds are better at finding drug leads than public academics. You know, you don't get academics to design your car and you probably shouldn't be getting them to design your drugs either.

Where the public expertise really starts to increase is further downstream. Neglected diseases, developing countries, African regulatory authorities, what the patients look like, how the drug's going to be used—that's their strength. That's where they're really good.

So what we have as a model, where people work out of their area of expertise and interest, so the area where they're less expert and where their risk for them is higher, and the costly need to get someone to do something they don't want to do and they may not be particularly good at are very high.

So then you need these working incentives down here to try and motivate people.

Now the new model swaps the roles around. Industry moves upstream, they do high innovation, lower cost, less risky for them in terms of liability risk, drug discovery. That's where they're really good.

And the public groups move downstream and they help with the clinical development. They help with the clinical trials dealing with the regulatory authorities in developing countries, patient groups and so forth. They help trial the candidates.

Because industry's cost and risk and are ring fenced [?], they're not covering all the cost and risk of trials now. They can produce the final drugs at not-for-profit prices. So at the end you get an at-cost product. So you don't have to worry about some high-priced product, how we can afford it and how are we going to do this and that, cause you've swapped the model around. It's much more efficient.

The problem is this model relies on an endstream public partner. The companies have moved upstream, they've established these drug discovery facilities and they're producing leads. But someone's got to be there to help trial them. That's the public partner. That's the PPP.

And this is where we run into problems. So you've got this partner that's crucial to making the model work and we're not funding them. That's ongoing, funding shortfalls that you see on that graph there, and they're very substantial, and increasing, because as these products are moving into trials, we don't have the funding to support that. We're not

putting in funding. Only four countries had funded any drug PPP's by the end of 2004, and for tiny sums of money. That's across all of those projects that I had on my first graph.

And who's actually funding this is, well, essentially Bill Gates, and he's playing the venture capital man. He set up the model, he's taken the risk, he's funded it, and he's brought this big portfolio forward and now you know, now we need the public to step in and take it to the next stage.

But before I go on, I'll just explain. So that's activity. So it's great to have 60 projects and it's great to have things happening, and high-quality innovation at the front end, and bringing things to trial.

But activity's not enough. I mean, is this efficient activity? Would it be better to just have companies do this on their own, or they just have public groups do it on their own, cause both of those have been brought forward as alternatives.

So what we developed was a series of performance metrics and the results for those were surprisingly clear. The public-private partner drugs were far higher in health value.

So twelve of the 13 drugs that had been brought to market by industry alone have been barely used in developing countries and the honorable exceptions are Bendazol developed by GSK. But the others, barely used. Now it's a huge waste of good will, effort, and resources.

The partnered products, three of the eight, had had a very significant impact. Halving the global burden of river blindness in ten years. Now that's really something. That's a big achievement.

Eradicating schistosomiasis in major parts of the world for a country as big as China. Bringing a new pediatric anti-malarial, knowing that the children represent the bulk of malaria mortality.

But these are big useful achievements. So health value, it was a tick for the partner model.

Level of innovation. Industry working alone under the old model, very low levels of innovation. By innovation, we defined innovation as a breakthrough drug. So not something that's innovative for the patient, like once a day rather than twice a day, but something that addresses the parasite, so it breaks parasite resistance by using a new mechanism of action.

That's what we really need for these infectious diseases, to get overresistance.

Now under the old model, industry, it's very expensive for them to take a product all the way through, so they tended to focus on adaptive work at the end pipeline, which is lower innovation, but it is less expensive and less risky.

Under the partnered model, there's an eightfold increase in the level of innovation. Industry working in partnerships focus on drug

discovery. That's innovative new products. And those 200 scientists I talk about, all sitting in discovery plants working on new products, high-innovation products.

Partnership model overall, 50 percent of projects in the high innovation category.

Then we looked at cost. The costs that you see here are just for PPP projects. That's because, I mean, commercial incompetence requires that you don't disclose industry costs, obviously.

But when we look at these, but we all know the rough figure, we've all read the Tufts report, we know there's a figure out there for industry costs, albeit those costs will be much lower for neglected disease drugs that are infectious disease products, often short of trials, not always, but often, and in developing countries.

But still we've got that ball park out there. These are actually real project costs, though, for partnered projects. I draw your attention to the fifth project down, synthetic peroxide. That's 11.5 million to go from the laboratory; it's a novel product, halfway through Phase 1 trials. That's extraordinarily cheap, and some of those projects are cheap because they're in kind, but even projects without in kind are very cheap.

This doesn't include cost of failure. This is just your project cost. But still, these are real figures based on real budgets, real payments

made out. You add them all up and these are the figures, actual spend to date on a project.

Now these graphs were really interesting. This is my last performance graph, so you know it's coming, I'm coming to a conclusion.

It's really hard to see it. Can you see, there's a pale green stripe down the middle of that graph on the left? I hope you can, because that's the key point. That's the industry standard to develop a new chemical entity, standard development timeline.

Now you can see that the industry alone projects, as you'd expect, roughly match that timeline. Albeit it for new chemical entities, there's some fall-off. The public projects form well below, I mean well below that timeline. Some of these projects are 25 years to get to a late finalization stage.

Now for malaria patients, that's just unacceptable.

What you also see, the dotted lines, is when you introduce an industry partner, and you start to see acceleration in development.

And then we looked at PPPs to see their timelines. And this graph is also interesting. The red lines are WHO TBR [ph] projects.

Again falling well below standard timelines. That's when you, to make a product. What was interesting is, the partnered projects were on or above the industry standard timeline.

This is projects where the PPP worked with an industry partner. All kinds of different partners as well. Some of these were developing country firms, some were contract researchers, some of them were big companies, but the actual process of bringing in an industry partner to the public scene seemed to improve, certainly improved public timelines, and match, or, as I said, exceeding the two timelines.

So at this stage we have all this information which told us there's a lot of activity in the field, and that it seemed to be the data showed, fairly clearly, that you were getting good performance out of bringing people together in the areas of comparative advantage.

It's neglected disease drug development. You need neglected disease expertise and you need drug development expertise.

I mean, when you think about it, it's pretty straightforward, really.

And we identified what the correlates were for a successful project. What makes some things work and some things not? We looked at projects since 1975. We looked at every neglected disease drug and project that we could find from 1975 onward.

And only five things that were indicators of success, and that was that the group had a sole focus, that "focus, focus, focus" just on neglected disease drug development, not only capacity building or not on

other commercial things they might get out of it. Just on neglected disease drug development.

Early public involvement right from the start, when you're trying to define what your lead should look like. Early industry involvement, medical chemistry—make sure you've got a decent drugable lead, that you're not pursuing something that's never going to be a good drug.

Management. You have to have industry mindset and experience in management.

Groups that don't have experience in drug—the less experience they had in drug making, the less good they were of bringing their portfolio along.

And adequate funding. The two fastest-moving projects that I showed you before both had accelerated funding from Gates.

That was the only thing that moved them up amongst the other projects in that portfolio was that they were given funding to do that.

The second thing was it was very clear that the PPP approach, the partnered approach, performed better than either industry alone or public alone. That was very clear. Because it had a structural fit. PPPs traditionally do that. They have that focus. They involve public. They involve private.

And to some degree, industry mindset in funding. And that brings us to point three.

Within that superior construct, performance still varies. Some groups perform better than others and some projects perform better than others, allowing for scientific variability as well.

The two factors that came up every time behind poor performance were lack of funding and lack of sufficient industry, important expertise.

So when we design a policy, and we do design a policy based on all this, that's where you should be targeting. That's where you should be targeting. You fund the best approach and you fund to improve performance within that approach.

I think my time's—am I done for time?

MS. BRAINARD: [inaudible].

DR. MORAN: I'll quickly run through the proposal, so you can get an idea of how we think policy makers could benefit from approaching this.

Got a mechanism called the industry R&D facilitation from IRFF [ph], and what it is, it's a very simple mechanism but only funds industry input into drug PPPs. But across all the neglected diseases. One mechanism that funds all industry input into all PPP for all neglected diseases.

They designed to encourage, to use the most efficient approach. So it encourages industry to partner and it encourages the PPPs to increase industry input. So you start to get a kind of virtual cycle happening.

It's also been designed to be very pragmatic from a donor perspective, for a number of reasons. This is the first one. It's very cheap. Seven million per year per OECD country. These figures are very solid out to 2010 because they're based on real projects and real budgets, real trials that are coming up.

So that's a very feasible figure and if you can't get 7 million a year, then I mean we should really just stop having these conferences and just say, actually, we don't really care. And if you can't do 7 million, then, you know, they ought to shut up shop I think.

That plateaus out because these PPPs aren't ever-expanding. They're not like companies that maybe get continued return for product. Most PPPs are only for stable portfolio. They start to get destabilizing out, average 200 million a year, that's for all the neglected disease drugs. The other advantages for donors is because you're funding a global portfolio now, your risk is greatly reduced. You don't have to pick which project, which partner, or which approach. You fund the whole portfolio.

It also means you're not getting competition. You don't have different groups coming to you saying fund my group, I'm best, TB's more important than malaria.

You know, we should do this, not that, which is very difficult for donors, and reduces many of them to the point where they just say I'm just not funding anything.

It gives you centralized information on the performance. Funders have every right to, and I really encourage them to use their money, leverage it for better performance and get performance statistics back to determine what you should and shouldn't fund. Because you've got a centralized funding mechanism, now you know how much you're giving to each disease, how much to each group, which projects are moving quickly, which are moving slowly, what things are coming on line, what's in Phase 1, what's in Phase 2. It's a very useful approach for donors.

Very rapid returns. These portfolios are due to register nine to ten drugs, new neglected disease drugs, by 2010. That was unthinkable five years ago.

Before this new business model, before the partnered approach, we would have considered ourselves lucky to have—you know, we were grateful for one new drug registration. So we're now getting a whole bunch of products coming through by 2010.

And because this has been developed based on real facts and reality, and what people are really doing, I mean there's a model out there that already works. It's supported by groups from all sides of the table.

A number of companies have come forward and said we'd like donors to look at this more closely. The drug PPPs support it. It's much easier and more effective to fund an approach that's working now—we've got a portfolio of 60 products right now, or it had been thoroughly piloted by Mr. Gates, thank you, and we just need to pick it up now and help it across the line. And we're very close to the line already.

So thank you for listening. The full, gory detail is in the report which is out there, back, and I'm very happy to take questions.

MS. BRAINARD: All right. Well, let me now turn to the panelists and I want to explore, first of all, the broader context, and then talk about the different roles of the different participants in these partnerships.

And then I'd also like to open it up to the audience in a few minutes.

So starting with the broader context, and I want to start with you, Amanda, place this set of developments in the broader context and give us a little bit of the compare and contrast with some of the other models that are out there.

MS. GLASSMAN: Okay. Well, I hope that I achieve that, but first, I'd like to congratulate the authors on a very interesting, carefully documented account that consults with the affected actors of the current initiatives in neglected disease R&D.

I think the study makes a very persuasive case for public finance, for those modular health outcome focused institutional mechanisms that work most cost-effectively, but it also highlights the current fragility of the PPPs. Their dependency on philanthropy financing, 80 percent of total, their financing shortfalls and the lack of information on the performance of the PPP projects with the exception of the WHO/TDR products, with respect to their health value, since we're still waiting for the registered drugs to be produced.

Now the timeline, as we've said, is extremely short compared to the industry standard, but unfortunately, the financiers are development assistance agencies. They're not accustomed to financing pharmaceutical R&D, so they don't have much of a reference point on that.

I've heard talk in different fora of the opportunity cost of these funds that are invested in neglected disease R&D, but at $85 million a year to PPPs, this seems like a very irrelevant debate.

In some cases there's not much still happening, if measured in terms of the total size of the investment going to these areas.

And yet this is financing a public good, research and development; and for me, the key finding from this study is the low level of government participation.

Now most agree that the poorest countries need not contribute to global R&D creation but there is consensus that the wealthier countries should.

But the contribution of governments is laughably small. There's almost no public in the public/private partnerships. So at the center of this is how best to structure incentives for increased R&D for neglected disease, for use in poor countries, and as the report points out, the view in 1999 was that the incomes were too low and markets were too small to incentives the finance of these drugs R&D, and hence, the development of the PPPs.

But what is the current reality? First, there are new global funds and innovative financing mechanisms on the table, that make effective the international markets that would incentivize neglected drug R&D, and I think it's clear that a PPP could respond to pull mechanisms just as well as industry.

Second, the WHO estimates that more than half of total health expenditures, private, out of pocket in most developing countries, and roughly two-thirds of this is on the purchase of drugs.

So it seems likely, as suggested in this report, that firms just don't know how to access these developing country markets very well, and this is why I think the suggestion of public support channeled to small companies, to recognize the potential of existing commercial markets, is quite welcome.

Now this axis, in combination with some of the pull mechanisms, and perhaps the differentiated patent policy that was suggested by Jean Lanjouw in an earlier Brookings publication, would allow the incentives and the system to work better.

So we should recall that an ideal system would use two instruments, the best incentives for creating knowledge and recovering fixed costs that are involved in the R&D process, and the PPP model is very competitive. The fixed costs are extremely affordable. So this myth that it costs a lot to produce doesn't seem to be borne out by the data that's presented here.

And second, once created, the drugs have to be made available at the marginal cost of production to maximize the benefits.

And the potential public role in this is still understudied. A recent article by Lachs Menarin [ph], I'm going to pronounce his name very wrong, but a recent article in Health Affairs highlights the health and efficiency effects that a subsidized international drug purchase facility for malaria medication could have for developing countries. And WHO, last week, has convened a meeting on this topic and I believe that yesterday, donors agreed to develop this international drug purchasing facility but they stipulated a caveat that's important. Provided it did not overlap with other existing initiatives.

I hope that they take this recent proposal and the other proposals that are on the table into account. Two more points.

I think it's worth remembering that a 2004 WHO report on neglected diseases pointed out that our narrow definition of neglected diseases, which is tropical diseases, and TB, overlook current threats such as pandemic influenza, anti-bacterial drug resistance, stroke, and others that represent a high burden of disease, and for which there are few and no effective remedies, and this only increases, then, the global drug financing gap that is being faced here, and also puts into bleak perspective the very limited public finance for this work.

And I'd like to end with a concern regarding the institutional architecture of the financing. The multiplicity of similar institutional arrangements to achieve similar objectives is raising the administrative and transaction costs of global health cost financing, in general, and this is true for drug R&D as well.

We have PPPs for each different type of disease, separate financing funds, and mechanisms, for similar types of products, and this is a result, as Ruth Levine has pointed out to me, of the political realities of fund-raising for global health.

But by transplanting these fund-raising structures, implementation arrangements, we may be missing economies of scale and dispersing scarce human resources. Thank you.

MS. BRAINARD: Now I want to turn to the private sector participant, in particular Lynn Marks, and ask a little bit to tell us why a company like GSK invests in these drugs, and is it the no profit, no loss model, that Mary was talking about before? What's in it for you and how do you sell your shareholders on this?

DR. MARKS: Thank you. Well, first of all, I want to thank the organizers for inviting me to attend. I certainly, as an infectious disease physician, this is an area that is personally and professionally near and dear to my heart.

So I head up the Infectious Disease Medicine Development Center at GlaxoSmithKline, so I do the medicine side of the business, I don't do the vaccine piece and we're engaged with HIV/AIDS, hepatitis, herpes, any bacterial—sepsis, malaria, tuberculosis, leishmania, and hopefully I can talk the company into doing [inaudible].

So we believe, and even if you look at the heritage companies prior to the merger of GlaxoSmithKline, each was engaged, in some way, in tropical diseases of one shape or the other.

So the time of the merger, in December of 2000, the company—this has to be done at the highest levels of the organization, so this is the board of directors level, this is the corporate executive team level.

These kind of decisions need to be made at that degree. We decided that we would remain engaged in infectious diseases, and in terms

of increasing our focus on primary drug discovery and development. So we even went so far as to put together a dedicated side interest, Katso [?], which is outside of Madrid in Spain, which is chemistry and biologists working with NMD and BATB, focusing on two of the major killers in the world.

So our commitment around specifically HIV/AIDS, malaria and tuberculosis as being three of the major killers remains ingrained in the company.

So for people like me, who enjoy developing medicines and working with people, if I didn't have that engagement from the highest levels, this wouldn't be possible.

So while my social responsibility point of view, we believe that there are four main efforts for that, for calling for that. One has to do with pricing. Responsible pricing around not-for-profit models in the 64 least-developed countries in the world, so that if we find new drugs for malaria, we'll sell them at what it cost us to make them, just as we do for HIV/AIDS.

We talk about voluntary licensing, so that manufacturing can be done in these low-cost countries, least developed parts of the world, in ways that get outside of our cost structure.

And then committee investment. So donation programs like lymphatic filariasis, where we're trying to eliminate that disease in partnership with the lymphatic filariasis elimination fund, and with groups

like Positive Action which are on the ground, educational groups, looking at dealing with social stigma around HIV/AIDS in Sub-Saharan Africa and other areas of the world, and one of my favorites which is PHSE, which is personal hygiene and sanitation education, which is if you're going to take these medicines, take it with clean water, a fundamental principle such as that.

And then the fourth prong where I get engaged is around R&D. So we mentioned the health gaps. In fact the November 2004 report from WHO talks about the pharmaceutical gaps for Europe and the rest of the world, I believe was the title. Six out of those ten were infectious diseases, ranging from antibacterial resistance, where we still remain engaged, and we hope to be able to leverage that part with our malaria and our TB efforts, to have critical mass around [inaudible].

Number two on the list is pandemic flu and we're engaged in that from a medicines and a vaccine perspective, and then you get into malaria, tuberculosis, HIV/AIDS, other neglected diseases. So out of those top ten, six, we're engaged with each one of those in some form, shape or fashion, either on the vaccine perspective, we're on the medicine perspective, or on both.

MS. BRAINARD: Let me just push you for one second. So you're not making money on this part of your activity. How are you covering your costs?

DR. MARKS: I think the biggest cost is the opportunity cost. So if you take 100, 200, 300 people and you have them working on areas where you know you're not going to try to seek a return on investment, they're not working on other important diseases, Alzheimer's, cancer, stroke, et cetera.

So you have to make those decisions at the board of directors level, in my opinion, at the CEO level, head of R&D, where you sit down and you say the kind of cooperation that we want to be, moving forward in the future, is one that has a responsibility to society at large, and throughout the globe, and you have to make those decisions and you believe that there are people like myself who may choose to be inside the company because of commitments such as that.

You believe there are groups of investors who may decide to invest in your corporation based on those types of communications and those types of alignment and scope and direction, and that it's the right thing to do, simply.

MS. BRAINARD: So it's a differentiating factor for you in your markets, with your employees, with your investors.

Let me now ask Jerald Sadoff to comment. I think Mary's report said all of these developments, these positive developments, are in the areas of therapeutics and not of vaccines. Is that right?

VOICE: Our report is only on drugs.

MS. BRAINARD: You only looked at drugs, whereas your initiative is on vaccines. Can you tell us a little bit about how your group works and whether the vaccines area is different in important respects, which might require a slightly different model?

DR. SADOFF: Well, first of all, Thank you very much for inviting me, and being the only vaccine person here, it's always interesting. But just for the audience information, the difference between a vaccine and a drug is that a vaccine prevents disease and a drug is used to treat disease.

I mean, I get asked so many times that question, that I just thought I'd put that on the table first.

And the other advantage of a vaccine, or the difference between a vaccine and a drug is that vaccines are given once, twice, maybe three times, where drugs are given for the entire course of the illness. So from a public health perspective, in terms of implementation, vaccines have advantages that you don't have to have very much contact with the individuals that you're dealing with, which is the number one problem in dealing with many of the diseases of the developing world.

So those are two advantages of vaccines, but the big disadvantage is that you have to give a vaccine to a healthy person and so therefore it has to be extremely safe, because they don't have any disease.

So those are some differences, and from a development point of view, vaccines differ from drugs in a very significant way, in that drugs,

now with modern techniques, mass spectrometry, NMR, we can tell exactly what the drug is. We don't have any problems with that.

Vaccines are still like all the people around the elephant, trying to describe it. There's no real definite way to describe the v perfectly, and so it's got a lot of variability, which translates from a practical point of view into manufacturing.

Manufacturing and release of vaccines is much harder than manufacturing and release of drugs, and that's why the barrier for industry into entry into vaccines is so hard. So that's just a couple of generalizations that you might not be aware of.

Now our disease is TB and as you know, there's about 8 million new cases, there's 2 million deaths a year, and there's about 2 billion people infected with the organism.

In other words, one person in every three has the organism in their body and the implication of that is now, with HIV coming through the world, all these people that are already infected with TB then break out in TB, whether they may have had it under control, and TB is the leading cause of death among people that have HIV.

The other fact is is that there hasn't been a new TB vaccine for the last 80 years. IT was made in 1923, and the studies show that it has very variable effects. So the irony is the world's most used vaccine—BCG is

given to almost 90 percent of the children of the world, and it's probably the least effective of all the vaccines we use.

And that's because we give a single dose. For all other childhood and adult diseases, we have at least a three to four dose series.

Now our product development partnership is made up of 60 people with funding primarily from the Gates Foundation, although we get some in-kind funding from NIH and we get some funding from the Danish government and CDC.

But I want to say something about the 60 people that we have. 90 percent of them are from industry. So we are more like a company than most groups are. We are a company, because we're defined by who we are, and our model's a little different from what Mary had. We embrace the partnership model and we have major partners, including GSK and biotechs such a Crusell [ph], where we're working with them closely along the model that you said.

But we also believe that we can develop things on our own. What is the advantage of industry over government and traditional public? Two advantages. Focus. I was in Merck for eight years, heading their development program. Focus is the key and product developed for their customers. That's their big advantage. And they don't have government regulation primarily, except at the end stage, where they have to show that the product works. That's the advantage of industry over government.

What's the advantage of public/private partnership or organizations like ours which are working with them but also working on our own?

We don't have industry bureaucracy because industry is big and bureaucracy comes with largeness. We all know that. It's just a law of nature. And so by being small, we're more flexible.

So starting from scratch, with a new adenovirus vaccine, starting from scratch we're in Phase 1 in two years. Starting from scratch where there was nothing even made, we're in a new recombinant BCG that could replace the old BCG in two and a half years, from scratch. That's the advantage of having focus and flexibility.

So our model is a little different and in fact we've even built our own manufacturing facility, so that we can manufacture this new replacement for the old vaccine in bulk, and then transfer to the developing world manufacturers for lyophilization, put it in bottles and filling.

So we have a mixed model, a model just like Mary described, with partnerships, with wonderful partners, and then we develop our own things as well, so that within, there's a competition between the partnership and our own. So therefore, we feel the same pressure that every industry feels and we have people from industry, so that they know how to respond to that pressure, and we think we can make a new vaccine for TB with our partners, and by ourselves, in the next seven years, so that we can probably

make a vaccine that we think will eliminate 30 to 40 percent of the disease in the world with a better vaccine.

And eventually, with second and third generations, eliminate a disease that has been with man as long as we've had any record of human beings on Earth.

MS. BRAINARD: Let me just ask you, quickly, how much confidence do you have that the market will be there if, in fact, you get to that point, both in terms of developing countries spending the amounts they need, the very discouraging numbers that Mary was showing us on some of the major donors?

DR. SADOFF: Yeah. How much money to purchase, or how much money to develop?

MS. BRAINARD: No, to actually purchase and—

DR. SADOFF: It's not really "build it and they will come." We've had a, working with another public/private partnership; we have commissioned a study by the Boston Consulting Group to estimate the market for a new TB vaccine. And surprising to us, and I don't actually believe it's this high, the market for a single replacement for BCG is $600 million a year. Mixed market, worldwide, and public and private. And the market for a new combination regimen, which I alluded to before, where we'd have more than one vaccine trying to protect against the disease, is around 1.2 billion.

Now these are industry type estimates made by the Boston Consulting Group, and I have to say that my faith in all market estimates is not very good, based on my experience industry. They're usually too low or too high.

But it's probably within a ball park figure. We think there's a market, if we can develop the product.

MS. BRAINARD: And how much of that is in the First World as opposed to developing countries?

DR. SADOFF: The ability to pay, almost 80 percent of it comes from not just First World but people in the developing world that actually can afford to pay, because that's a lot more people than we recognize. There's a huge middle class in India, there's people in China and other places that can actually afford to pay, and it's a little bit complicated to go into how you access those because of everything. But at least it looks like there may be some support there.

MS. BRAINARD: Okay. Let me finally turn to Chris who is involved on the side of malaria in a similar kind of public/private partnership, and if you would give us a sense of how your model fits along some of the dimensions that Mary was talking about more broadly, and what successes you've had so far.

MR. HENTSCHEL: Right.

I would just like to respond before getting into that. I will do that. A bit to what Jerry has said in relation to drugs and vaccines. I personally don't feel the difference is quite as large as was described there, because actually with drugs today, some of them can be developed to prevent disease, not just to treat it, and that's one of the strategies with malaria drugs, and indeed there are drugs like the drug that was mentioned for Ivermectin [ph] in which you just take one pill and that basically prevents you from getting the disease for a year, which is a similar sort of target for some of the vaccines.

So I think there's actually a bit of a convergence occurring. The other aspect is that some of the drugs, for example, some of the anti-malarial drugs that are being developed now, actually, at population level, prevent the disease from being transmitted because [inaudible].

So drugs, both preventative and curative, not just curative.

Now the most useful thing that I can do is to go a little more into detail about how this public/private partnership mechanism works. Sometimes it's called a product development partnership, which is probably a better name than just public/private partnership.

First of all, and something which hasn't been mentioned so far, we manage a portfolio of projects which are integrated and considered as a totality, not just a series of discrete projects. That's a very important part. It's a portfolio approach. There are three phases to this portfolio. The first

phase is trying to figure out what project should come into the portfolio and that's done with the advice of advisory groups that include industry participants.

Actually, I recognize in the audience Tom Wellen [ph], who's one of advisers from NIH. So the advisory groups are a mixture of industry and public health experts, who look at projects that we may decide to adopt, and over five years we've looked at over 500 different potential projects.

Now that, in itself, tells you one reason why these are successful models. We actually can look at a very large number of potential products.

If I was just in industry and I've spent quite a bit of my time in industry, and I was trying to develop a new drug, and I said look here—there are 500 different possible opportunities for you to appraise, that would be a very, very good number. That would be a tremendous resource to look at in terms of what you want to do.

The second phase is actually the project management phase. That is done, hand in glove, with the industrial partner. So there's nothing really different about how we manage research and development than the way it would be done in industry.

The question was asked, well, how can it become cost neutral? Well, one reason it can become cost neutral for the industry partners is because some of the money to do the project actually comes from the

partnership, whether it's originally from the philanthropic donors, which is mainly the case in the U.S., or from governments, which is mainly the case in Europe.

So a key component of the partnerships is that they bring in money to do the R&D, to reduce the costs, the industry costs. Now the last but very important phase of the portfolio management is what you might call life cycle management.

When you already have a product, you want to get the maximum potential value from it. So, for example, there already is a quite good anti-malaria drug developed by one of our partners, Novartis, and we're developing a pediatric formulation with them, which they otherwise would not have done because there was no commercial incentive.

So that life cycle management component also adds value at a relatively low cost. Get the whole life cycle from appraisal to project management to life cycle management going, and you have a virtual circle. We know this is working and I think Mary's data has shown that it's working, and actually it's working better than most people thought.

But it's not only her report which shows this. On April the 6th, the World Health Organization published a report which was really to look at intellectual property and its relation to innovation and health.

And they also concluded that the main drivers for new product development in public health are these public/private partnerships.

So I mean, the data, I would say is overwhelming and compelling but it works. We still have not collectively, from a government policy point of view, particularly in the U.S., because I thin in Europe it's more accepted at the moment, that this is the way to go, have not really fully processed this data and come to the conclusion, yes, this is what governments should back.

Oh, I should say that at the Gleneagles G8 conference last year, all of the G8 countries did say that they supported the public/private partnership model. However, saying it and doing something about it is different. Some of the European countries have actually done something about it, have actually increased their budgets to support public/private partnerships.

I think in the U.S., there's still a certain amount of analysis going on, but certainly the U.S. has also signed on in the G8 statement to that objective.

MS. BRAINARD: Perfect.

Well, now I'd like to turn it over to the audience and I would love to hear from your colleague from NIH. We wanted to have somebody representing the public sector here this morning.

So I would invite him, wherever you are, to comment, if you'd like, and then also, Ruth, I'd like to put you on the spot in a minute or two,

if you'd like, to maybe talk about the advanced market commitments and how this fits with that.

Yes?

MR. WELLEN [ph]: Well, I came here to listen, not to comment, so my comments will be totally extemporaneous.

MS. BRAINARD: Nobody will hold you responsible.

MR. WELLEN: And I'm not here as—well, I am, actually, representing National Institute of Allergy and Infectious Diseases, and am in the mission of fundamental understanding of biology and the pathogenesis of malaria. Our section there has about 70 to 80 people and we do everything from fundamental genomic investigation of malaria parasites to and through its biology, the way the parasites infect children in Africa.

We have field projects in Mali and South America, and in Southeast Asia, where we interface our basic research with the clinical work that's being done in those countries.

We have colleagues and collaborators there. And so that's very much on the medical side of things. And we also have about half of our laboratory or department devoted to insect vectors of disease, these blood-feeding insects that transmit diseases, with most of the focus on malaria.

So our mission is very much fundamental research. Our interaction with the public/private partnership, and particularly with MMV now, is in questions of just how to bring this fundamental research into, and

advise MMV, which is my position on the board, how to bring this fundamental research into transitional developments and activities, and discovery of new drugs.

We also have colleagues, very close to us, who work in malaria vaccine development grants. So we also are cognizant of vaccine development.

And we also work and have had interfaces with industry in the past on how to develop new diagnostics for the disease. So one of our works in the 1980's and 1990's was in the dipstick test that's now used for malaria. It sometimes replaces the diagnosis of [?].

So what we found of very much value here is not only the rich rewards, professional and the like, in seeing basic research brought forward into practical aspects of malaria control and disease prevention and treatment. But also, what we find here is a bridge, and wearing another hat, I've been able to work as an adviser for a group within this department, that had a fundamental discovery, a new target for drug development and the question was how to bring it forward, and we were stuck.

Clearly, we didn't have the pharma component with the major pharmaceutical—so we were able to reach out, and this particular individual, through an application to MMV, was able to go before the scientific advisory board. I was in recusal on this particular one, as Chris will remember.

And then bring it forward and ask the scientific board, and MMV, now, how to interact, and it's now in some discussion with Trace Kantos [?], GlaxoSmithKline, how to bring this fundamental discovery now, and candidate leads that might work in this way. So I was very much interested to come down today and listen to the conversation, and realize there's much strength in these partnerships and, in the future, I think if continued funding, they're going to continue to grow and have a very strong impact, public health-wise in developing countries.

MS. BRAINARD: Thank you very much.

Ruth, would you care to comment? The financing questions have really been put front and center on the table, and you spend a lot of time over at CGD working on these issues. I'm wondering if you wanted to make a comment.

MS. LEVINE: Yeah. I'm Ruth Levine from the Center for Global Development and we did some work on the advanced market commitment, which is fundamentally a pull mechanism, in the case that we worked on, and Lael, you were on that. That working group, we looked particularly at developing incentives for industry engagement in the development R&D, and then scaling up manufacturing for vaccines, for problems that are primarily affecting developing countries.

So it was a little bit different sort of focus in terms of vaccines versus drugs, and as Jerry said, the vaccine world does have some important

differences. I also came to listen and maybe to ask a question or two, and not so much to comment.

I think we're working on putting together a session where there will be a more direct discussion about the pros and cons, and potential complementarities between the pole and the more PPP "pushish"—I know it might not be how people want to characterize it—but approaches around the time of the Global Health Council. So we'll keep people apprised of that. So then there'll be time for sort of a more formal and detailed discussion.

A couple comments, though. I think one of the sort of minor breakthroughs that we helped contribute to in our work was to try to move away from a kind of push or pull set of discussions, and what we found was that there was a lot of both good substantive conceptual and empirical reason for thinking that both push and a pull mechanisms are valuable, and certainly the PPP's among those.

But that making a strong sort of case in one direction or another was, at least in the case of vaccines, probably not ideal, and as I said, there's a lot of receptivity for kind of breaking down that distinction. So I hope that that can sort of, going forward, be the spirit of the discussion. So that we'd be looking for where the real complementarities are and where one approach might dominate versus another. Or in concert with another or something.

I'd like to make a comment about one interesting sort of theme that came through in the presentations, all through perhaps.

And that was this concept of the importance of an industry mindset in the management, the decisions, I guess, about which of the possible candidates to support, because, Chris, I don't know, I'm not close to your work, but my understanding is that you've been so successful, that you have a number of entities that are at a point where it's time to move them into large-scale trials perhaps?

Again, you're obviously in a better position to focus on that. But, clearly, at some point, you can have, you know, 500 entities, molecules being developed, and at some point you have to make really hard-nosed decisions about which ones to push forward to the expense of clinical trials and beyond, to licensure.

And then which are the follow-ons that might improve over the first to market, to make a best market. And in that, clearly, I think Mary, everybody has said, having an industry mindset is crucial to the success and the efficient use of capital, be it from public or private sources.

And so I'd actually like to hear from whichever panelists would be interested in talking about that. What does that really mean, industry mindset? Does it mean that you have an MBA? Does it mean that your pay is linked to whether you get to first or best to market? What does that industry mindset really mean, because I think that's partly at the heart of

what we're talking about in an interesting way. So anyway, that's also a little teaser for the event that we're hoping to put on around the time of Global Health Council, and Lael, maybe we'll talk to you about doing it in conjunction with Brookings.

MS. BRAINARD: Did you want to—Mary, Chris—anybody want to comment on this last question?

DR. HENTSCHEL: Well, sure. What is an industry mindset? Well, I mean, the first thing to say, and I think Jerry already mentioned it, is that a lot of the staff who manage the public/private partnerships actually come from industry as did I, although I worked in the public sector as well.

The group that gives us scientific appraisal, although it certainly contains actors from the traditional public health bodies like NIH, actually, ours has always been chaired by somebody from industry.

So the original chair of our advice came from Pfizer. The current chair was originally in Wellcome which became, eventually, a part of GSK.

And they all come with an industry way of thinking about how do you make decisions, not only about whether drugs are, or potential drugs are suitable for bringing into portfolio, but are they making progress—

[Start side B]

DR. HENTSCHEL: [in progress] very importantly, how do you kill projects? Because one of the traditional problems in the public sector

has been the sort of, well, you know, let's try something else, or let's try this or let's try that, and it goes on forever.

Well, unfortunately, we can't go on forever with all of our projects. If they're not meeting milestones, we have to kill them, and we operate exactly like industry in that way.

DR. SADOFF: I'd characterize the industry way of thinking by three major points. The first point is that there's sort of an eternal triangle between time, risk, and resources. So that if you want to shorten the time, you can take more risk but put more resources on it.

Or you can lengthen the time. And so time is an absolute critical variable in the mindset of industry. The second point I characterize as industrial thinking, is everything's oriented around a product profile. In other words, you look at your customer, you decide what your customer needs as best you can, you match that up with what's technically and scientifically feasible, and then you go after it, ruthlessly, and to the exclusion of every other good idea.

In other words, ideas are bad, creativity is bad, once you set your product profile, because it destroys your focus.

So that's a characteristic of it. But I will say this. I've developed ten vaccines that are licensed. Out of those ten vaccines, every one of them took 95 percent perspiration and 5 percent inspiration from

someone, not necessarily me; but someone. So there's a little creativity that made it all possible.

And then the third thing which is very important is manufacturability at a cost that can maintain whatever you want to sell it at for your product profile. That characteristic is where most—I was at Merck for eight years. I used to look at hundreds of projects, 90 percent of them went down on that factor—can't be made at a cost or in a reliable way, for the millions and millions, if not hundreds of millions of doses that you'll need.

Now there's many other characteristics, but I think those three are the essential, that I think of when I think of an industrial model, especially for vaccines.

MS. BRAINARD: Lynn, did you want to comment.

DR. MARKS: Yeah. Industry mindset, for me, really doesn't differ between diseases of the developing world and those that we do for more traditional market-based reasons. So we try to focus on a patient set with a medical need and make the decisions and drive the activities towards making meaningful contributions to the management of those patients. And in my meetings, there's no discount or there's no slack given to the group working on malaria or lishmania versus another disease.

The productivity targets at Trace Kantos [ph] for our discovery unit are no different than the targets for productivity at any of the other

research centers. The expectations are for quality, deliverables, and that's on my end of the business, which is on the development end—my deliverables are meaningful medicines in the hands of patients and health care professionals around the globe, as best we can do. It's not trying hard; it's not having lots of meetings. It's deliverables. It's medicine.

MS. BRAINARD: Questions? Yes. Please identify yourself and your institution.

QUESTION: My name is Nan Colby [?] and I'm from the Global Alliance for TB Drug Development where our product development partnership's working on new drugs for tuberculosis, and I have a question both for Chris and for Mary.

Mary, to start with you, and then maybe get a reaction from Chris. You talk about an incredibly exciting idea. You talk about a fund which will basically fund all of the existing drug PPPs to get products through Phase 3, which is the expensive part of clinical trials, and actually bring them to market. And you talk about a very low cost base. You're talking about, if I heard you right, $7 million per OECD government per year.

How would this work? Is this just sort of like a "big pie in the sky" GAD commitment thing? Or how would this actually work? Have you thought through that a little bit?

And Chris I know you've also been working with Mary, to some extent. Does this sound like a feasible, realistic idea in terms of funding of, increasing funding for a group like MMV?

MS. BRAINARD: Mary?

DR. MORAN: Yes. Obviously, we think it would work because what it's based on is many of the projections about what are made are based on theoretical portfolios, you know, what it would cost us to have a new TB drug every five years, or a new this or a new that, and we don't actually have those. So this is based on what we really have and what it really costs to take it forward, and the per-phase costs are quite low in drugs, much simpler than vaccines.

The reason it's so cheap is partly because the PPP model is very cost effective. I would like to come back to that in a minute, why is it so low? Because there's a point that I should make.

But the key reason the RFF is cheap is because it funds the most cost-efficient model. But these, because you don't need new infrastructure. How it works is that it reimburses existing PPP payments to industry. So all that structure of making contracts and putting payments together and paying them out, is already done by the current system. That's what PPPs now do.

You need a very simple, almost like a bank account function, I suppose, to do the reimbursement process. I think you need a very small additional layer to take that payment information and analyze it for donors,

to explain to them what you've paid out, where it's gone and what you're getting for your money.

So I think the reason it's effective, as I say, is because it's funding, not trying to create a whole new model, which is expensive, but funding an existing model that's very efficient, and then using the existing structures rather than superimposing these structures on top.

MS. BRAINARD: Chris.

DR. HENTSCHEL: I think if we talk about costs, it's very important that people understand, you know, compare apples with apples. So there's no doubt that our out-of-pocket costs are not nearly the kind of costs that it takes within industry to develop drugs. But if you look at it, the differences aren't quite as big as it might first seem.

First of all, a lot of what we do is leveraged by industry in kind contributions. In MMV's case, it's probably at least one to one. So every dollar we put in, we probably get an additional dollar from our industry partners. And secondly, we don't count opportunity costs at all. Of course industry has to count opportunity costs.

So if you actually looked at all of these things, then yes, we would be cheaper, but not nearly as much cheaper as just the, you know, we tend to say in our business plan between 150 and $200 million is what we think it takes, including the cost of failures to develop a new anti-malaria drug.

If you look at the industry figures, they tend to be quite a bit higher than that. But then if you look at them, more or less in the same way, then the differences aren't quite as big.

Now are there policy ways of developing new sorts of money? I mean, I think the really amazing thing is that we're talking collectively, globally, from the OECD, such small amounts of money, that it's a little sad that the governments don't just say great idea and cough up. Some of them do but they're relatively few that do that.

Mary has one particular idea, an innovation—a new bit of idea of how to raise this sort of money. To be quite honest, I get a little scared about new ways of raising money, because I think that what we should be doing is really going to governments and saying, Look—whatever mechanism you have, this is money well spent. If we spend another year, or two years analyzing new ways of raising money, to me, that's two years lost, and that is one of the reasons why I get a little nervous, whether it's ABC's, or even Mary's group. These are not very large sums of money.

Within existing mechanisms, we can raise these sums of money, if there was a political will to do so, and I think the real breakthrough is getting the political will to do so.

DR. MORAN: Can I comment on that?

MS. BRAINARD: Sure.

DR. MORAN: I take Chris's point entirely. You can spend a lot of time, and a lot of patients wait while we get the money. The reason we propose this is because it doesn't require something new. But the idea—we see this as running alongside direct funding, and in some ways, I do have hesitancies about giving all money to PPPs by direct funding, and the reason is that our data fairly clearly shows that some groups perform better than others.

Now if you give money straight to ever group, your group's a good performer, you know, everyone's happy that the money's well spent.

Other groups who don't perform, we've designed the RFF to fund high-performance activities and to kind of force people towards those. So if groups say, actually, my preference is to use an unskilled academic, or I'd like to find a developing country partner, or I'd like to try some new approach—and groups do do that. We've got projects where people have done that. Then you're perfectly free to do that but we don't fund that.

We fund you to hire the most skilled person. If you want medicinal chemistry, you get an industry medicinal chemist. If you do project management on trial, you get a CRO that knows about trial project management.

The advantage of that is that if you improve efficiency on that side, then your core funding is also used much better. So when you core fund, you're funding more efficient groups.

So I take the point that let's just pay everyone for everything. It's public money and I think it should be much more proscriptive, that it's used properly, and much more closely monitored. So sorry about your [inaudible].

[Laughter]

MS. BRAINARD: It sounds like there's two [inaudible] that Mary's really proposing here. One is the mechanism of actually raising more public funding, and the other is how do you distinguish, and for some of the donor governments they probably don't have as much capacity and so there's a quality control mechanism that you're putting together.

Amanda, yes?

MS. GLASSMAN: Can I ask Mary a question? Is there a government that's taken this idea on, on the potential proposal?

DR. MORAN: Bless you. We only put the report out fairly recently, and then I moved to Australia which is lovely. So we've started talking to people. Late December, we started talking to the PPPs and we started talking to companies in January. We only talked to two, Bifim [ph] and Dorstet [ph]. We went and talked to the Irish government, who got quite excited, and said we'd like to invite you back to give us, to talk about this some more.

So it's had a, yeah, it has had a pretty warm reception, and the reason we're here is of course the U.S. government already is the main donor to PPPs.

And, you know, a little bit of a leadership kick—and Gates, you know, a U.S.-based businessman, set the model up essentially and funded it, and a little bit of the kick from the U.S. to say to other countries, including the Europeans, you know, time to get—you know, they need to come to the table.

MS. BRAINARD: We had a question back here.

QUESTION: Peter Woeber [?] from the German Overseas Institute in Hamburg, Germany. The financial mechanism, it seems to me we do have to [inaudible] the global fund, which is a public/private partnership, mainly publicly oriented for the time-being and, obviously, this newer fund, I assume everybody has agreed that the findings of the study obviously are clearly agreeable, that number one, you have A, activities going on in drug developments which most people have overlooked in the last five years, and number two, we have a new development model that, indeed, from now on these kind of diseases can be better fought, if the second part is done by the public sector.

So if everybody agrees on that, then the financing shouldn't be that difficult, should it?

DR. MORAN: Yeah. Are you in government? We need a lot of money.

MS. BRAINARD: Does anybody want to—

DR. SADOFF: I think the idea is a good one, because anything that brings more money into this area I think is desperately needed, because there's still a market failure here despite what everybody says, and we need more money for pull and push.

But I would recommend that if this fund is run like a venture capital fund, by experienced people that know how to value, look at risk, rather than a government fund which is based on rules, I think it'll be successful.

What I'm trying to say is that every single project has individual characteristics about it, that will either make it successful or not, and it takes real instinct, not a set of rules, and fairness, to pick that up. That's why successful venture capitalists can pick good projects versus bad, and they have portfolios.

I don't think government is very good at doing that because they have to be responsible for every dollar, as you said, and you can't be responsible for every dollar because to pick good projects takes risk.

It took ten years to find out that this model had four good projects versus two. When you're making investments where 2 to 10 million people are dying every year, you don't have ten years to look to see what the

performance is, and therefore you need to have people, individuals, human beings, that can look at projects and take risk assessments like they would in their normal practice.

So that's my fear, that it'll become government rather than venture capital like. I'm not saying you have to take a bunch of venture capitalists and run it. I'm just saying people wit that kind of experience should do it. That's my only recommendation, because I think the whole thing is very good.

DR. MORAN: I have to say one of our recommendations is that it not be sited in government or in a bureaucracy, and some firms have already approached us, and the European Investment Bank as well, to say we'd be interested in helping to design it, because it should be small. I mean should be tiny. It doesn't need to be big. It's like a Visa statement. You know what you paid out and then someone analyzes your Visa statement for you and says, oh, this is what you did this month, this is what you got this month. So very simple.

MS. BRAINARD: Amanda, Chris and then Lynn.

MS. GLASSMAN: I just want to go back to where the funds come from, from the PPP, on the public side. If you look at the United States, how their contribution is being channeled, it's through the National Institutes of Health or it's through the Centers for Disease Control. SO it's part of specific research initiatives.

But it's not part of development assistance for health, which would be the logical place to get more magnitude on the financing, and I think the European donors, they're also having this discussion through their development assistance agencies, not through their research institutes, and so that's why we're seeing the small-scale increments. To make the leap to getting the, you know, the development assistance side involved, there's going to be, I think, a time where they need to get comfortable with these ideas because I don't think that they're accustomed to working with industry and with R&D in this sense.

So that's I think a major barrier. And I'd also like to ask back, why aren't venture capitalists coming to finance your PPP, given the potential market?

DR. SADOFF: Well, that's a nice question.

First of all, we don't want them.

DR. MORAN: You don't want them.

DR. SADOFF: A venture capitalist requires double the return on investment in the first five years and we are going to make a vaccine in seven years which won't give return on investment for at least ten years, and so therefore it wouldn't be reasonable for a venture capitalist to invest in us, I mean, and anyone that would I would think would be doing it for other reasons.

But that doesn't mean that there aren't funds in the capital markets that are going to be necessary, because in vaccine development, and I presume in drug development, although not to the same extent, at the time that you enter Phase 3 trials, that's the time you have to make a major investment of somewhere between 50, 150 to $300 million in manufacturing, at risk.

And if you don't do it at risk, then there'll be a large gap between the time that you get licensure and the time that you can deliver your product, which translates into lives in our case. Two million lives a year is not something acceptable when you've proven that a vaccine could save those lines.

So the at-risk capital that's really big is going to have to be made at the time of the Phase 3 trials and what's happening in the field is that because nobody's willing to make that investment at risk, including the HIV field, which is well-funded, people are talking about proof of principle trials, so that they actually have the data before they have to make the investment.

That's good. That's a good sound fiscal policy, except for the fact that every year, so many people are dying and this lengthens the process out by many, many years. And so this is a major issue. Venture capital type thinking and investment risk will save lives more than anything else.

Also, one little disagreement I have. Cause I come from the vaccine world, I don't know if it's true for drugs, but the cost of clinical trials in the Phase 3 for vaccines, we estimate for TB it'll be somewhere around 25 to $50 million for a Phase 3 trial.

I did a rotavirus trial that cost about $100 million and a herpes zoster trial that cost about $50 million.

So I mean, these are real costs, and the second point is except for product development groups, partnerships that have a lot of industry people in it, the product development partnerships have the expertise in the field but they don't have the GMP reporting, statistical analysis and data management expertise that's required, and that's what comes from industry, or extremely expensive CROs which, in industry, we don't like to use unless we have to.

DR. MORAN: I should have said that. When I said the public group, I had some pluses in the public groups predominantly due to clinical trials. But in fact what industry does is provide the regulatory backup, the data management, how to make sure that the trial results are solid enough that you get registration.

So that's not the most expensive component but a very important one.

The drug trials are substantially cheaper, I'm delighted to say, than vaccine trials.

DR. SADOFF: That's good.

MS. BRAINARD: Chris.

DR. HENTSCHEL: I just wanted to react a bit to the comment about the global fund. The global fund of course exists, it's raised several billion dollars. There are other funds that are involved in purchases like Petfar, here, in the U.S. There's another one specifically in malaria drugs. These are in fact pull mechanisms for R&D, or in theory, they ought to be pull mechanisms for R&D, because they are funds to purchase product.

So it's not as though pull mechanisms don't exist. They have dissipated into several different ones. But the thing is, those mechanisms, they came out of the commission for macroeconomics and health, a very large report that reported in 2001, and the report actually said we need two funds. We need a fund that is involved in the purchase and distribution of products, and we also need a fund for innovation.

Well, one happened and the other didn't. We're still here, six years later, talking about how we can get a fund for innovation.

MS. BRAINARD: Lynn, did you want to—

DR. MARKS: Briefly. All I wanted to react to was the implication that by being on the panel we endorsed everything in the study, which wouldn't be accurate.

As I told Mary, I found it refreshing, well-researched, comprehensive, and when I read the full report on the airplane from Croatia

yesterday, I still had those feelings. But there are elements in there that I don't know if they connect well or not. And so I don't want just pure being on a panel as being a blanket endorsement of a proposal, because we probably wouldn't agree, you and I, on every aspect of that, because you're trying to represent industry in large chunks, Big Pharma, smaller companies, and inside that, as your report notes, there's much variability, even among the large companies as to rationale, the drivers, what incentives and what plans we would participate in and which ones we wouldn't.

MS. BRAINARD: It wouldn't be a panel at Brookings if everybody on the panel agreed with each other cause that's a hallmark of Brookings, that we try to get different points of view. Or at least my part of Brookings, which is the Global Economy and Development Center.

We're sort of running out of time, so I'm going to take one more question over here, and then I'm going to give you all a chance to respond to the question and give us your last minute or two of wisdom on the topic. So right over here.

QUESTION: [off-mike]

MS. BRAINARD: That's fine.

QUESTION: My name is Roy Withers [ph]. I got three short comments on this cause it's an area I worked in a little bit. I agree with Mary's analysis around the need to fund product development partnerships more. I think they're a proven mechanism. But I would think more needs to

be thought about in terms of distinguishing structures for channeling money and motivating people to give more money to particular things, and the history, as Mary says, is that a certain number of governments have funded product development partnerships but there's quite a range of governments, particularly European governments, we needn't name any, that are still ambivalent, at best, that public/private partnerships simply channel money to industry for things that industry should be doing.

So I think one needs to better articulate why product development partnerships are the preferred mechanism and what they add, in addition to getting the money to industry.

The second point I think, Mary might want to go on and do another study. This question of industry, no profit, no loss, is around manufacturing, but I think there are enormous benefits to industry that industry acknowledges in terms of economic benefits, in terms of [inaudible] recruitment of staff, positioning with corporate social responsibility, a license to operate with regulatory agencies.

If we understood better the precise benefits of industry collaborating in these sorts of things, I think we would be better able to recruit industry to collaborate.

I think thirdly, since product development partnerships are in competition before the Millennium Development goals are going to be reached, with applying existing tools, the argument about what benefit can

come from investing in product development partnerships needs to be cast in terms of public health benefit that can be achieved relatively quickly, not in terms of product registered in a particular short time. The public health benefit comes ultimately from applying these products.

MS. BRAINARD: Okay. What I want to do is ask each of the panelists to give us their final comments, and feel free to react to the last comments.

I also just want to put another question on the table which is Mary's really focused our attention on the last five years as being a time where we've gotten a discontinuous change in this field with a lot more innovation against these diseases, and we've just heard the governments really aren't doing a whole heck of a lot more here.

So I can't help but ask the question, Is this simply a Gates effect? Is this a philanthropic community effect only, on Gates, plus some others, and if that's true, I mean, I think that leads us to make some conclusions about the power of financing to be able to really change this landscape.

Let me start perhaps in reverse order, so that Mary has the last word, and start with you, Jerry.

DR. SADOFF: Okay. First of all, I think this is a new era in developing products for the developing world. I've been working on these, in one way or another, for 30 years, and I see this as the most exciting time

that we've had, and this is due in part, in answer to your question, for two reasons.

One, we're on a very steep technology development curve, in other words, we're learning how to do things a lot better, a lot faster. That gives us tremendous opportunities to actually bypass the old structures and pick up new structures.

For example, we've developed an entirely new viral vector growing bacteria that can be given earlier and produced for pennies, that could make these vaccines—this whole problem go away. So that's new technology to try and solve a problem.

Now people criticize people that say technology will solve the world's problems because part of the world's problems are due to technology.

That's true. But we should take the advantages of technology that offers us and try and make it for what it is. And that's my second point, in answer to your question. That's what Bill Gates believes. And I can't speak for him.

But I think he believes, aside from all the other things, because he gives $750 million every year to the global funds. So he believes in using the tools we have now to help public health.

But he still believes, strongly, that the new technology will overcome these problems in ways that we can't envision. Just like

computers and everything else have changed the world, technology will change the world here.

And that leads me to one other point I'd like to make. None of this would be possible, none of it, without the fundamental research that the NIH and European agencies have put into just understanding the basics of biology, which has led us to be able to do any of these things.

And I want to make sure that everybody realizes that unless that support for basic research continues, this technology curve will collapse, because it's based on that fundamental research which is not necessarily oriented toward a practical problem, that all the practical things, all the vaccines we've made, so quickly, are based on NIH and European funding of basic research which we can build on as a product grew. So the final thing I'd like to say is I strongly believe in new technology.

I think it can help but not completely solve the world's problems. But of course that wouldn't be me, if I didn't believe that.

MS. BRAINARD: Lynn.

DR. MARKS: Just three quick points. One, thank you again for allowing me to participate on the panel.

Second. I don't know if it's all because of Bill Gates. My bias is there's been a change in conscience, in terms of the way people think, the way corporations behave, the way lots of people are engaging with the crises around the planet.

We had already decided to dedicate the facility, Trace Kantos [ph], to malaria and tuberculosis, before we ever had all the details ironed out with Chris as to how that would work with work with the medicines for malaria venture.

Much less with Maria Freire, and the TB Alliance, where we hadn't even started discussions with her, and we already decided to dedicate that center to it.

And also lymphatic filariasis donation programs, and things of this nature, all occurred before the philanthropic donors.

But I do believe that through the philanthropic arm, the third point being, for me, the biggest differences are now in the age of public/private partnerships, if we get a lead coming from somewhere, NIH, or academics, or wherever, we have a facility where chemists and biologists are dedicated to trying to do the lead optimization work and candidate selection work inside of that, focusing on malaria, and if we have an anti-bacterial that looks like it's good for respiratory tract infections or other areas, that might have activity for tuberculosis, rather than just taking it through for the primary indications around respiratory tract infections, and hoping that it has anti-tuberculosis activity, now very early on, we can decide to take that chemistry and split it off, and optimize it for tuberculosis, optimize it for the harshest conditions, storage-wise around the

planet, try to drive out drug-drug interactions, get down the cost of goods on it to levels that are applicable for those most in need.

So that's the biggest tangible difference in my day to day activities, based on the public/private partnerships.

MS. BRAINARD: Amanda.

MS. GLASSMAN: Well, I think that it's clear that the time is ripe for a lot of lobbying, and it seems to me that some major decisions are being taken by the international assistance agencies, and that perhaps there's a need for the PPPs and industry to come together around some kind of proposal that would allow government to structure their contribution, because one of the suggestions in Mary's report—and I don't know how our representative from GSK would like this—is to say okay, we're going to give a commercial drug fast track and you're going to use the savings to capitalize this account.

So that's one possibility. You probably have a better—that's how—I read it very quickly.

But it seems to me that government is not playing its role in this field.

MS. BRAINARD: Chris.

DR. HENTSCHEL: We have to be ahead of the curve in our strategic thinking and I think Ruth Levine asked the question, is it true that we have a number of things in late development? Yes, it is absolutely true.

The expectation is that a number of them will be registered or licensed over the next several years.

And what we have to start thinking about now is not just how do you pay for clinical trials but what happens after you have these registered products? Because I think if you look at the database that Mary has put together, you realize that there's going to be a lot of new products, and we haven't really, as a community, figured out how this is all going to work downstream.

Within NMV we're starting to do a lot of thinking with our donors. I think what we already realize is that we can't just hand over products to the big global agencies like WHO and the various other global actors, and that what we really need is to continue to have this public-private partnership model, not only for the R&D phase but also for the downstream access phase.

MS. BRAINARD: Mary, bring it all together for us.

DR. MORAN: Everyone said it already. I think I agree. It's just a new opportunity and change is hard for people to recognize sometimes, and that's why we did the report, really, to say to people it all looks so complicated but if you sit down and look at it, it looks like this.

And the way it looks is very good. So I suppose my plea is now for policy makers, especially, to sit down and perhaps have a look at the information and say, what does this tell me? Should I think differently?

And I think we should. And what's my new policy direction? And that would be, I think, a fantastic outcome, including from today.

MS. BRAINARD: Well, thank you very much. I think this is one of the most positive global poverty events we've held in recent days. So I hope everybody will walk out of here with a renewed sense of mission and join me, please, in thanking our panelists for a terrific discussion.

[END OF TAPED RECORDING.]

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