SECOND DISCUSSION

ARE ADVANCE PURCHASE CONTRACTS THE ANSWER ?

11 November 2004, 13h12

Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum
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This posting was submitted by: "Muge Olcay" olcaym@who.int

Are advance purchase contracts the answer?

A proposal for accelerating vaccine research has been made by a Working Group sponsored by the Centre for Global Development. It is available on our website at the following link: www.who.int/intellectualproperty/submissions/en.

The basic idea of this is simple. Governments, international organisations and other possible funders such as foundations would enter into a contract which would promise the developer of a vaccine (with defined characteristics) a guaranteed market at a price which would reward investment in the R&D necessary to develop such a vaccine. A specified number of doses would be purchased at this (higher) price. Thereafter the contract would specify distribution at a cost-plus price.

As a concrete example, it is proposed that sponsors (funders) would make a legally binding promise to pay 90% of the cost of up to 200 million treatments for a malaria vaccine at $15 a dose (i.e. $3billion in total). This is intended to mimic the working of the market for a sub-blockbuster drug. In order to qualify, the vaccine would need to meet various technical requirements concerning efficacy, duration of protection and others.

The idea of this scheme is to stimulate R&D on vaccines needed by developing countries, but to reconcile through the tiered pricing scheme the incentive for R&D with the objective of affordable access in developing countries.

But there are many issues in making such a scheme operational:

- Specifying the exact characteristics of a vaccine to qualify for the "prize". In the real world, there will always be uncertainties as to whether or not these had been met.

- A Committee is proposed to rule on such matters, independent of sponsors or companies. Would such a committee have sufficient credibility? Would it not become politicised, given the potential rewards at stake, and the potentially conflicting interests of sponsors and companies?

- Will potential funders, governments or non-profits, be prepared to make cast-iron legally binding promises in the undefined future to potentially large financial commitments? Even if they do, can one guarantee that their successors will not try to avoid such commitments when they arise?

- Given the uncertainties generated by the above, are companies likely in practice to shift resources to work on vaccines needed by developing countries?

There are many other issues but these seem to the Secretariat of the Commission to be key ones. We would welcome other views on this particular scheme.

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12 November 2004, 00h05

This posting was submitted by: Jeffrey Williams

Muge and all,

Respectfully no I don't believe that "advance purchase contracts" are the answer, as such implies a market fixing quality that has ramifications that could easily be detrimental in terms of cost, and supply. Ergo a supply side approach that dramatically effects costs usually upwards. This would in turn have the effect of making all essential drugs or other goods and services that have great demand, limited by predetermined contracts that would adversely effect those in need the most unable to afford the essential drug/service/good.

Regards,

Jeffrey A. Williams

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13 November 2004, 05h04

This posting was submitted by: "Aidan Hollis" ahollis@ucalgary.ca

Advance purchase contracts provide an excellent method to enhance our existing patent system. They allow for innovators to anticipate obtaining a substantial return on an investment into a vaccine. As I understand the proposed mechanism, a vaccine authority would stipulate vaccine characteristics, including effectiveness, side effects, morbidity, ease of vaccination, pricing, and a co-payment to be made by the vaccine authority, in advance. Innovators who developed such a vaccine would be free to take up the offer if they wished to do so. The anticipated price would presumably be approximately average production cost, with the co-payment by the authority adequate to provide a suitable risk-adjusted return to the innovator.
Assuming 200m doses provided, the idea is that the co-payment would be around $15 per drug, or about $3bn. The innovator would be required to continue to price the vaccine at approximately cost for doses above 200m.

The key benefit of this proposal is that it would likely draw extra resources into developing vaccines which met the pre-specified technical requirements. If no suitable vaccine was developed, then no money need actually be paid, so that it is a case of pay for performance, an important characteristic of any scheme trying to elicit effort when the costs and abilities of firms are unknown.

The key problem to such a scheme is that it requires the authority to know in advance the characteristics of the vaccine, including effectiveness, side effects, duration, costs, etc. But are these things knowable? It might be more attractive, in such a circumstance, to promise different co-payments, depending on the characteristic of the vaccine developed. Those which are better should receive more, and those which are less effective should receive a smaller reward. In addition, it is possible that other treatments for the relevant diseases might appear -- for example, a course of drugs which eliminated the parasite effectively. Such drugs would fail to meet the terms of the purchase commitment, of course, and would not be eligible, although it might be desirable to stimulate development of those drugs too.
So it would be helpful if the purchase commitment could include other medical innovations which addressed the relevant health needs.

There is an alternative model which could address exactly these concerns: a model in which any patented medical innovation which was useful for treating the diseases of concern -- tuberculosis, malaria, schistosomiasis, and perhaps HIV/AIDS -- would be eligible to receive rewards for treatment of those diseases in developing countries, based on the incremental therapeutic effect of the innovation on health status in those countries. To ensure low-cost pricing, and to claim the rewards, the developers would have to give up patent protection in those countries. The reward to the innovators would come entirely from rewards paid by the authority to the innovators. Instead of specifying technical characteristics, price, etc in advance, the rewards would specify the desired health impacts (eg, an increase in QALYs).
A vaccine or medicine which had small sales, or had only small impact on health status, would receive small rewards; a vaccine or medicine which had large sales and a significant impact on health outcomes would receive large rewards. A more complete description of the sort of scheme proposed is provided at http://econ.ucalgary.ca/fac-files/ah/drugprizes.pdf (revised Nov 12 2004)

One criticism of the scheme I am proposing is that it is difficult to determine what the health impact of a given vaccine or medicine is at the time it is given. Admitted. But then how hard is it to know the health impact of a vaccine before it is even developed? This latter problem is the problem facing the advance purchase commitment scheme.

The proposal described in my paper (above) suggests a complete reform of the system of rewarding drug innovation. A much more modest implementation of it would, I think, be comparable to the advance purchase commitment. A reward program could be set up which would offer rewards for medical innovations relating to a specific disease, such as malaria. Any new patented treatment of malaria would be eligible to attract rewards, with total payments set at say $200m per year, for a period of say 20 years. Firms would have a choice between keeping their patents witih no reward, or allowing zero-royalty licensing in the relevant countries and obtaining a reward. The $200m would be divided between treatments based on their incremental therapeutic effects in the selected countries. It would be necessary to make estimates of these incremental therapeutic effects, based on the effectiveness of the medicine and the total amount of the medicine or vaccine sold.

I want to address a few of the questions posed by CIPIH below.

One of the problems with advance purchase commitments is the uncertainty of meeting the authority's technical and pricing requirements. My proposal does away with that concern, since the only relevant criteria are whether the drug or vaccines are sold widely and are therapeutically effective.

The authority dispensing such rewards (or deciding on whether a vaccine
qualifies) would likely face considerable political pressure. However, pricing authorities such as Australia's PBS have successfully faced down political pressure, so this appears to be possible.

I hope that these comments will be helpful in thinking about the advance purchase commitments proposals, which I believe would in any case be a significant step forward. I would welcome any response.

Aidan Hollis

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14 November 2004, 03h30

This posting was submitted by: "Aidan Hollis" ahollis@ucalgary.ca

Jeff,

I don't believe that my proposal requires any giving up personal medical records. At most, it might take surveying of doctors as to how they prescribe, but IMS Health already does this.

To everyone else, sorry to fill up your inbox; but I didn't want to leave this uncorrected. If you have questions about the proposal or seek clarification, I would of course welcome a direct email.

Aidan Hollis

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14 November 2004, 04h10

This posting was submitted by: Jeff Williams jwkckid1@ix.netcom.com

Adian and all,

The biggest problem I see with what your proposal requires is that the patient has to give up his/her medical and personal privacy in order to be treated with these lower cost developed vaccines. That is far to high a price as well as far to big of a risk to receive said treatment at a reduced price and one of the biggest risks is that of identity theft of misuse of those medical records...

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14 November 2004, 05h42

This posting was submitted by: Jeff Williams jwkckid1@ix.netcom.com

Adian and all,

Ok thank you Adian for your clarification... My remaining question would be than, what specific information would the doctors be ask to provide regarding how they prescribe that would/would not require patient specific data? I ask this because most patients have nearly unique other complications, or at least most would.
Hence leaving the at least a possibility that some specific patient medical information would be necessary given MRI complications ect...

And BTW I believe discussing this in the open is advantageous as well and informative given that this is a "Discussion"...

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16 November 2004, 06h07

This posting was submitted by: "Tarcisio Hardman Reis" thardman@uol.com.br

Dear Mr. Muge Olcay,

After having recently finished a paper about the WHO and the legal aspects of immunization policy and after having quickly reviewed the draft submitted by the Center for Global Development I'm of the opinion that although the financing of future vaccines by a partnership might help the development of new vaccines, there are some legal aspects that may challenge its implementation.

As the project showed in the draft implicates in government financing of private companies. I understand that Advanced Purchased Contracts might be considered as subventions for the purposes of EU and possibly represents unfair competition for WTO.

Regarding the creation of a Committee to rule such matters, the implementation of a committee with both the financial and political power to implement a series of decisions in order to adopt advance purchased contracts is unable to exist neither under WHO nor WTO Constitutions (although there might have different opinions on this issue).

To conclude I understand that advance purchased contracts presents two legal difficulties:

1) Competition law
2) The lack of an international organization properly empowered to define the companies that are subject of those APCs.

Best Regards,

Tarcisio Hardman Reis

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17 November 2004, 06h16

Proposal is theoretically excellent. But how to overcome political and legal constraints? Is there any pilot project implemented of such nature? Harmonization of international systems and other IP related issues are widening opinion gaps between developed and developing countries. Approach towards these issues is becoming harder day by day. For example in India, new Communist supported government is again taking old stands. These practical problems are also be taken in consideration.

Avinash Ganbote

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19 November 2004, 00h56

This posting was submitted by: "Owen Barder" OBarder@CGDEV.ORG

Colleagues and friends

Thank you for taking the time to look at, and respond to, the Center for Global Development Working Group's submission proposing AdvancedMarkets as a way to stimulate R&D on vaccines.

I work for CGD on this topic, and I thought it might help if I responded to some of the points that have been made so far.

The discussion so far has highlighted some very important and pertinent issues. It is worth noting that some of the issues raised relate to advance purchase contracts generally, and that the particular proposal in the Working Group's report is somewhat different from other proposed advance purchase arrangements.

1. Is this interventionist market-fixing?

Jeff Williams expressed concern that government intervention would tend to result in higher costs and lower supply. There are good reasons to be wary of government intervention; but this particular proposal is in fact very market-oriented. It aims to create for neglected diseases the sort of market incentives that are in place for diseases of rich countries. On this proposal, Governments would not direct investment, and would only define product characteristics in the most general sense. Unlike other proposals for advance purchase commitments, quantities to be purchased would not be guaranteed, so firms must still produce high quality products to be sure of securing sales. The ideas is that private investment would underpin R&D by private firms, who would compete for a more lucrative market. Indeed, part of the goal is to limit the effect of Government intervention in the market for vaccines, which can drive down prices and undermine incentives for R&D.

2. Can governments make irrevocable commitments? Are there political and legal constraints?

Avinash and Muge both asked about this. The Working Group concluded that there are no obstacles to Governments doing this, for reasons set out in the report. Governments enter into long-term contracts all the time, for everything from aircraft to catering. One good example is the issues of Government bonds, which legally bind them (and their successors) to make payments in the future. Markets have no difficulty accepting these as binding contracts, even though future Governments could, in principle, renege on them. If the political will is there to do this, there are no institutional obstacles that would prevent Governments from signing such a contract.

3. Are there legal constraints, such as competition law or procurement rules, which would prevent this?

Tarcisio Hardman Reis was concerned that there might be legal obstacles to this. The Working Group believes that it has described a proposal which can legally be implemented by the US and members of the EU. The report includes draft legal contract term sheets, drawn up by experienced corporate lawyers, which illustrate how it would work. Some other schemes for advance purchase commitments might be problematic from this perspective; but this proposal contains sufficient competition. (If there any lawyers out there who think that this is wrong, and this proposal would not be legal, I'd be most grateful to hear from them.)

4. Can an arbitration committee be credible and independent?

It is critical for the success of this proposal that the private sector has confidence that the sponsors' commitments will be met; and that they will not try to evade them after a vaccine has developed. The Working Group proposes an independent committee to decide whether a product meets the specification, and is therefore eligible for the guaranteed price. This group would, at first, have no record or reputation to give it credibility. It is therefore important that the membership and institutional arrangements are sufficient to give private sector confidence. The Working Group believes this is possible, and has set out a detailed proposal in the report which have had positive responses from senior industry figures. But it is important to get this right.

5. Aidan Hollis has proposed a mechanism to create more general incentives based on the good that medicines do. Would that be better?

This is a very interesting, intellectually coherent proposal. It would require a more fundamental shift away from market-based rewards based on temporary market exclusivity towards a framework of Government payments based on an assessment of therapeutic value. I believe that it will be much harder to build a consensus for this approach than for the AdvancedMarkets idea, which is much more closely based on existing market principles. AdvancedMarkets has the merit that it would not require more general changes in the arrangements for the market for medicines: it could be introduced within, and complement, existing arrangements based on patents and markets. I do think that Professor Hollis's proposal should be considered further, however.

Conclusion

The points raised so far have all been very relevant and real concerns. The Working Group proposal has been put together with the help of experts in the industry, lawyers, public policy specialists, and global health specialists, as well as academic economists, with the aim of devising a proposal which is simple, easy to understand, and practical to implement.

The consultation draft of the proposal is at:
http://www.cgdev.org/globalhealth/proj_pull.cfm

We look forward to further comments on the proposal, both to inform the thinking of the CIPIH, and to help us to improve the proposal further for the final version of the report.

Best wishes

Owen

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19 November 2004, 14h28

This posting was submitted by: James Love james.love@cptech.org

Kremer has done a great service in renewing interest in prize fund models for supporting innovation, and exploring some practical issues.
However, in our opinion, the Advanced Purchase Fund, as proposed by Kremer and others, it not a good approach. It really does not capture the nature of R&D on neglected diseases, which has a strong public and non-profit sector role, and the high degree of variability in terms of the incentives needed to finish the important work of a broader community of researchers. It also suffers much, I believe, from the difficulties in engineer like definitions of outcomes, and poor understandings of drug development costs.

We are proposing, as an alternative, for the USA, a prize fund of 2 basis points of the US GDP, that would pay anyone who developed any treatment for neglected diseases, a reward based upon the incremental benefits to patients. This would be more along the line of what Hollis has proposed.

We do have some thoughts and are also working on what we think is the important and manageable problem of ensuring that early movers are adequately rewarded, even when products are eventually replaced by better drugs.

This is part of a larger framework for rewarding innovation in medicines. The neglected diseases component would be part of a larger package for medicine innovation prizes.

Jamie

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19 November 2004, 20h30

This posting was submitted by: "Aidan Hollis"

Owen Barder has argued that the advance purchase commitments could be more easily introduced within, and complement, existing arrangements and patents, than the proposal I had suggested in which rewards would be based on assessment of therapeutic value. While this is certainly true of a wholesale implementation of my proposal, there is a limited version of the proposal which would be optional, exactly as with the AdvancedMarkets idea, and would apply only to specific diseases. With such a limited version, I think that my proposal could equally be introduced within, and complement, existing arrangements. The differences between these limited proposals seem less about political/industrial acceptability than about the effectiveness of implementation.

Here are the key trade-offs as I see them.

* The AdvancedMarkets proposal is attractive because it has clear standards for payment, compared to the QALY approach. Firms know what their reward will be per vaccine sold as long as they meet the technical standards.

* The disadvantage of this is that it requires clear technical standards and does not necessarily reward vaccines which don't quite meet the standards, or drugs which have similar effects on health.

* The AdvancedMarkets approach also has smaller requirements for information, since technical standards are easier to verify than QALYs are to estimate.

It seems to me that the balance of usefulness between the proposals is therefore largely determined by the probability that a vaccine meeting identifiable technical requirements is likely to be developed, assuming the AdvancedMarkets proposal is implemented. If the probability of this occuring is sufficiently high in the near future, then that seems like the best approach, since an effective, low-cost vaccine would be ideal. If, on the other hand, there is a high probability that no such vaccine will be developed even with the advance purchase commitments, then there is a strong argument for the rewards to be available for a more diffuse set of treatments, as in my proposal.

Having said all this, I should add that I believe the AdvancedMarkets proposal would offer a large improvement over the status quo.

Aidan Hollis

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19 November 2004, 22h11

This posting was submitted by: "Owen Barder"

Colleagues

I thought Aidan Hollis's summary of the respective advantages and disadvantages of AdvancedMarkets and his QALY approach was very fair and clear.

I wanted to add one gloss, however. Aidan rightly notes that an it is an advantage of his proposal that it can be flexible in rewarding innovations which meet the desired criteria in part, or in unexpected ways. However, the AdvancedMarkets proposal that the Working Group has put forward does allow the independent arbitration committee (which decides if a vaccine meets the technical criteria) to lower the bar. This would enable a vaccine which substantively meets the desired criteria, but fails on a technicality, to be rewarded. (By contrast, the arbitration committee would NOT be allowed to raise the standard after it had been set, to reduce the risk that sponsors seek to renege on their commitment.) The proposal also allows potential developers to have a dialogue with the arbitration committee about whether the ideas they are developing are likely to be considered good enough to get the reward.

This means that Aidan's concern about the difficulty of setting a rigid technical specification in advance is met, at least in part, by the flexibility built into the AdvancedMarkets proposal.

Owen Barder

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19 November 2004, 22h38

This posting was submitted by: "Owen Barder" OBarder@CGDEV.ORG

James Love expressed scepticism about a using a prize, or Advance Purchase Fund, as a way to create incentives for vaccine development, because of (a) the need to set the right incentives for the varied community of public and private researchers that collaborate on neglected diseases; (b) the difficulties of specifying the desired outcome; (c) uncertainty about the costs of development; (d) the need to reward both early movers and subsequent incremental improvements.

These are all valid criticisms of a winner-takes-all prize, or an Advance Purchase Fund. However, the Working Group convened by the Center for Global Development is not proposing a prize or an Advance Purchase Fund. In fact, all these potential criticisms are explicitly taken into account in the design of the (rather different) AdvancedMarkets proposal put forward by the Working Group.

The AdvancedMarkets proposal is to create a viable market, in which developers are confident that they will be able to sell their product at a reasonable, guaranteed price; but there is no guarantee of the quantity that will be sold, and there is no winner-takes-all-prize. First movers would have the benefit of substantial revenues for as long as they are the only market supplier that meets the criteria, but other suppliers with better products can enter the market and compete, and so be rewarded for their incremental innovation. Furthermore, the idea is intended to complement other public funding of research and development, through grants, public private partnerships and other approaches.

I do not want to clog up everyone's email with a full description of the AdvancedMarkets proposal; a consultation draft is available at:
http://www.cgdev.org/globalhealth/proj_pull.cfm

As I think the earlier email exchange with Aidan Hollis suggests, the AdvancedMarkets proposal is much more similar to his idea than it is to a winner-takes-all prize for innovation.

If, having read the proposal, you think that it does not adequately deal with these concerns, I'd be happy to discuss this further, and to feed those thoughts back to the Working Group, for them to consider whether and how they can be better addressed in this framework. But as expressed so far, they appear to be a critique of a different proposal from the one that is being put forward here.

Best wishes

Owen Barder

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20 November 2004, 09h07

This posting was submitted by: Jeff Williams jwkckid1@ix.netcom.com

Terry, Jamie and all,

I would also have to agree with Jamie in his remarks and/or observations regarding the proposed "Advanced purchase" proposal and for other already stated reasons which I have provided for our members.

However the proposal to which Jamie is developing as I understand it thus far, also seem to suffer from a few realities and expectations that may or may not be either reasonable to assume or unrealistic as adequate incentive in order to achieve the goals the proposal seems to be attempting to achieve. That said, Jamie's suggested proposal does have potential if a few significant modifications are considered...

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24 November 2004, 21h10

This posting was submitted by: "Charles Clift" cliftc@who.int

Dear Participants

I am not sure of the status of this initiative, but please see the BBC News Report below. What Gordon Brown actually said in his speech was:

"The recent breakthrough which for the first time gives us a vaccination to prevent malaria that could be ready in three to four years time is a revolution in our time. The challenge is in an area where there are insufficient purchasers with funds we need to ensure that the vaccine does go into commercial production and is available at affordable prices. And therefore I can announce that the British Government working with other Governments is ready to enter into agreements to purchase these vaccines in advance to ensure a secure market and that the vaccines are available more cheaply and thus avoid many of the 1 million deaths from malaria each year."

Is it in respect of the GSK vaccine specifically? Or is it a general offer on the lines envisaged in the paper we are discussing? Is it anything more than a willingness to consider such a scheme?

Regards

Charles Clift
CIPIH

Britain backs anti-malaria fight
Gordon Brown has backed a global campaign aimed at tackling the malaria epidemic in the developing world.

The UK has joined with other nations in buying up doses of a new anti-malaria vaccine to ensure a stable market for the drug, the chancellor revealed.

Malaria kills around 3m people each year but there have been concerns poorer nations would not be able to afford the new vaccine.

Mr Brown described the new drug as a "revolution in our time".

'Affordable'

He told the BBC World Service Trust conference in London: "The challenge is in an area where there are insufficient purchasers with funds.

"We need to ensure that the vaccine does go into commercial production and is available at affordable prices.

"And therefore I can announce that the British Government, working with other governments, is ready to enter into agreements to purchase these vaccines in advance, to ensure a secure market and that the vaccines are available more cheaply."

The multi-million pound investment will take place over a number of years and may include aid organizations as well as governments.

Britain expects to purchase between 200 million and 300 million doses.

Placebo

The vaccine, developed by GlaxoSmithKline has few side effects and in trials in Mozambique prevented nearly 60% of cases of severe disease in children.

Each year in poor countries 500 million new cases are recorded - 90% of which are in Africa.

The majority of victims recover but the disease can damage the liver, kidneys and nervous system and up to a million of the three million fatal cases are children.

The trial of the new vaccine involved 2,022 children, half of whom were given a placebo.

Story from BBC NEWS:
http://news.bbc.co.uk/go/pr/fr/-/1/hi/uk_politics/4038377.stm

Published: 2004/11/24 12:45:17 GMT BBC MMIV

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25 November 2004, 12h07

This posting was submitted by: Michel.Pletschette@cec.eu.int

I wonder what this BBC transcript is about who has been briefing M.Brown as GSK has made very clear that altough the recent malaria vaccine trial results are very encouraging , the product still needs much further development and is not supposed to be ready before 2010.
The remark hit a point in the discssion about advance purchasing : who decide whether a product is ready, worth its money , better than alternatives etc ?

Michel Pletschette

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25 November 2004, 15h15

This posting was submitted by: Rachel Glennerster rglenner@MIT.EDU

As I understand what Brown is saying is that he will commit to purchase a malaria vaccine if and when it is ready for market. This will provide and incentive for GSK to put in the investment needed to bring it to this stage.
Clearly there are many issues that need to be worked through but this is a very exciting and encouraging development! It makes it much more likely that a product will be available in the next 5 years or so.
Rachel

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25 November 2004, 15h52

This posting was submitted by: "Maurice Nelson Graham Dukes"

From what I have heard about informal inter-governmental discussions on this issue, any government considering entering into such an arrangement will demand an extremely thorough and audited breakdown of the costs of research, development and production of the product in question, in order to ensure that the price being asked is fair. It is here that any specific agreement might run aground, since firms have as a rule been extremely reluctant to provide detailed and audited data to justify their prices, preferring the price to be assessed in view of the product's value in terms of public health (life years saved etc.)-

Graham Dukes

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25 November 2004, 18h39

This posting was submitted by: Rachel Glennerster rglenner@MIT.EDU

The idea of an advance market guarantee or advance purchase commitment is to avoid the problems associated with basing on prices on cost. Instead, before a product is developed policy makers decide what a vaccine would be worth (based on number of lives saved etc). They then say--if someone can develop a product that meets the following specifications (eg FDA or equivalent approval), we will purchase this amount at this price. An external committee is then set up to judge whether the products that are created meet these criteria.

Rachel Glennerster

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26 November 2004, 14h18

This posting was submitted by: Jon.D.Pender@gsk.com

A number of valid points have been made in this and other postings regarding Gordon Brown's announcement. The availability of funding is a key issue in improving access to medicines and vaccines in the developing world. Although Gordon Brown's announcement was not the result of any briefing by GSK, we welcome the commitment expressed by the Chancellor to deliver new funding. Commitments such as this, if structured correctly, are important in ensuring that, should a successful vaccine be developed, it is made available to those who need it most. They can also act as incentives to encourage R&D investment. We would be happy to work with the Chancellor, and his Ministerial colleagues around the world, on this initiative.

Jon Pender

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26 November 2004, 17h51

This posting was submitted by: TREVOR JONES

A) What happens in the hypothetical case that 2 or 3 companies develop vaccines that meets the pre-agreed criteria but Company 1 gets a product licence 6 months ahead of Company 2 and 12 months ahead of Company 3. The Company 3 vaccine turns out to be superior in efficacy to the Company 2 vaccine which is equivalent to the Company 2 vaccine ?
B) Which agencies would guarantee the cash and on what legal basis ?
e.g Suppose that a company decides in early 2005 to start a programme of work that takes 8 years to get to Product Licence and 10 years to market .How will the Company be assured that the cash at the end is GUARANTEED ..i.e in 2015 and beyond(assuming they are successful ?)

C) Would someone like to put up a few criteria now that would be regarded as the "conditions" that would be prescribed for success for a malaria vaccine ?

d) In the specific case of a malaria vaccine (and I appreciate that the proposals may have wider implications) would someone like to give a market size estimate for 2010,2015 and 2020 now please?

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27 November 2004, 20h32

This posting was submitted by: "Owen Barder" OBarder@CGDEV.ORG

Professor Jones asks some excellent and pertinent questions about all this.

I can't speak for the UK Government, but I can tell you how the proposal in the Center for Global Development Working Group tries to address these issues. Professor Jones's challenges to earlier proposals - particularly highlighting the need to take account of the evolutionary nature of drug and vaccine development - have been very influential in the design of this proposal. It is for this reason that the Working Group does NOT propose a "winner-takes-all" solution. His insight is part of the reason why the proposal aims to reproduce as closely as possible the incentives created by rich-country markets.

Q1. What happens in the hypothetical case that 2 or 3 companies develop vaccines that meets the pre-agreed criteria but Company 1 gets a product licence 6 months ahead of Company 2 and 12 months ahead of Company 3?

A1. In the Working Group proposal, the sponsors guarantee to pay the developer a pre-determined price for the vaccines they buy, but they don't guarantee how many they will buy. The sponsors commit to topping up token co-payments by developing countries. So while Vaccine 1 is the only vaccine available, it will sell well, and Company 1 can expect good revenues. But when Vaccine 2 is approved, and if it is a substantive improvement over Vaccine 1, then it too is eligible for the guaranteed price. For those markets in which Vaccine 2 is more effective, demand will shift to that vaccine, and Company 2 will begin to earn revenues from sales at the guaranteed price. The aim of this proposal is to simulate the conditions in industrialized country markets: a firm can expect to sell their product at a reasonable price, but there is no guarantee that a better product won't come along and cut into the market share. By guaranteeing the price, sponsors remove the problem that vaccine prices are driven down by the lack of available funds for purchasers, and by the public policy priority of ensuring access to essential medicines.

Q2. How will the Company be assured that the cash at the end is GUARANTEED ..i.e in 2015 and beyond(assuming they are successful ?)

A2. The cash would be guaranteed through legaly binding contracts (draft contract term sheets are in the Working Group report). It is not unusual for Governments to enter into legally binding contracts: think, for example, of issuing Government bonds (which are contracts to repay money at a future date): these are legally binding, and credible with the private sector. Goverments also enter into long term private finance contracts, and procurement contracts, that the private sector is happy to accept.

Q3. Would someone like to put up a few criteria now that would be regarded as the "conditions" that would be prescribed for success for a malaria vaccine ?

A3. There is a draft in the Working Group report (see pages 123-4). It could be something fairly simple and high-level: eg that it should prevent at least [50%] clinical episodes of Plasmodium falciparum malaria in infants and young children for at least [5 years], with no qualitative or quantitative exacerbation of subsequent disease; requiring 1 to a maximum of [4] immunizations; presented in multi-dose vials; with regulatory approval from an approved regulatory authority (eg the FDA).

It would be important that the experts from industry, the public private partnerships, the sponsors, and the public health industry, work together to finalize the technical specification.

Q4. In the specific case of a malaria vaccine (and I appreciate that the proposals may have wider implications) would someone like to give a market size estimate for 2010,2015 and 2020 now please?

A4. The Working Group report has not attempted to forecast the market in this way. The Working Group proposal is to guarantee to pay the guaranteed price (say, $15 per person in today's prices) up to a maximum number of treatments (say, 200 million). Together with some sales to other buyers (eg travellers, military, middle income countries etc) this would give a market size of around $3 billion in today's prices. This is a market size which is comparable with the sizes of industrialized country markets for which new medicines have been developed. The purchase commitment would therefore provide a reasonable market size for firms to target their R&D investment towards.

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Michel Pletschette asked who would decide if a vaccine was ready. Under the Working Gorup proposal, the technical specification would be set in advance and included in the contract (see above). An independent adjudication committee would be established to decide whether a product meets the specification. The decisions of the adjudication committee would be subject, if necessary, to legal challenge in court. (The reason for this structure is that it is important not to allow the sponsors to back out of their commitment once firms have invested in developing a new vaccine).

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Please note that the Working Group report is a consultation draft. CGD would welcome comments on these ideas and suggestions for improvement from the industry, potential sponsors and the public health community. The full draft report is here:
http://www.cgdev.org/globalhealth/

Best wishes

Owen Barder

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28 November 2004, 14h01

This posting was submitted by: "Sano" bcb12283@nifty.com

In this context of the guaranteed price, the limited fund and the access to innovative drugs, I would like to introduce you the Japanese Governments price setting for a new drug.
Japanese heath care system is funded on 25% from tax and 75% from public insurance.
So, Health expenditure is more strictly controlled due to being the fastest aging speed and long recession, but the pricing to medial fees and drugs is taken considerations into the balance of expenditure, quality of medical service and access to it. Then, in order to keep the balance of a limited beget and access to innovative drugs, Japanese Government applies the Comparator and Premium method to the official price setting for reimbursements to 2nd and later drugs below, and penalty rules to 4th and later drugs which are not eligible for any premiums(1)-(3).
(1) Innovativeness premium (40~100%*)
New drugs meeting A, B, C
(2) Usefulness premium (I) (15~30%*)
New drugs meeting A or C and B
(3) Usefulness premium (II) (5~10%*)
New drugs meeting B, C, or D
*Premium rate is determined according to daily cost Drugs which;
(A) Have clinically useful new mode/mechanism of action.
(B) Have been objectively shown to have efficacy or safety superior to the comparator.
(C) Have been shown to improve the therapeutic methods for the target disease or injury.
(D) Have been shown to have efficacy or safety superior to the comparator as a result of modification in formulation.

Example, the 1st drug is 100 yen and the comparator to the 2nd, if the 2nd drug has evidences to prove Innovativeness premium, it can obtain maximally 200 yen.

Takeshi Sano

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29 November 2004, 04h50

This posting was submitted by: "Kevin Outterson" Kevin.Outterson@mail.wvu.edu

I don't know why costs are relevant at all. Experience with rate-setting and strategic behavior by firms and regulators should give us pause before following that road. Net clinical benefit should be the standard.
Certainly we may have sincere reasons to view industry data with skepticism; we must demand global transparency on clinical trials data; we must grapple with the euro or dollar value of a DALY in a LMIC setting; but none of these indicts the wisdom of paying for performance rather than effort.

Kevin Outterson

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29 November 2004, 11h53

This posting was submitted by: "Charles Clift" cliftc@who.int

Dear Participants

The London Independent (see below)reports today that GSK, in a letter to Tony Blair, has suggested various other ideas to stimulate R&D on diseases mainly affecting developing countries. Do we have any views on these i.e. tax credits, fast track regulatory approval or "transferable exclusivity?

Regards

Charles Clift
Secretary
CIPIH

Glaxo tells Blair to press G8 for patents reform By Stephen Foley
29 November 2004
GlaxoSmithkline, the UK's largest pharmaceuticals company, has written to Tony Blair to demand new tax credits and patent concessions to encourage the development of medicines for the world's poorest countries.

The company is also urging the Prime Minister to use Britain's presidency of the G8 group of industrialised nations to strengthen global agreements on intellectual property rights.

The Government has said it will put the healthcare problems of Africa among its priorities for the G8 presidency, which begins in January. But GSK's letter highlights the difficulties of getting compromises in this area, and sets the scene for another showdown with non-governmental organisations such as Oxfam.

GSK, which produces some of the leading HIV treatments, proposes a system of "transferable exclusivity" for patents, where the development of a drug for a developing world disease is rewarded by an extension of patent protection for a developed world medicine.

This would, in effect, mean Western governments paying more for their most commonly used drugs to help subsidise medicines in poorer countries.

Jean-Pierre Garnier, GSK's chief executive, said the international community must find ways to incentivise the pharmaceuticals industry to produce life-saving medicines for tropical diseases where companies would not otherwise invest. GSK's letter also suggests the G8 adopt tax credits for developing world disease research and a fast-track approval process for tropical disease medicines.

Michael Bailey, senior policy adviser at Oxfam, said the G8 must not bow to industry pressure on the rigid enforcement of patent rights.

Meanwhile, GSK is poised to drop work on its drug Avandia as a possible treatment for psoriasis, the skin complaint.

Separately, a BBC programme this week will accuse GSK of backing drugs trials in the US in which underpriviliged children were forced to test Aids treatments against their will.

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29 November 2004, 15h15

This posting was submitted by: "Richard Mahoney"
Colleagues,

Congratulations to the Working Group for so diligently exploring the very complicated nature of the proposed AdvancedMarkets Proposal. Clearly it would be good to ensure markets for vaccines addressing diseases predominantly affecting the poor. I have read the Consultation Draft and have several questions to pose:

1. Within what legal body does the IAC operate? On p. 83 of the Consultation Draft, it is stated, "..product specifications set not by the WHO, but by an independent sponsoring group or adjudication committee." To be a party to a contract, won't the IAC have to have a legal personality? In what way will it be legally independent?

2. Since the recipient countries must make a co-payment, should they be parties to the AdvancedMarkets legally binding agreement? Don't the recipient countries, in effect, have a veto over the program? How would they wield this veto power? How many recipient countries would have to be parties to an agreement for it to have credibility?

3. Donors already know that vaccines are cost effective but have not met the needs of the Vaccine Fund. How does the AdvancedMarkets program change donors' views about the relative value of investing in different health interventions or in other development strategies? Do we know why they don't put up the funds required today to buy hepatitis B vaccine?

4. There a numerous references to consultations by the Working Group with industry. Given the rapidly growing capabilities of manufacturers in countries such as Brazil, China, Cuba, and India, why did the Working Group interview only the Serum Institute of India? Also how does the program account for the almost certain major changes in the vaccine industry during the coming 20 – 30 years? For example, what if by 2020 almost all R&D and production for vaccines needed in developing countries takes place in these advanced developing countries? Who predicted in 1970 that Korea would become one of the major developers and suppliers of hepatitis B vaccine by 1990? How could the computation spreadsheets take into account costs in developing countries?

5. Given the known failure risk of biotechnology firms, how does an AdvancedMarkets agreement involving these firms have credibility given the long lead times for vaccine

development? Will the existence of an AdvancedMarkets agreement on the books of a biotech firm raise or lower its value to potential investors?

6. How does the IAC distinguish a "me too" product? What if the only differences between the first and second products are that a) the second product is offered at a substantially lower price and b) the second product is produced in a country where the patents had not been filed for the first product and there were many developing countries that are potential users of the second product in which the patents for the first product also had not been filed?

7. Appendix C: Draft Term Sheet for Guaranty Agreement specifies that "The Designated Supplier shall own all right, title and interest in and to the Approved Vaccine." How can the agreement do this? Aren't patent rights (and other IP rights) granted by sovereign governments and aren't patents rights protected or voided in the courts of sovereign governments? What if the inventor chooses not to obtain patent protection (as mentioned above) in various countries of interest?

8. The Consultation Draft notes on p. 56 that the price would be per course and not per dose. To what extent is the cost of development and of production of a vaccine dependent on the number of doses required to achieve the desired level of protection? The proposed strategy is said to be justified because it will encourage developers to produce single-dose, long-acting vaccines. But what if the science does not allow this and yet the vaccine costs more than $5 per dose to produce (a three-dose vaccine course where the AdvancedMarkets agreement had laid out $15 for a course). To what extent has the Working Group debated the issue of a procurement mechanism seeking to drive an R&D effort?

9. How will liability issues be handled for the individuals involved, for example, as members of the IAC? Will the suppliers agree to hold these parties harmless in all jurisdictions for all causes? What if the suppliers are the ones to sue the IAC?

10. The issues with respect to legal aegis are illustrated by Appendix B, Draft Term Sheet for Framework Agreement. For example the "Representations and Warranties" section is indicated "TBD" (to be determined). It is in the Warranties that the signatories verify that they have the right and authority to make the commitments contained in the Agreement. What legal entity(ies) will have these rights and authorities? Governing Law is shown as New York. Will Cuba, for example, be able to participate in the program?

I presume there can be answers constructed to these questions (which probably reflect my lack of detailed knowledge of the discussions), but it is likely that each answer will have include many if's. It seems that the Next Steps section of the Consultation Draft is a bit premature. (I feel the tone of the document detracts from its credibility. It has a continuous optimistic tone indicating that all problems can be solved while in fact many of the problems have never been solved before and may represent insuperable barriers. The document should be more balanced.) Before major agencies should and would commit the required level of resources, the questions posed above and many others should be satisfactorily resolved.

In sum, I have two major concerns. First, the current strategy seems to lock out developing country companies for some time when in fact they may be the major sources of innovation in the future for health products for the poor in their countries: consider Cuba. Is it possible to arrange for these groups to participate from the start? As currently constructed, the program seems to discriminate against developing country producers in favor of large developed country developers/manufacturers. My second concern is that it seems more attention needs to be paid to issues concerning the legal aegis under which this program would be conducted. Vaccine regulation and IP are sovereign nation issues. (I use the term "sovereign" to include International Organizations such as WHO and the World Bank which must operate in accord with various treaties that have legal force. Foundations must operate

according to the laws of the countries in which they are based.) A good beginning would be to specify the exact legal status of the IAC even though that specification may lead to complex political considerations.

Again, I applaud the truly thorough and thoughtful effort of the Working Group but believe much more work has to be done to ascertain the feasibility of the proposed undertaking. The further exploration should set out clear go/no-go milestones for determining if further resources should be allocated.

I hope these questions and comments are helpful and recognize that the Working Group has probably addressed them in great depth.

Sincerely,

Richard T. Mahoney

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29 November 2004, 15h29

This posting was submitted by: "Kevin Outterson"

Tax credits are widely used in the US for orphan diseases. Criticisms include the industry practice of slicing the proposed market for a drug quite thinly to qualify for orphan status (in the US, less than 200,000 patients), and then expanding the drug to many other conditions after the orphan tax credit is received. The language in the US tax code permits the credit to be paid for drugs which are not really orphans in the traditional sense.

Fast track is also the current US FDA practice for innovative, priority medicines. The FDA has also promised fast track service for WHO PQ drugs which desire procurement under PEPFAR.

Transferable patent extensions are a very controversial and under-studied idea. Why offer a multi-billion dollar jackpot to a cholesterol drug for R&D on neglected diseases? This would mask the prize (pull) incentive by running it through the patent & reimbursement systems. A more transparent and accountable system would reward such R&D directly, and there are several major proposals afloat to do exactly that.

Kevin Outterson

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29 November 2004, 21h40

This posting was submitted by: TREVOR JONES

I am most grateful for these comments
Having now re-read the proposal I have some additional questions/comments

A.Government Committment

Based on their experiences to date ,the industry representatives expressed concerns over the operation of advanced purchasing schemes ..viz: 6.1

- Weaknesses in the current system of procurement and delivery of vaccines for the developing world are a major deterrent to investment. Most firms supplying developing

> country markets through public procurement are frustrated with inefficiencies in the current system – the lack of long-term credible contracts, unreliable demand forecasts, under-use of existing vaccines – and this reality colors their view of future promises from the public sector. The public sector can improve its credibility by increasing use of existing products and by improving demand forecasts.

Thus a GUARANTEED contract seems attractive.

Section 7 provides comments on only 2 government approaches ...USA and UK

Do you have any feedback from other government bodies on these proposals ;particularly with respect to such long term guaranteed commitments ?

B.Push :Pull

Section 2.2 provides examples of successful Push programmes .....but.....these were fro vaccines which ,arguably, use known technology.The difference with a vaccine fro say TB or Malaria .....and especially HIV AIDS is that the science is relatively unknown ..and hence "success" much less predictable.

Is it not preferable, therefore to ask sponsors (who would be those that eventually pay for the vaccines) to fund existing global /regional consortia /PPP's so to share the uncertainty and ,hopefully, accelerate the discovery /development programmes

e.g for Malaria a major injection of cash over the next 5 plus years into MVI and into EMVI (and perhaps others)

This would be a more tangible proof of sponsor commitment (as it is by The Gates Foundation) and could usefully "lock -in " donors to the eventual o,hopefully successful, outcomes

(Crudely "jam today please not a promise of jam tomorrow" !!)

c. **Sponsor's Commitment**

I am grateful for the figure of ,say, $3 billion as the GUARANTEE that would be the basis of a legally binding sponsor agreement for malaria vaccines (..note .. I now use the plural term !) .Indeed you did mention it at the IFPMA meeting in Barcelona

Do you have a total figure for a "bag of vaccines" for a few of the diseases for which we desperately need new vaccines (and indeed medicines)

e.g What do you anticipate would be the cumulative total sponsor commitment over the next 10-15 years for a collection of new vaccines for ,say only 5 diseases, ...TB ,HIV AIDS,Malaria,a multivalent pneumococcal vaccine ,dengue.

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29 November 2004, 22h02

This posting was submitted by: "Aidan Hollis" ahollis@ucalgary.ca

A comment on "transferable exclusivity" for patents ("TEP")

In this comment, I try to address the following questions. Is TEP efficient?
How would TEP work? Are there any better alternatives?

Some background, according to the Independent story quoted in full below:
[GSK, which produces some of the leading HIV treatments, proposes a system of "transferable exclusivity" for patents, where the development of a drug for a developing world disease is rewarded by an extension of patent protection for a developed world medicine.

This would, in effect, mean Western governments paying more for their most commonly used drugs to help subsidise medicines in poorer countries.

Jean-Pierre Garnier, GSK's chief executive, said the international community must find ways to incentivise the pharmaceuticals industry to produce life-saving medicines for tropical diseases where companies would not otherwise invest.]

*How would TEP work?
Since the lead time in developing drugs is so long, it appears that the only way TEP could work is if, upon development of a useful developing country drug, the patentee were to waive rights for exploitation of the relevant patents in developing countries, in exchange for extension of some patents in rich country drugs. This implies some process of negotiation between the patentee and rich country governments. The patentee would, for example, seek an extension of the patents on Lipitor in exchange for giving up patents on its new malaria drug.

How would TEP be different from simply buying off the patent rights for the developing country drug? If, as the Independent article suggests, this would simply involve Western country governments paying more for some drugs, so that the burden falls mainly or entirely on governments, then it is hard to see how this differs from a cash payment to the patentee. To the extent that some of the burden falls on consumers of the drug in the rich country, then the effect is to impose a special tax only on sick people in Western countries, which hardly seems desirable. (While governments may wish to avoid having all the burden placed on the general tax system, having a special tax on sick people seems even less desirable!) So it would, at least, be better to make a simple payment to the patentee.

To summarize, either TEP is formally identical to a simple payment to the patentee (if government pays the cost of all drugs) or it is relatively inefficient, since it imposes the burden of taxation on sick people.

If Western governments were simply to pay the patentee for giving up its patent rights for the developing country drug, then the question arises of how much it should pay. There are a number of mechanisms which have been proposed in the literature. Some well-known proposals (Kremer 1998; Shavell and van Ypersele 2001) essentially propose systems in which the patentee is compensated by just a little bit more than it could earn by exploiting the patent. However, if rich country governments pay only enough to compensate the patentee for giving up the patent, then the incentives will still be inadequate. What is required is a system of rewards which are not merely adequate to compensate the patentee for giving up the patent right, but actually incentivize R&D into drugs for developing country diseases.

How then, can governments determine how much to offer? (Note that even in a system in which no cash payments were made, but patentees were rewarded by extension of drug patents in Western countries, the same question would arise -- how large a reward should the patentee obtain?) There is one straightforward answer to this question: the rewards to the patentee for giving up its patents should be based on the health impact of the drug. In essence, of course, this simply implies a system of payments based on estimated QALY impacts.

A very important consideration here is that the size of payment must be determined in advance of the development of the developing country drug. If the payment is decided only after the drug is developed, firms are likely to be suspicious that they will be low-balled by Western governments, which may offer them just enough to give up the patents, but not really enough to have provided a proper incentive to undertake R&D in the first place. The result will be that firms won't have an incentive to undertake such R&D. Of course, it is not possible to determine the size of payment completely in advance; what is required is a system of rules for determining how large payments will be. This is, of course, exactly what is provided for in my proposal ("An efficient reward system for pharmaceutical innovation" available at http://econ.ucalgary.ca/fac-files/ah/drugprizes.pdf, particularly Section
6.9) or in the AdvancedMarkets proposal for vaccines.

Yours,
Aidan Hollis

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30 November 2004, 15h57

This posting was submitted by: "Georg Weizsacker" g.weizsacker@lse.ac.uk

As someone who was involved with CDG in the process of putting together the AdvancedMarket proposal (2003, I was a PhD candidate in Business Economics at Harvard then, working for the CDG working group), let me follow up on some discussion on this forum, particularly on Aidan Hollis suggestions and comments.
His very interesting proposal is close to an advance contract like the one in the CDG proposal, and I understand there are some major differences along the following lines:

- rewards would be promised not only for vaccines, but for any medical advancement with regard to a specific set of diseases
- the level of the reward is determined by the number of QALYs saved (or other benefit measure)
- to receive a reward, an eligible industry player would have to give up patent protection

Lifting the restriction that the program applies only to vaccines (as Hollis suggests) seems to be an attractive generalization, because it is not guaranteed that vaccines are the most cost-effective innovation. But: The most important hurdle that any advance purchase program needs to overcome is the credibility problem. Potential investors need to know clearly what they are getting into, and that they are not held up after they provided their share. Designing a market advance program to spur immunization research is therefore most appropriate: First, for vaccines the appropriate specifications of the product including practicability criteria are relatively straightforward to specify. Second, the restriction to vaccines makes it possible to ensure a high cost-effectiveness of the target product.

If, one the other hand, any suitable medical product were allowed to make companies eligible for the reward, then for each new product or invention in the pipeline we would need a methodology to calculate the incremental benefit generated by the entity, and the appropriate reward. A large set of factual and political questions would have to be clarified and negotiated with a large set of stakeholders. Plus, all of this would have to be done within a short amount of time, because the further the development has proceeded, the larger the credibility problem becomes. Once the product is developed, the sponsor has no reason to pay out funds any more. If there is too much discretion at this later stage, the program has no bite. Ideally, we would need a transparent and legally verifiable set of tools and criteria that would allow anyone to calculate the benefit

generated by a project in advance (so developers could calculate their expected reward and would not be subject to renegotiation), but such a technology is not available.
Let me offer a different but closely related reason for the design choice: Simplicity. How are we going to attract a large group of potential developers if the program comes with a complicated rulebook that would make it appear unclear to each investor how much they can expect to receive?

On the question of patent protection, we could spend many fruitful academic discussions, but for the design of the CGD proposal it was my impression that the most important consideration here was the practicality concerns both from the public sector and industry partners. Changes in the patent protection would demand too much time and additional negotiations to let a project like this have an impact even in the medium run.

In sum, the current proposal is clearly shaped strongly by credibility and practicality concerns. This is also an additional argument in favour of using pre-existing institutions (such as the US Food and Drug Administration, or its European counterpart, the European Agency for the Evaluation of Medicinal Products), which are charged with tasks such as determining safety and efficacy. In my view this all resonates well with the other comments on the forum, and in particular with those by Hollis.

Regards,
Georg Weizscker

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1 December 2004, 19h42

This posting was submitted by: "Charles Clift" cliftc@who.int

Dear Participants

Gordon Brown has now announced plans for an advance purchase scheme for an HIV/AIDS vaccine, in addition to the malaria scheme announced last week. See article below, and extract immediately below.

"We will also be willing to join with other countries to explore how to increase investment in Aids research, and [in] a jointly agreed advance purchase scheme to make new HIV vaccines accessible to Africa and meet our millennium development targets on health."

In case you are wondering, there is no connection between Gordon Brown's announcements and the existence of this particular discussion (as far as we know!)

Regards

Charles Clift
CIPIH

Brown announces plan to pool Aids research

Press Association
Wednesday December 1, 2004

The Guardian

The chancellor, Gordon Brown, today outlined plans to support a global system to pool research on Aids vaccines.

Speaking on World Aids Day, he told MPs the government would back proposals to pre-purchase any future vaccine in bulk quantities, making it more readily and cheaply available.

"Today, the secretary for development [Hillary Benn] and I are issuing proposals that - on the basis of early research showing that, for every year we bring forward the discovery of an Aids vaccine we would save two million lives that would otherwise be lost - commit the British government to push forward the G8 decision of last summer to establish a new global Aids vaccine enterprise, an infrastructure for co-ordinating research in Aids," the chancellor said.

"We will also be willing to join with other countries to explore how to increase investment in Aids research, and [in] a jointly agreed advance purchase scheme to make new HIV vaccines accessible to Africa and meet our millennium development targets on health."

Britain is due to take over the presidency of the G8 group of countries for six months from January, and Mr Brown said he would use that presidency to explore how to increase investment in Aids research.

His statement highlighted the international finance facility (IFF) initiative to increase development aid to the poorest countries from $50bn (26bn) to $100 billion a year.

The plan uses richer donor countries' long-term funding commitments as collateral against which money could be borrowed in the international capital markets. The cash could then be put into the poorest countries to build up infrastructure, ensure clean water supplies, or deliver vaccination programmes.

"In our G8 presidency, the needs of Africa, development and delivering the Doha [trade] round will be our focus," Mr Brown said.

"In the documents of the pre-budget report tomorrow, the secretary for international development and I will set out our proposal for ensuring through our proposed new IFF that Africa and other poor countries have the resources to fund education, health and anti-poverty programmes and are able to meet the millennium development goals."

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3 December 2004, 9h11

This posting was submitted by: "Charles Clift" cliftc@who.int

Book: Over the rainbow: the pot of gold for neglected diseases

Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases

Michael Kremer, Rachel Glennerster. Princeton University Press, 2004. Pp 152. $2495. ISBN 0-691-12113-3

Over a hundred people in developing countries will have died of infectious or parasitic diseases by the time you have finished reading this article. Many could have been saved by access to viable vaccines and drugs, and much pain and suffering could have been avoided. Yet, barely 1% of global expenditure on pharmaceuticals goes into the research and development of products for diseases affecting 90% of the world's population. It is a sign of hope, of frustration, and of the

craving for human dignity that the best way to redress this imbalance is currently under wide-ranging--and sometimes argumentative and painful--debate.

Michael Kremer and Rachel Glennerster's Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases, part of a larger body of work by the Washington-based Center for Global Development, is an important contribution. They begin with a succinct summary of the problem--the pity is that it needs repeating. But it does. Of the dramatic improvements in health and life expectancy in developing countries consequent on relatively cheap medical advances, the extreme cost-effectiveness of vaccines stands out. Vaccines (in particular for HIV, tuberculosis, and malaria) are thus the focus of this book.

British readers of a certain age will be familiar with the notion of "strong medicine" as a drastic root-and-branch operation on the body economic. The spin here is much less radical: the body pharmaceutic is deemed to be in robust health, just in need of a little nip and tuck, as it were, in the shape of "advance purchase commitments", which are sort of blockbuster end-of-the-rainbow pots of money to be divided between vaccine developers, paid for later by taxpayers. "Strong" refers to the alleged superior strength, dollar for dollar, of this mechanism compared with current approaches: up to four-and-a-half times "stronger" than publicly funded research and joint ventures. But, after a 6-year campaign to get this policy proposal to the top of the heap, it is disturbing to find so little of the underlying mechanism laid bare, and no evidence to support the assertion that the mechanism is indeed "strong" for these vaccines. In fact, the authors promote advance purchase commitments in much the same way that some pharmaceutical companies promote "wonder drugs": emphasising the positives, burying the negatives, and ending up suggesting that we now have all the answers--or rather just the one answer--that we need. This is a shame, because the underlying idea has potential as part of something greater.

Kremer and Glennerster expend most of their firepower on early-stage vaccines (where there are no viable vaccines on the horizon and many scientific problems have not been resolved) and this is the main source of Strong Medicine's weakness. To strengthen their case, they simplify the state of difficult and unpredictable science to one that it is fixed at basic and applied levels with, among other artifacts, no benefits from information sharing, no patents on anything except end products, no coordination problems across public and private sectors in research or vaccine purchase decisions, and an idealised set of financial markets. Once these simplifications are thrown out--and we enter the real world--we face an elaborate trade-off between, on the one hand, inflexible rules based on expectations of future vaccine science, and on the other, layers of discretionary committees, treaties, and centralised control of the global public research process.

The authors' core justification for their approach is that it massively improves the choice of research leads. They deliberately favour large pharmaceutical firms over small and new biotechs and not-for-profit, university-based, and developing-country-based research. Yet, they present no empirical evidence that such firms are the most efficient at vaccine research. As the only evidence of the "plague" of failure of current programmes, we get the USAID Malaria Vaccine Program debacle of the early 1980s (which wasted a couple of ten-thousandths of 1% of the total US National Institutes of Health budget of the past 25 years). This is sad. And ungenerous to the many who, often at great personal sacrifice, give their lives to research into these difficult areas.

In its cloak of strong patents and secrecy, Strong Medicine also sets up an unnecessarily confrontational stand-off with those who argue for more open, collaborative approaches. The Gates Foundation and the G8 have been exploring these alternatives, following the recent proposal of a "Global Vaccine Enterprise" (Science 2003; 300: 2036-39) along the lines of the successful human genome project. The strongest setting for a purchase commitment for a complicated vaccine like HIV is likely to be as a fairly late, and small, part of a much larger package of measures, with the information revealed by earlier collaborative mechanisms used to set the terms of "contingent" purchase commitments. This would allow for more guidance on the

quality of vaccines, fewer institutions and rules, more control over the eventual intellectual property, products priced pretty close to production costs, and quicker release to competitive generic producers. The real challenge is to work out how each part of this larger mechanism creates and handles information and risk, and how different parts fit together to reduce overall costs, speed up discovery, and ensure high-quality vaccines.

That Strong Medicine has "growing political support" is a testament to the persuasiveness of drastically simplified ideas, the lack of desire to think through tough issues, and the political appeal of programmes for which the payment can be pushed way off into the future. One of Kremer and Glennerster's main criticisms of the current system is that if publicly funded researchers don't have to prove the worth of what they're doing by results, vested interests will lead them to overstate the chance of success. Their book is an excellent demonstration of this principle in action. We will never truly know whether early-stage advance purchase commitments will work for HIV, tuberculosis, and malaria until after they have been tried. Given the authors' assertion that public-sector failure is at the heart of the current system's inadequacies, it would be ironic indeed if such failure happens when choosing the mechanism itself. Kremer and Glennerster should refuse to tolerate political support that comes without awkward questions or demands for solid empirical evidence.

All sides in the debate over the funding for neglected diseases exaggerate to get noticed; it is always nice to think that one's ideas are those chosen by policymakers. Disagreement is part of the discovery process. When, at the end of Hans Christian Andersen's tale, a small child squeals that the emperor has in fact got no clothes on, the emperor cringes but carries on the procession to its bitter end, while his chamberlains continue to hold up the train of his cloak, even though they know that it is not actually there. Let's hope that, after reflection, policymakers do not uncritically swallow all of Strong Medicine. It will make them feel better for a while, but the effect would be short-lived. Sooner or later, we will need to develop something stronger.
Andrew Farlow

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4 December 2004, 14h19

This posting was submitted by: "Charles Clift" cliftc@who.int

Dear Participants

The proposal that the incentive for R&D on "neglected diseases" should be a transferable intellectual property right raises some common issues with the advance purchase contract. In this case it is proposed that the incentive would be a right to an extended patent or market exclusivity on a best selling drug in the developed world. Below, Trevor Jones of the Commission, asks some questions about the proposal.

Regards

Charles Clift
CIPIH Secretariat

TRANSFERABLE INTELLECTUAL PROPERTY RIGHTS (TIPR) TO INCENTIVISE R&D FOR NEGLECTED DISEASES

Prof Trevor M Jones CBE
December 3rd 2004

A number of persons have suggested that pharmaceutical companies should be granted Transferable Intellectual Property Rights (TIPR) in exchange for dedication of in-house company resource to discover/develop drugs (and vaccines) for neglected diseases.

The proposals, in summary, are that a company would undertake to develop and launch a product for a disease which predominantly affects the developing world and be rewarded by means of extended market exclusivity in the developed world for a product of its own choice. Several diseases have identified which might qualify for such reward are as follows:

Chagas disease
Dengue fever
Diarrhoeal diseases
Helminths (intestinal)
Hepatitis E
HIV/AIDS (Developing World clades)
Hookworm
Leishmaniasis
Leprosy
Lymphatic Filariasis
Malaria
Onchocerciasis
Schistosomiasis
Trypanosomiasis (African)
Tuberculosis.

The purpose of this paper is to list a number of questions relating to TIPR which require cogent and convincing responses if TIPR is to progress to an agreement with companies and with national and international authorities.

1. Geographical Issues

Would TIPR be granted by USA and by all EU Member States (including the new accession countries) and Switzerland or on a broader (or narrower)basis.?

2. Who pays?

TIPR is essentially a social contract whereby countries in the rich world provide cash to pharmaceutical companies in exchange for their dedication to developing medicines for use in the developing world. Payment for medicines within , for example, Member States of the EU ranges from virtually all Government-funded (UK) to a mixture of Government, insurance companies and personal copays (e.g. Germany). Why should, for example, older people who co-pay for medicines contribute more than others in the same Member State (i.e. where is the social contract) bearing in mind that, on the whole, older people are the largest users of medicines.

3. Does TIPR apply to any product nominated by the Company?

Since the overall development time of a new medicine to regulatory approval/launch can be as long as 15 years and is typically 13 years, it is not possible at the start of a development programme to nominate an existing product (or an emerging product) that would be the subject of extended IP cover. Indeed, the market size/value would need to be known close to the point where such benefit was agreed.

Will companies be free to nominate ANY of their products for TIPR with no conditions relating to the nature of the product, e.g. products for erectile dysfunction as distinct from, say, breast cancer; products for depression or for obesity as distinct from, say, products for transplantation.

4. At what stage of development would TIPR be granted?

Will TIPR be granted on a named product at the point where the regulatory authority (e.g The US FDA ;the EU EMEA) formally approves the product for the developing world or will the product need to have been launched and, if so, in which country/countries would the product need to be launched?

5. Where would the product for a developing world disease need to be approved?

Would the product need to be approved by one of the main developed world regulatory agencies, e.g. USA, EU or Japan, rather than approved by a local regulatory agency, e.g. in a sub-Saharan African country.

6. At what time can companies start to benefit financially from TIPR?

(Following from 4. above) could companies start to earn revenues from the date of regulatory approval or would they be granted TIPR at this time but with their time of exclusivity discounted by the equivalent to the time lag between regulatory approval and, say, launch in the first developing world country?

7. Is the list of developing world diseases complete?

In recent months, there have been suggestions that other diseases of the developing world may require establishment of PPPs, e.g. diabetes. Furthermore, is the basis for the construction of this list, e.g. mortality, morbidity, health impact (e.g. Dalys), cost-effectiveness (e.g. QALYs)? And would there be differential (tiered) exclusivity periods for different diseases?

8. What criteria will be established, ab initio, for a product to be used in exchange for TIPR?

It must be assumed that authorities are unlikely to grant TIPR to products that, although capable of obtaining a Product Licence, manifestly have an unsuitable profile for developing world countries (whether this be in terms of their limited efficacy against the particular disease type or because they are so expensive (even at absolute cost) that they are unlikely ever to be funded).

Therefore, will the product profile (best and worst acceptable) be agreed, and by whom and at what time?

Of particular significance will be that element of the product profile relating to its potential cost. Clarity on this issue is vital.

9. Will the company need to register its intention to develop a product to qualify for TIPR and when would such a registration be required?

Since the incentive is, essentially, intended to stimulate companies to develop entirely new medicines a process that can take up to 15 years will companies need to register their intention once dedicated resource is committed? If not, on what basis will authorities be able to estimate the impact on their health budgets from TIPR to major products? If registration is not on initial application of resource, then at what stage prior to regulatory approval (and/or launch in territory) would such notification be required and to whom?

10. What happens to followers whether fast or slow?

If a company is granted TIPR for, say, an anti-malarial drug and one year later another company requests TIPR on another anti-malarial with a similar therapeutic profile (e.g. effective against particular strains and suitable for use in both pregnant women and children as treatment rather than prophylaxis), will both companies (or more) be granted TIPR?

What happens when the follower is clearly superior in profile. Will the first company be allowed to retain its TIPR even if prescribing switches to the follower?

Will authorities set criteria for superiority for followers or for the first entrant following agreement to a TIPR scheme?

11. What will be the length of TIPR?

What criteria will be used/agreed (for all nominated/agreed diseases) and for all types of development at the point where TIPR becomes an agreed scheme?

12. What type of development will be eligible for TIPR?

(Following on from 10 above)Truly therapeutically beneficial disease treatment can be delivered by combining existing drugs (e.g. Artemesia combinations in malaria), by specialised formulations of existing products .e.g. Microbiocides for prevention of transmission of HIV, paediatric formulations of existing compounds and intravenous formulations of existing oral formulations; in addition to entirely novel chemical/biological active substances NAS).

Will the same TIPR be granted to each of these types of development, i.e. whether or not they are entirely NAS? If not, on what basis would a sliding scale of TIPR be determined and at what point in time in the development of such formulations/range extension?

(It is important that the response to this question is presented in some quantified manner rather than conceptually).

13. Will TIPR be discounted on the basis of the potential volume of use of the product?

The number of truly lifesaving formulations may apply to a very limited population, e.g. cerebral malaria, intravenous formulations or suppositories where oral formulations are not possible (very sick patients or children), paediatric liquid formulations OR the agreed diseases.

14. Will TIPR be dependent upon a commitment to provide formulations for all age ranges?

For example, will the requirement that paediatric formulations (in ,say, 4 to 5 different age ranges) be developed (including clinical studies etc.) be a necessary condition of granting TIPR on an adult formulation?

15. How will the TIPR be shared when there are several groups involved in development?

Companies who wish to benefit from TIPR may have, or will form, agreements with organisations such as public or private research institutes, the pharmaceutical or biotech companies to assist in the discovery and/or development of medicines for the developing world. On what basis would these agreements include benefit relating to an extension eventually gained from TIPR on a different product?

16. How will TIPR be tradable?

It has been suggested by some that there should be full tradability of TIPR if the R&D benefits are to be maximised. Will companies be entirely free to trade TIPR with any other organisations/companies and at their discretion, or will there be restrictions imposed by the authorities and, if so, at what time?

17. What quantity of new drug development will the agreement to TIPR stimulate?

Currently, only a handful of major companies are conducting work on the diseases listed above.

How many more companies are likely to be stimulated to establish work on those diseases following agreement on TIPR? (Currently, very few would have any in-house expertise in any of these areas and would need to tie in/link to science/scientific groups with specific knowledge of the vector, micro organism and disease.)

18. Will TIPR have a legal base for its guaranteed application?

It has been suggested that in the EU Article 308 (previously Article 235), Article 95, Article 133 and Article 177 of the EU could be used as a legal base for action in the EU.

Is this correct and will it mean that, say, 12-15 years after TIPR has been agreed, companies which have expended resources to bring a product to successful registration can definitely rely on the legal basis of the agreement?

Is there a similar legal basis for extending the TIPR concept to the USA?

19. Does it matter where the research is carried out?

Would the EU be prepared to grant TIPR if most or all of the research is done outside the EU, e.g. in the USA (with, of course, much of the clinical work being done in the developing world) and the product so developed approved only by the US FDA? ..and vice versa ..the USA for work carried out essentially in the EU and elsewhere

20. Who owns the IPR once the product is registered?

Does the originating company (together with any agreements it has with other organisations) still own the IPR for the intended use? If not, who would own the IPR?

21. Would TIPR permit companies to develop products for which there is no IPR value?

There could be a number of combination products or compounds with limited IPR which could be of significant value in treating the diseases listed above. Would companies pursue such programmes or focus solely on those which should generate new IPR? How would TIPR be regarded by the public?

23. Will TIPR be linked to the actual cost of R&D of the developing world medicine?

Would companies be prepared to allow inspection of their R&D costs for the developing world product and their sales and profit retention from their TIPR nominated product?

If not, how will they negotiate the profit obtained on the TIPR product against the relevant cost of the new medicine for the developing world ?

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5 December 2004, 02h09

This posting was submitted by: "Moree, Melinda"

Thanks to Trevor for his comments. We at MVI would be pleased for more dollars to be invested in push funding!

This said, we are also very strong proponents of pull funding including advanced purchase contracts. There is much that can be done with push funding but it still does not "fix" the economic equation for industry. It certainly lessens the risk for companies of investing in R&D but really does little to assure a company that someone will buy that vaccine once developed. The days of cheap vaccines--pennies per dose--are over. This is especially true of vaccines for diseases that have as a primary market the developing world since there is no high paying market from which to tier the prices. We very clearly face a pipeline that is filling up with new vaccines but lack a clear mechanism to finance these new products.

MVI has commissioned a market assessment by a top market research firm. The results will be available Q1 05. The intent is to put the information into the public domain. This will help with defining the technical aspects of a "successful product" and in defining the key drivers of demand.

Melinda

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6 December 2004, 14h15

This posting was submitted by charles Clift

Please article below from the Guardian and attached letter.

Brown criticised on malaria cash

Sarah Boseley, health editor
Monday December 6, 2004
The Guardian

Two eminent malaria scientists have sent a letter to the chancellor, Gordon Brown, criticising his decision to fund a future vaccine against a disease which, they say, could be wiped out from parts of Africa right now with cheap drugs.

The two professors say that Mr Brown's announcement that the government would pre-buy 300m doses of a vaccine being developed by the British drug company GlaxoSmithKline at a cost of Â£3bn to the taxpayer is a misguided good intention.

"Malaria really can and should be conquered - and we now have the necessary tools to do the job," they write. "We are concerned therefore that while millions of people suffer every year, you are proposing allocating precious funds to a future uncertainty."

Nick White, professor of tropical medicine at Bangkok and Oxford universities, and

Bob Snow, professor of tropical public health at the Kenyan Medical Research Institute, Nairobi, and Oxford University, say that simple interventions such as free bed-nets to keep malarial mosquitos away from children at night and new but cheap drugs based on the artimisinin plant grown in China could eliminate malaria from parts of the world where there is low transmission, such as South Africa, Angola and northern Kenya. This would allow a more intensive focus on the bigger problems in other places, such as India and Burma.

They applaud Mr Brown for recognising malaria "as a major cause of poverty, suffering, and death in the developing world" but question the promise of funding for a vaccine which he made 10 days ago, just after publication of GSK's trial results in the Lancet. These showed that the vaccine worked in 30% of a small group of children in Africa, though as yet nobody knows for how long.

They ask why the British government has chosen to fund a vaccine, rather than drugs and bed-nets. "One argument might be that the bill does not have to be paid today. And when it does, it will probably be paid to a British multinational pharmaceutical company," they write.

Two approaches could save more than one in five childhood deaths, they write. Bednets impregnated with insecticide cost under Â£2. The new artimisinin-based combination drugs which are being brought in to replace old drugs like chloroquine, to which the malaria parasite has become resistant, cost less than 50p to treat a child.

Prof White said the two researchers were delighted that the chancellor wanted to help the fight against malaria.

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KEMRI-Wellcome Trust Collaborative Programme, P.O.Box 43640, 00100 GPO, Nairobi, Kenya.

Wellcome Trust Mahidol University Oxford Tropical Medicine Research Programme, Faculty of Tropical Medicine
Mahidol University, 420/6 Rajvithi Road
Bangkok,10400, Thailand

☎: 00 662 354 9172 Fax: 00 662 354 9169 E-mail: nickw@tropmedres.ac

Rt Hon Gordon Brown

Chancellor of the Exchequer
HM Treasury
1 Horse Guards Road
LONDON SW1A 2HQ

3 December 2004

Dear Mr. Brown,

We write regarding your recent announcement that the British Government is ready to enter into an agreement to purchase a large quantity of malaria vaccine in advance to ensure a secure market. We think you can do more for less – now.

The results of the trial published in the medical journal The Lancet on October 16 were exciting indications that, for the first time, a clinically relevant protection against malaria (vaccine protective efficacy 30%) could be provided by a vaccine in young African children. This was associated with vigorous and eye-catching publicity, notably the banner headline in The Times the preceding day claiming that "New malaria vaccine will save millions of children". We have waited a long time for evidence that an effective vaccine against falciparum malaria might be possible, but we have had false dawns with malaria vaccines before – and it would be prudent to be cautious. Under normal circumstances this report would herald a concerted effort to confirm or refute the findings in different populations in different parts of Africa with studies large enough to measure the impact on mortality from malaria. One study is certainly not enough to be sure of anything. But instead you announced a week ago that the British Tax payer would pre-buy 300 Million doses of vaccine for sub-Saharan Africa, costing probably 3,000 Million pounds.

The UK government is to be applauded sincerely for recognizing malaria as a major cause of poverty, suffering, and death in the developing world. Malaria weakens and debilitates developing world societies perpetuating a vicious cycle of illness and grinding poverty. Consistent negative economic growth in Africa over the past half-century has been ascribed to malaria. Childhood deaths from malaria are on the rise in sub-Saharan Africa. The UK government has shown its concern and commitment to reverse this appalling trend while some other rich countries have turned away, seeing this as an interminable and insoluble problem. But it is not; malaria really can and should be conquered –and we now have the necessary tools to do the job. We are seriously concerned therefore that while millions of people suffer every year, you are proposing allocating precious funds to a future uncertainty. This good intention is misguided. We fear you have been advised poorly. We have interventions now that are more effective and much less expensive than the weak vaccine reported in The Lancet.

Just two simple approaches could halve the numbers of malaria attacks in young African children and save more than 1 in 5 of all childhood deaths. A mosquito net treated with a long-lasting insecticide costs less than £2. We now have highly effective and well tolerated antimalarial drugs (Artemisinin based Combination Treatments; **ACTs**) to replace those drugs such as chloroquine that have fallen to resistance. These cost less than 50p per child treated. Less than £10 would guarantee a poor African child access to life-saving interventions. The cost of a malaria vaccine will be in excess of £30 per full immunization.

The sad truth is that despite having now developed these effective tools (with substantial support from donors such as the UK Government) the international community has failed in their promise to make them accessible to people most in need. Partnerships such as the World Health

Organisation, Roll Back Malaria, and the Global Fund against HIV, TB, and malaria, also supported generously by the UK Government, have missed opportunities to go to scale with comparatively cheap, life-saving interventions. Weak strategic leadership, donor-driven agendas making poor people pay for bed-nets, inadequate planning for drug needs and policies, and lack of sufficient funds have all resulted in less than 5% of children sleeping under an insecticide treated bed-net, and a handful of African countries struggling to implement new effective drug policies. Communities in Africa under the constant threat of malaria and maintained in a constant state of poverty cannot afford to spend £10 per child to save them from malaria; rural households have to make difficult choices of putting food on the table or sending their children to school. Their government's also cannot provide for them adequately, and depend largely or entirely on donor support. No-one likes to be dependent on aid, but we will not Roll Back Malaria without substantial donor support. If we could persuade the developed world to match commitments such as those made generously by you, and these were spent wisely on insecticide treated bed-nets and **ACTs**, then we would have made substantial inroads into malaria by the time any malaria vaccine became generally available.

Why then has the UK Government decided to invest in an intervention that is more expensive and less effective than bednets and effective drugs? One argument might be that the bill does not have to be paid today. And when it does, it will probably be paid to a British multinational pharmaceutical company. Another is that vaccination is a simple tool that has been highly effective in combating some of the greatest infectious disease scourges known to man – including smallpox, diphtheria, and polio. We could add to this list pneumococcal disease (the main cause of pneumonia in the world), tetanus, and measles. But in the developing world these diseases still kill over two million children every year. We have truly effective measles and tetanus vaccines (they are much more effective than the current malaria vaccine), and we have had them for decades, but these vaccines still do not reach all those who need them. Together measles and tetanus kill over a million children each year (World Health Reports 2003, 2004). We have a pneumococcal vaccine, but it does not reach anyone because it is so expensive that no developing country Government can afford it. The prospect of a new vaccine against a killing disease has a seductive "high-tech", "feel-good" allure which is appealing to donors, who seek neat solutions in modern technology. There is also the argument that vaccines could reduce the incidence of the disease, thereby reducing the need for other interventions. Yes, prevention is better than cure, but this works both ways; if we provide insecticide treated bed-nets and make effective drugs available this will also reduce the incidence of malaria, and we will achieve better effects than with this weakly effective vaccine –and importantly we will spend less money. The burden of malaria is increasing alarmingly; we could and we should **ACT** now.

We are not arguing against support of malaria vaccine development, only for a sensible direction of your genuine humanitarian initiative with the most efficient and effective allocation of

precious resources. Investment in developing a malaria vaccine is critical. The trial in Mozambique has shown us that despite all our earlier reservations we may well have a vaccine against malaria for African children. It is not a question of whether we spend money on vaccine R&D or expanding coverage of bed-nets and effective drugs –we must spend money on both, but spend it wisely to give the greatest benefit.

Mr Brown, please do the right thing. The disempowered, poverty-stricken millions who cannot afford even basic, but well- tested and effective, bed-nets and drugs to protect them and their children against malaria need you. They need leadership and commitment to drive a concerted humanitarian global effort to tackle this soluble but lethal problem. We need to raise sufficient funds from the rich world to support scale up and deployment of what we know works best, and we must do it now.

Professor Bob Snow
Professor of Tropical Public health
Kenyan Medical Research Institute, Nairobi & Oxford University

Professor Nick White
Professor of Tropical Medicine
Mahidol University, Bangkok & Oxford University

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8 December 2004, 11h42

This posting was submitted by: "Moran,M" <M.Moran@lse.ac.uk>

Dear CIPIH readers

The Pharmaceutical R&D Policy Project (PRPP) is a new policy unit, based at the London School of Economics. Our brief is to provide the UK Government, and others, with quantitative and qualitative information on different approaches and incentives for developing drugs for neglected diseases, in order to support development of policy tools in this area. (We are not examining vaccines.)

We had not intended to release our first draft findings until February 2005, however the current debate on TIPR/APCs has encouraged us to offer these early thoughts.

Regards

Mary Moran

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Our research to date shows that around 45% of drug development projects for neglected diseases involving industry are now conducted by companies under the in-house "commercial" model, while around 55% are conducted by companies in low-cost partnerships with public groups. However, proposed new R&D incentives have largely neglected this second lower-cost approach, with the result that governments may be unwittingly steering companies away from low-cost partnerships and into a higher-cost commercial model. We suggest that both approaches deserve review.

As CIPIH readers are aware, there are currently a plethora of current and proposed incentives aimed at stimulating R&D for neglected diseases, including push incentives (e.g. tax breaks, R&D grants, protocol assistance) and pull incentives (e.g. TIPR, APCs, Orphan Drug market exclusivity). These incentives impact differently on the different drug development pipelines, in particular in their effect on multinational drug companies (MNCs), small and medium sized companies (SMEs) and public-private partnerships (PPPs).

To date, we have researched approximately 55 of the new drugs in development for neglected diseases since 2000 - this includes both projects with and without industry involvement. This does not include all drugs in development by small and medium sized companies (SMEs), which we will complete next year.

Of these 55 neglected disease drug development projects:

* Approximately one-third are being developed in-house by multinational drug companies (MNCs).
* Approximately two-thirds are being developed by PPPs. Of those PPP projects with an industry partner:
o Around half are with MNCs, often working on a low-cost basis and contributing substantially in-kind.
o Around half are with SMEs and developing country (DC) pharmaceutical firms. These SME and DC partnerships often operate as fully subcontracted projects, with the "partner" company being paid in full.

The various approaches differ substantially in performance (cost-effectiveness, efficiency and quality of outcomes) and - importantly for the current debate - in the type of incentives most likely to catalyse and facilitate them. Incentives to stimulate new in-house activity by MNCs tend to be large, since they focus on commercializing the market through the use of pull incentives such as TIPRs or APCs. This is particularly the case if the incentive seeks to draw in MNCs who have already left the field of infectious disease (let alone neglected disease) and who may be reluctant to rebuild a skill-base in this area. It may be worth reviewing the response of MNCs to Project Bioshield incentives in this context.

On the other hand, PPP partnerships and subcontracts with MNCs and small firms are structured quite differently, with the PPP usually providing regular and relatively small cash sums to the partner to either a) minimize costs (for large companies with shareholders to satisfy) or b) provide cash-flow (for small companies and biotechs). Incentives to support this type of activity are likely to be substantially smaller, and delivered along the development timeline rather than as a lump-sum end payment.

Each approach offers different advantages and disadvantages, including for MNCs, who benefit in different ways from the different models. Under the first model (commercializing R&D) MNCs can achieve significant profits, while under the second model they can share risk, keep costs to a minimum and reap substantial PR

advantage.

In addition to these two approaches, our research shows that many MNCs who have left the neglected disease field do not wish to re-enter it, but are nevertheless willing to participate in other ways, including via in-kind contributions to R&D by PPPs (e.g. provision of expertise or compounds; packing and shipping trial drugs etc).

We note that most of the current incentives, and the debate on new incentives, is focused on the first model i.e. in-house drug development by MNCs. However, there are no incentives currently in place or under discussion to support the predominant model of PPP partnering by MNCs and SMEs, although this low-cost model may offer opportunities for cheap, smart solutions and - if company participation is anything to go by - can be attractive to both large and small companies. Support for companies choosing the partnering route is still tenuous, relying largely on US philanthropic grants routed via PPPs. Likewise, there is no recognized vehicle or structure to facilitate in-kind contributions by MNCs to PPPs, which do not fit easily into the "all or nothing" approach to R&D incentives.

Given that funding for neglected disease drug development is likely to be limited and must be used as cost-effectively as possible, we believe it is important to look at all options, weighing them up on the basis of hard evidence before we move to expand existing policies or implement new ones. It is also important to ensure that companies are not systematically discouraged from choosing a lower-cost partnering or contribution route, simply due to lack of attention to these options.

We are therefore conducting a quantitative analysis of the cost and performance of the different approaches and incentives, and of current and new policy tools that can best support each approach. Draft results will be released in Q1 2005. Preliminary work includes:

* Analysis of Orphan Drug legislation, implemented in the US in 1983 and in the EU in 2000. This shows OD legislation to be ineffective in stimulating drugs for neglected diseases, and defines areas where substantial improvements could be made. (Paper to be posted with the CIPIH by end-December).

* Analysis of TIPR is underway (released Q1 2005), including predictive cost of a TIPR based on analysis of data on existing patent extensions (SPCs; paediatric extension).

* A possible new financing measure - transferable fast-track - aimed at providing the cash to underwrite PPP payments to industry partners and subcontractors across the 40 drug development partnerships PPPs now have underway. (Paper to be posted with the CIPIH shortly.)

We would be grateful for all comments on our fast-track proposal - and our other proposals as they come forward - as we are well aware that any strategy, no matter how theoretically attractive, must also be workable, attractive to stakeholders and politically feasible.

The Pharmaceutical R&D Policy Project (PRPP) is a new independent policy unit sponsored by the Wellcome Trust and hosted by the London School of Economics. Our Steering Committee includes Sir Michael Rawlins (Chairman of NICE), Sir John Sulston (ex-Director of the Sanger Institute and Nobel Prize winner), Professor Win

Gutteridge (previously Chief of Drug Development at WHO/TDR and Chief Scientist at Wellcome plc), and Professor Alistair Mcguire (Professor of Health Economics at LSE).

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8 December 2004, 21h41

This posting was submitted by: "Gardner, Charles" CGardner@rockfound.org

Dear Mary:

Wouldn't "pull" incentives tend to stimulate BOTH in-house R&D and private sector willingness to partner with PPPs? And PPP-SME partnerships may still need to partner with big pharma when it comes time to scale up.

For your analysis, I suggest you also look at: SBIR and STTR awards by the US Government (I could imagine analogous awards to stimulate product development for neglected diseases), and Lieberman's proposed extension of BIOSHIELD II to provide R&D tax breaks, liability protection and faster FDA approval to neglected diseases.

--Chad

Charles A. Gardner

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8 December 2004, 22h25

This posting was submitted by: "Charles Clift" <cliftc@who.int> Dear Participants

These may be a naive couple of questions but here goes.

If a PPP, or a public research institute or a university, develops a vaccine (or drug) is it eligible for the APC prize, although the R&D has mainly been funded by non-profits or governments?

Is a transferable intellectual property right only an incentive for companies with products to transfer the right to? So it would not be an incentive for biotechs, or public research institutes, usually with few or no other products in the market?

Regards

Charles Clift

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8 December 2004, 22h55

This posting was submitted by: "Gardner, Charles"

My apologies for cluttering up inboxes. I have been asked to explain further. All US technical agencies that make over $100 million in annual extramural funding are required to put 2.5% of that into Small Business Innovation Research (SBIR) awards and 0.3% into Small Business Technology Transfer (STTR) awards. See the following website of the US National Institutes of Health (NIH) (http://grants.nih.gov/grants/funding/sbirsttr_programs.htm). SBIR awards are for small businesses, while STTR awards are to link small businesses with university research efforts. These are a major instrument of US innovation policy -- US incentives for high-tech industry. For NIH, 2.8% of about $24 billion USD is rather a lot of money going to small businesses, mostly biotechs. Senator Lieberman has spearheaded BIOSHIELD, originally as incentive for US companies to develop products to counteract bioweapons. Below, I have attached text from a recent speech by the Senator regarding proposed changes to the legislation (BIOSHIELD II). Note that Dr. Moran mentioned BIOSHIELD in her very thoughtful earlier message.

--Chad

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Third World Diseases and Antibiotic Resistant Pathogens

As we draft BioShield II, we are actively exploring the scientific and economic implications of applying BioShield and BioShield II to infectious diseases generally, not just pathogens deemed to be "terror weapons."

As a matter of science, the research and development on countermeasures to bioweapons is inextricably linked to research directed to pathogenic virus, bacteria and fungus that cannot be weaponized. Consequently, it makes sense to enact incentives for research that addresses the pathology, diagnosis or therapeutics that relates to virus bacteria or fungus whether it has been or could be weaponized or not. Research on infectious diseases seeks to understand how organisms cause disease, the immune system responds to pathogens, and antibiodies and other medicines protect against them. This research is broadly applicable to both bioterror and non-bioterror pathogens. In the end, we need broad-spectrum antibiotics, anti-virals that can be utilized against a variety of viruses, and vaccines that can be adapted to a variety of organisms.

As enacted into law, BioShield could be applied to the development of new antibiotics, which can serve as a Bioterror countermeasure. The Administration's draft of BioShield provided that if there was a "significant commercial market for the product other than as a homeland security threat countermeasure" BioShield would not apply (S. 15, section 203, as introduced on March 11, 2003). This anti-dual use provision, which would have squandered the potential benefits of this legislation for the development of new antibiotics and other dual-use medicines, was deleted in the final version of the bill. We need these antibiotics as countermeasures for Bioterror pathogens and we

especially need them to respond to Bioterror pathogens that are engineered to be antibiotic resistant.

We also need new antibiotics to respond to a public health crisis in our hospitals - one documented in great depth by the Infectious Diseases Society of America in Bad Bugs, No Drugs (July, 2004). IDSA finds that about 70% of the two million bacterial infections in America each year are resistant to at least one antibiotic. If our current range of antibiotics loses its effectiveness - and signs of resistance to our last line of antibiotics, vancomycin, are appearing - then we will face a public health crisis even if there is never a Bioterror attack. The relentless rise of antibiotic resistance in bacteria and the exit of all of the major Pharma companies conducting R&D in this area due to lack of incentives will leave us vulnerable in the extreme by the end of the decade. At some point society will be badly bitten by this trend, with pandemic influenza being the most likely candidate in the short term. I fear that someday we'll be forming another 9/11 commission after large numbers of Americans (and others around the world) die as a result of failure of our government to engage the problem proactively.

While BioShield could apply to the development of new antibiotics, it is not likely that new antibiotics will be listed as a priority of the Administration for Project BioShield. BioShield focuses on procurement by the government of medical countermeasures, so it is likely that it will mostly or entirely be utilized for procurement of countermeasures where the government is the sole market. There is a substantial civilian market for antibiotics, with the government only a marginal player. It makes more sense to deploy the tax, intellectual property, and other incentives in BioShield II to this research. This would both be consistent with our needs for Bioterror preparedness and provide a much-needed benefit to our public health infrastructure.

In terms of infectious disease generally, it is likely that the biopharma companies that we might engage in developing Bioterror countermeasures will have expertise, and capital from investors for research on a broad range of infectious diseases, going well beyond those that might be weaponized. In fact, it may well be easier for these companies to form or deploy capital for this research if it involves development of medicines where the Federal government is not the sole or principal market. In the end, we need to establish an Infectious Disease Industry, not just a BioDefense Industry. We need companies capable of development effective platforms that have a broad application to a variety of infectious diseases - research tools of immense power and importance. We certainly need many more companies with expertise in developing vaccines. So, it makes little economic sense to stovepipe these lines of research, providing incentives for research to develop medicines for only a select few pathogens we label as "bioterror pathogens." It is also true that in some cases we may not know if a particular pathogen can be weaponized. For example, some believe SARS could be weaponized.

Accordingly, it makes good sense to apply BioShield II to research and development of countermeasures for "infectious" diseases

even if they might not be pathogens that can be weaponized. BioShield could also be applied to these countermeasures with a proviso that the government could organize a procurement fund comprised of its own funds, funds form international public health agencies like the Global Alliance for Vaccines and Immunization (GAVI), foundation funding, and other sources. This is an issue that we need to explore with organizations such as the IDSA, The international Aids Vaccine Initiative, the Alliance for Microbicide Development, the Alan Guttmacher Institute, the AIDS Vaccine Advocacy Coalition, Biotech Ventures for Global Health, the Aeras TB Foundation, AmFAR, the Global Alliance for TB Drug Development, the Malaria Vaccine Initiative (MVI), International Partnership for Microbicides, Medicines for Malaria, and similar groups.

The need for additional research to develop therapies, cures, and vaccines for infectious disease - both Bioterror and natural - is clear. Worldwide, seventeen million deaths annually are caused by infectious and parasitic diseases, 33% of the total and 71% of all deaths among children under 5 years of age. This compares with fourteen million deaths from famines, wars, violence and aging, the same number from circulatory and obstructive pulmonary disease, and five million due to cancer. AIDS is out of control in many countries and mutating to create new strains. In the end, we may lose one hundred million people to AIDS. Malaria is developing resistance to the newest prophylaxis - with nearly three million deaths a year. Antibiotic resistant TB is surging - with over three million deaths a year. One million die each year of hepatitis B and one billion are infected. 165,000 each year die of hookworm and roundworm. We have seen waves of emerging diseases, including AIDS, SARS, West Nile virus, Lyme disease, and hantavirus. The public health agenda - for bioterrorism and beyond - is compelling and amply justifies enactment of new incentives for development of effective medical countermeasures.[20]

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9 December 2004, 08h02

This posting was submitted by: "Moree, Melinda"

Letters in the Guardian

http://www.guardian.co.uk/letters/story/0,,1368524,00.html
Letters
Remedies for malaria

Wednesday December 8, 2004
The Guardian

We share the analysis of the threat of malaria by Professors Nick White and Bob Snow (Brown criticised on malaria cash, December 6), but their assertion that the government has chosen to fund a vaccine, rather than drugs and bednets, is wrong. The UK is funding existing interventions and proposing to fund future interventions.

Since 1997, the UK has committed over £1.5bn to fund health interventions in the poorest countries, including anti-malaria drugs and bednet programmes, and we are now doubling our contribution to the Global Health Fund for TB, Aids and Malaria. These are the most effective means of tackling malaria and other diseases.

We are also proposing to work with other donors to agree an advance purchase scheme for malaria and Aids vaccines. This would mean that if there were effective vaccines, we would share the costs of purchasing millions of doses. If the market for can be guaranteed in this way, it will provide incentives for the world's drug companies to increase investment in vaccine research and stimulate competition to produce the first affordable and effective vaccines.

In their letter to the chancellor, White and Snow said: "It is not a question of whether we spend money on vaccine R&D or expanding coverage of bednets and effective drugs - we must spend money on both, but spend it wisely to give the greatest benefit." We could not agree more.
Paul Boateng
Chief secretary to the Treasury
Every child who needs anti-malarial drugs and nets should have them - now. Let the world agree that three children dying every minute is not acceptable. Let us also consider what it is needed to put an end to these deaths.

Several years of working in childhood immunisation and malaria has taught me that ending deaths from malaria will require full implementation of appropriate drugs, insecticides and nets that are available now, as noted by Snow and White. It will also require new drugs and insecticides to prepare for the growth of resistance to those in use, and we need to develop and fully implement vaccines - especially to prevent the deaths of malaria's youngest victims.

This cannot and should not be an either/or proposition. If the global community so decides, we can do all these things. Children are dying who don't have to, and this sad reality will persist unless we do what we can now. Part of that "now" is investment in the future.
Carol Hooks
Malaria Vaccine Initiative, Path

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9 December 2004, 10h11

This posting was submitted by: "Charles Clift" cliftc@who.int

The indefatigable Gordon Brown made another speech yesterday.

(http://www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_105_2004.cfm)

The relevant extract is below. The point about this is another idea:

That is that by borrowing to provide funds now against future aid flows, which is the International Facility for Financing (IFF)(see http://www.hm-treasury.gov.uk/documents/international_issues/international_development/development_iff.cfm) money can be made available now (frontloading) to finance development interventions. There is a proposal to pilot this larger idea through a specific intervention with GAVI. That is, through the proposed IFF mechanism to make more funds available now, to finance purchase of existing vaccines.

This is linked in the speech also to an advanced purchase scheme for malaria and HIV/AIDS which works on the opposite principal i.e. making money available in the future (backloading) to stimulate R&D now.

This raises the question of whether incentives for R&D are better stimulated:

* by "backloading" e.g. APCs or TIPRs which depend on promises of future reward for R&D leading to new drugs and vaccines

* or by financial mechanisms (such as the IFF)which bring forward future funding and thereby stimulate current purchase and R&D incentives based on that funding stream ("frontloading").

* or indeed both.

Regards

Charles Clift
Secretary, CIPIH

"Let me give an illustration of what - because of the IFF model - is already possible.

The Global Alliance for Vaccines and Immunisation who have immunised over the last five years not a few children but a total of 50 million children round the world - is interested in applying the principles of the IFF to the immunisation sector - donors making long term commitments that can be securitised in order to frontload the funding available to tackle disease.

If, by these means, GAVI could increase the funding for its immunisation programme by an additional $4 billion over ten years, then it would be possible that their work could save the lives of an additional 5 million people between now and 2015.

So in one fund, with one initiative, we can glimpse the possibilities open to us if we act together. If we could do the same for health, for schools, for debt, for the capacity to trade, for research and advance purchasing of drugs to cure malaria and HIV/AIDS, think of the better world we can achieve."

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9 December 2004, 18h28

This posting was submitted by: "Hannah Kettler" hannahk@gatesfoundation.org

Hi Charles - some thoughts on your questions:

Pull incentves including the proposed advanced purchase contract and transferable market exclusivity should be seen as complements rather than substitute for PPPs approaches to R&D with the goal to encourage the private sector in particular to increase and accelerate its investments and engagements in diseases of poverty. It is expected that the value that PPPs play - upfront funding for R&D but perhaps more importantly their knowledge about the respective disease, what kinds of products are needed, complementary technologies and approaches, cost-effective approaches to R&D that include partnering w/ companies in developed and developing countries; contacts, networks within the countries where clinical trials will be conducted and approved and a potential link to the "users" (and the global organizations that influence the

"recommended list" will be as important in the presence of a larger, more predictable and stable "market". In fact in the case of the CGD's APC proposal where a "price" in promised as opposed to "volume", the companies that are serious will naturally seek out partnerships to ensure a well targeted product and improve their access to those key country decision makers driving regulatory, health budget, product introduction decisions etc.

Some thoughts about whether a PPP could gain the APC. These organizations are currently set up at not-for-profit organizations - i.e. do not seek the ROI that companies do (same is true for public research institutes). They are however all currently dependent on public funding - often on a very small list of donors - and do not have a "sustainability" model as such. The importance of pull incentives, in theory at least, is to encourage private sector resources to complement the public ones to get the R&D done.

These organization work directly with companies in their pursuit of products - and you could imagine some negotiation with the company about how to share the pie especially if they funded some of the R&D - though ideally the creation of the market will create incentive for large companies to invest their own resources and even encourage VCs and other funders of the small companies to help support their R&D efforts in diseases of poverty.

My guess is that if they work, the pull incentives will allow at least some of the PPPs to consider revising their business model - ideally reducing their dependence on public donors, perhaps charging for their services. But as a non-lawyer I cannot comment on how that would effect their not-for-profit status. They exist to help realize the goal of affordable, accessible, effective new tools - through whatever means. They are not about owning IP as such but about ensuring that the products they contribute to are made available as such. (it is interesting to think about not-for-profit and public institutes competing for "markets" as an alternative or important supplement to applying for grants and funding - what kinds of incentives that would create - but only feasible if they have the money upfront to do the work and my guess is they would pursue partnerships with the experts - i.e. the private sector in any case.)

On the case of transferable exclusivity, some thinking as gone into making this "reward" transferable - i.e. biotech companies, should they bring a product to market on their own (or via partnership) could "sell" that extension to another company in exchange for $. (Adrian Towse at OHE did a report for EFPIA). Or hold on to it until they have products, depending on their cash flow situation. Am not sure that this would be the model used to "motivate" public research institutes to do applied, product development but there is no reason, in theory why they too could not "trade" the right for funding from a company who could use it.

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9 December 2004, 18h53

This posting was submitted by: "Ruth Levine" rlevine@cgdev.org

Three pieces of the puzzle are completely complementary: First, making the market for currently available products less risky with multi-year purchase commitments; second, improving the delivery of immunization and increasing in-country appreciation of the value of vaccines; and third, making commitments for future products through an APC. It is clearly a very high priority for both public health and market reasons to make the current system of buying and using vaccines work as well as possible; a "frontloaded" IFF-style mechanism can help to make that happen. This sort of progress would vastly enhance the potential benefits of an advance commitment for a future product by helping to overcome the skepticism that industry currently has about the public sector's (donors' and developing country governments') resolve to make funds available for vaccines. Importantly, strengthening delivery systems today would also

increase the eventual social benefits that would be conferred by the future vaccine product(s) whose development would be stimulated by an APC. There's no purpose in speeding the R&D for a product if the system is not simultaneously built up to introduce and sustain the use of it. In sum, we should get away from thinking in terms of tradeoffs between short- and long-term aims and instruments, and move toward thinking about making the short-term actions truly serve the needs of developing countries over the long developmental timeframe of 20-30+ years -- something that until now, with Gordon Brown's leadership, has been largely missing.

--Ruth Levine, Center for Global Development

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10 December 2004, 00h09

This posting was submitted by: "Trevor Jones" trevor.m.jones@btinternet.com

Re the second question, my understanding of the proposals is that biotech's and academics (i.e those with no "other" products)could "trade " the TIPR for cash or other benefits (i.e sell the TIPR to a pharmaceutical company who has not been involved in the development of a product for the developing world so that that company may enjoy an extension of market exclusivity on the products of their choice.

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10 December 2004, 09h08

This posting was submitted by: "Peter Hall"

My concern about Trevor Jones' comment is that the underlying assumption is that the not-previously-involved pharma company will be able to access an eventually profitable product with market exclusivity. However, without suitable TIPR licensing safeguards (which the company is likely to baulk at) the company is unlikely to consider how to obtain the lowest affordable price of a product for developing countries.

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10 December 2004, 14h14

This posting was submitted by: "Charles Clift" cliftc@who.int

Because of posting difficulties, posted by the Secretariat on behalf of Andrew Farlow

CAPITAL COSTS, COST EFFECTIVENESS OF HIV APC, AND SPEED OF VACCINE DEVELOPMENT

(Please pardon the capital letters; italics and bold do not work on my system)

Dear all!

As Hannah Kettler correctly points out, the idea of APCs is to encourage large companies to invest their own resources and even encourage VCs and other funders of the small companies to help support their R&D efforts. As a financial economist (and capitalist) I take the view that pharmaceutical firms and VC firms are not charities and would be looking for a fair return on such investments; that is a return that compensates for ALL risks of such investment. In this case, being a high-risk investment, this would need to be a high return, and potentially form a large proportion of any APC payment, as I will demonstrate below.

Therefore, I would very much appreciate it if those who have evidence on the private capital costs of pharmaceutical firms and venture capital firms when investing their own resources into R&D for HIV vaccines, could please indicate where this evidence is to be found. It would be fine if the data were provided in the form of the per-year required rates of return on financial capital, taking into consideration ALL risks, including (amongst many other things): the risks of HIV vaccine science and the likelihood of ever getting a vaccine; the risks of not internalizing the results of privately-funded research for oneself (especially if data has to be shared or the vaccine turns out not to be a pure vaccine but instead a composite vaccine); the perceived risks of the APC mechanism itself (mechanism risk); etc. Early and complicated vaccine R&D would attract especially high rates of capital cost because all of these risk factors are much greater than for late and less complic ated vaccine R&D, as well as being compounded over much longer periods.

Since for an HIV APC to actually work ALL of this capital cost needs to be FULLY repaid eventually by taxpayers and philanthropic foundations through the APC, it is an important piece of empirical evidence for working out both the level at which to fix the HIV APC in advance but also for evaluating its cost effectiveness compared to alternatives. I presume the figure or figures must be being fed into the current calculations of HIV APC figures, but I have not found them yet anywhere in the literature.

Please, can these figures be placed in the public domain? Without the figures, one can only guess, something that I will now do (all figures below are nominal, i.e. not adjusted for inflation, and I would welcome them being challenged and recalculated in light of the actual evidence):

One would imagine that the stock market and venture capitalists would take the view that current HIV vaccine research is a particularly speculative investment especially in the first five years or so (maybe even much longer) after an HIV APC might be fixed. It seems reasonable therefore to presume that the required rate of return on financial capital would be much higher than, say, the required rate of return calculated by TUFTS for drug development a nominal rate of 14%-16%, with a mean of about 15% by the very same large pharmaceutical firms now being targeted with HIV vaccine APCs. Is this a reasonable statement to make?

Let us presume for the moment that there are no layers of crowding out in the workings of an HIV APC (highly unlikely). If the required nominal rate of return to financial capital invested in early-stage HIV vaccine R&D was 25% (not outrageously high compared to speculative investments that VC firms normally make, but is it too high for this case? Or, indeed, too low?) and the average expected horizon until repayment was 10 years (given my understanding of the state of HIV vaccine science, this is being generous I would imagine, though it also depends on what is being done on the push front), then each dollar of early pull-induced private R&D would cost about $7.5 of eventual APC payment; that is, each $1billion of promised APC would pay for about $133m of early out-of-pocket research costs. So, you can see, getting a hold on the figure for capital costs (and risks) is quite important.

If there was crowding out too of, say, half then this would lead to $1billion of promised HIV APC paying for about $66.5m of genuinely ADDITIONAL out-of-pocket early private R&D. Crowding out would show up (amongst many other things) in an inability to ONLY pay for privately-funded

R&D and to separate out and NOT pay for non-privately funded R&D through the APC, OR an inability to generate genuine addition to the vaccine market by preventing vaccine purchases made outside of the APC mechanism from benefiting from the APC mechanism - something that would be especially difficult to achieve for HIV vaccines. In this case, it only has to crowd out $66.5m of out-of-pocket research expenditure. So, a notion of likely levels of crowding out would be very useful too. Again, I presume the figure must be out there entering into current calculations, and it would be useful to have it in the public domain.

As you can imagine, extending the expected horizon to 15 years or increasing the required rates of return to financial capital or increasing the levels of possible crowding out creates increasingly dire looking figures.

It is important to get a handle on these figures, since if the ones above are even remotely correct, some of the current PPP-financed activity starts to look much more of a cost-effective way to direct fresh government (and G8) and foundation funding in the near term. Indeed, it is not clear why large pharmaceutical firms themselves would even prefer to be stimulated in the current environment by an APC.

If this is the view taken, then it becomes even less pressing to set the terms of an HIV APC any time in the near future before good information is available on how to permanently fix the terms (a permanent fix is needed to make an APC credible and to keep its risks and private capital costs down); it would be doing hardly any cost-effective pulling in the near-term (for example, if a $10billion HIV APC were permanently fixed yet could only generate at most $665million -$1billion or so of genuine additional early private R&D, then the most likely reaction of private firms and venture capitalists would be to hold off R&D, and, indeed, to simply not trust that the mechanism would ever work to repay them anything they spent early on), yet it would impose higher costs by being prematurely set (other financial economists will spot that there is an expensive option-price component in fixing the terms of an APC NOW before much of the information is available on how to efficiently an d correctly set it).

Even if policy-makers wished to fix APC terms now, expecting little activity in the near-term but intending that the APC be in place for later when it matters, it would be impossible to do so correctly and cost-efficiently without resolving the relative role of other parts of the mechanism first. Even then, fixing now when there is no urgency to do so is not even a good idea given that policy-makers would lose the flexibility to learn from, evaluate, and scale up the much more collaborative approaches that are more likely going to be needed to generate HIV vaccines (and this itself would help to more efficiently set a later-stage HIV APC as and when a vaccine is looking much more likely).

Obsessing about an early HIV APC for the next seven months running up to the G8 summit to the exclusion of obsessing about the other, perhaps more difficult and collaborative, parts of the R&D framework, will put private investors off EVEN MORE since they will come to understand (and price in to their investment decisions) that the risks of ever getting an HIV vaccine are so high, and the expected time to delivery so far off, that all the figures discussed above have to be multiplied so many fold that there is even less incentive to engage in early HIV vaccine research. I would urge those lobbying hard for an early APC for HIV to the exclusion of lobbying for the collaborative parts and front-loaded parts of the approach to developing a high-quality HIV vaccine, to reassess whether it is the wisest use of their influence and not, in fact, counterproductive.

The advice (for what it is worth) I would give to those pushing heavily for an HIV APC would be to concentrate on APCs for all the late-stage areas in which they might have some strength (pneumococcus and rotavirus and many of the currently existing, but underused, vaccines such as measles, Hib-related diseases, pertussis, tetanus, etc.), where the scientific risk is relatively low, yet the market risk very high, the capital proportion of APCs (relatively) low, and the

advantages of APCs in creating more certainty high. Later, use experience from this to work out how APCs might ever work for complicated vaccines such as HIV. Meanwhile, if anything, totally downplay APCs for HIV, and instead push home to policy-makers that they need to bite the bullet about paying for up-front HIV vaccine work through a much more collaborative system than we now have. The hugely positive signal of success on the APCs above, the credible knowledge that they will work and be used again, coupled with the bullet-bitten approach of policy-makers to doing something about driving HIV vaccine work forward and the front-loaded funding needed to do it, will make eventual HIV APCs if ever they are used for HIV vaccines more powerful, cheaper, and easier to set.

The way things are going at present, we will finish the G8 summit in July with policy-makers patting themselves on the back that they have $20billion of (weak) APCs in place, but none of the really difficult and powerful parts of the mechanism for driving HIV vaccine development in place. The latter is more important; the former can be made to be 'contingent' on the former.

I would very much appreciate seeing some of the evidence discussed above.

Thank you, and good wishes,

Andrew Farlow
Department of Economics and Oriel College University of Oxford
http://www.economics.ox.ac.uk/members/andrew.farlow/ for papers on this issue.

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15 December 2004, 13h43

This posting was submitted by: "Charles Clift" cliftc@who.int

Dear All

We plan to end this discussion at the end of this week, or beginning of next.

Thank you to all contributors for what has been for us a very useful discussion with many high quality and thought provoking contributions. We are now much clearer about the pros and cons of these schemes. We hope to circulate a summary in due course.

Nevertheless, there are still loose ends and unanswered questions which might be addressed in the next few days.

I think, for instance, of the questions posed by Richard Mahoney on APCs:

http://astro.lyris.net/read/messages?id=53378

Or Trevor Jones on TIPR:

http://astro.lyris.net/read/messages?id=53840

The next discussion will be on "me-too" drugs., and we will introduce it next week. For this purpose we have made a short reading list which can be seen at:

http://www.who.int/intellectualproperty/topics/ip/incremental_drugs/en/

An introductory text is at:

http://www.who.int/intellectualproperty/forum/3rd_discussion/en/

Regards

Charles Clift
Secretary, CIPIH

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16 December 2004, 18h25

This posting was submitted by: "Charles Clift" cliftc@who.int

Dear All

I am circulating the report below from the SCIDEVNET website which draws on our forum.

Incidentally I recommend SciDevNet as an invaluable source of up to date news and information on matters relating to IPRs, innovation and public health (as well as other matters relating to science, technology and development) If you are not already registered with them (for their weekly e-mail of new postings on the site) please do so at:

http://www.scidev.net/index.cfm?fuseaction=register&registrationtype=1&CFID=2184075&CFTOKEN=61661610

Regards

Charles Clift
Secretary CIPIH

http://www.scidev.net/News/index.cfm?fuseaction=readNews&itemid=1798&language=1

Potential for public-private drug research 'untapped'
The tsetse fly transmits the sleeping sickness parasite Priya Shetty
16 December 2004
Source: SciDev.Net

Wealthy governments trying to help develop drugs for poor counties have been slow to recognise the potential for public-private partnerships, according to the UK-based Pharmaceutical R&D Policy Group (PRPG).

Since May 2004, the PRPG has been assessing different ways of funding drug development for 'neglected diseases' such as malaria and sleeping sickness that affect many people in poor countries but receive little attention from the global research community.

The group's director Mary Moran says the evaluation is needed now more than ever. Indeed, the United Kingdom plans to use its forthcoming presidency of the 'G8' group of industrialised nations to promote drug development for developing countries. To demonstrate this, it recently announced plans to make advance purchases of malaria and AIDS vaccines (see Britain to create market for AIDS and malaria vaccines).

"Governments need solid evidence on which to make judgments about which approaches to back," she adds.

Moran shared PRPG's initial findings last week (8 December) in an email-based discussion forum hosted by the World Health Organization's Commission on Intellectual Property Rights, Innovation and Public Health.

The study shows that two-thirds of projects developing drugs for neglected diseases involve public-private collaborations. The remainder are undertaken by pharmaceutical companies as profit-driven projects, which are often more expensive.

This, said Moran in the discussion forum, means "governments may be unwittingly steering companies away from low-cost partnerships and into a higher-cost commercial model although this low-cost model may offer opportunities for cheap, smart solutions".

Moran told SciDev.Net that despite an increase in public-private collaboration in drug development for neglected diseases since 2000, incentives from governments such as the United Kingdom's still focus predominantly on purely commercial research.

There is little information on how cost-effective existing approaches and incentives are and some ineffective systems have been in place for decades, says Moran.

For instance, in 1983 the United States adopted legislation giving pharmaceutical companies financial incentives to research and develop 'orphan' drugs for diseases, such as multiple myeloma, that affect few people in the United States. Although it has had little impact, a similar law was enacted by the European Union in 2000.

"Some public-private partnerships are virtually pharmaceutical companies, developing their own drugs, whereas others take the form of funding agencies," says Antony Taubman, head of the traditional knowledge division at the World Intellectual Property Organization.

This means the way intellectual property rights are managed also varies from partnership to partnership.

Tauban says the public sector generally wants either to own drug patents or to be given guarantees that drugs will reach developing countries. Such guarantees could take the shape of low prices or free distribution in poor nations.

"Industry on the other hand seeks certainty and partnerships that are reasonably low risk," he says.

For instance, the multinational pharmaceutical company GlaxoSmithKline recently lobbied the UK government for a deal that would extend the duration of their patents in return for undertaking research into drugs for neglected diseases (see Drug giant pushes for patent reform 'to help poor').

Public-private partnerships can also reduce demands placed on large pharmaceutical companies to invest in drugs for developing countries for little financial return: instead, they create projects that benefit several parties.

Taubman explains that this can happen in 'pro bono' agreements. A pharmaceutical company recruited to develop a malaria vaccine, for example, might receive sufficient revenue from selling the vaccines to a significant, and potentially lucrative, 'travellers market' in the developed world, which would subsidise vaccines for the developing world.

Based at the London School of Economics, the PRPG project was set up with one year's funding from the Wellcome Trust in May 2004. Moran's team hopes their study will influence global health policies including any discussed at next July's G8 summit in Scotland.

Related links:
Pharmaceutical R&D Policy Group
World Intellectual Property Organization World Health Organization's Commission on Intellectual Property Rights, Innovation and Public Health

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16 December 2004, 23h06

This posting was submitted by: "John Hurvitz" jhurvitz@cov.com

Dear Richard:

The Working Group asked me to respond to the questions that you posted regarding the AdvancedMarket proposal. By way of introduction, I am a partner at the law firm of Covington & Burling and I served as Legal Adviser to the Working Group. In that capacity, I assisted with structuring the contracts. I also had an opportunity to participate in many of the meetings with industry. With respect to those questions that are outside my area of expertise, I have taken guidance from other Working Group participants.

I have broken out your questions below in the numbered paragraphs. My responses follow each numbered paragraph. I have also attached a copy of my responses in a Word document, which may be easier to follow.

Please feel free to contact me with any further questions.

Best,

John A. Hurvitz
Covington & Burling
1201 Pennsylvania Ave., NW
Washington, DC 20004
p: 202-662-5319
f: 202-778-5319
jhurvitz@cov.com

1. Within what legal body does the IAC operate? On p. 83 of the Consultation Draft, it is stated, ..product specifications set not by the WHO, but by an independent sponsoring group or adjudication committee. To be a party to a contract, wont the IAC have to have a legal personality? In what way will it be legally independent?

We assumed the IAC would be created by contract and would not an independent legal identity. The Framework Agreement would establish rules for its operation, which would include procedures and commitments by the donors that would ensure its independence and integrity. This could be secured by ensuring that the members are conflict free, that the funding of the IAC is secure (e.g., not dependent on the decisions of the IAC), and that there is a mechanism to replace members when and if they retire. It was contemplated that the IAC would also rely on existing institutions, such as WHO, to carry out its responsibilities.

2. Since the recipient countries must make a co-payment, should they be parties to the AdvancedMarkets legally binding agreement? Dont the recipient countries, in effect, have a veto over the program? How would they wield this veto power? How many recipient countries would have to be parties to an agreement for it to have credibility?

No, the recipient countries would not be party to the legally binding agreement. The co-pay does allow recipient countries to exercise a choice about how much of the vaccine they want to buy, when it becomes available. This is a failsafe mechanism to ensure that donors are not committed to buying a vaccine which, though it meets the technical specification, is for some unforeseen reason not suitable. It also ensures that, if improved products are developed, demand can shift to those better products. The legally binding agreement does not guarantee a quantity that will be purchased from a given developer, it only guarantees the price that will be paid for a fixed number of doses (courses of treatment) of qualified products.

This arrangement deliberately leaves some demand risk to be managed by the developer; this is intended to ensure that the developer has an incentive to develop the best possible product. But it removes from the developer the demand risk associated with the negotiating power of donors, and the risk associated with the lack of available resources to buy vaccines.

3. Donors already know that vaccines are cost effective but have not met the needs of the Vaccine Fund. How does the AdvancedMarkets program change donors views about the relative value of investing in different health interventions or in other development strategies? Do we know why they don't put up the funds required today to buy hepatitis B vaccine?

Making legally binding commitments in advance increases the productivity of aid spending, because more predictable spending will create stronger economic incentives for the private sector, and reduce risk. The AdvancedMarkets commitment should, therefore, increase donors willingness to invest in health, as the impact of the aid dollars will be increased.

4. There a numerous references to consultations by the Working Group with industry. Given the rapidly growing capabilities of manufacturers in countries such as Brazil, China, Cuba, and India, why did the Working Group interview only the Serum Institute of India? Also how does the program account for the almost certain major changes in the vaccine industry during the coming 20 30 years? For example, what if by 2020 almost all R&D and production for vaccines needed in developing countries takes place in these advanced developing countries? Who predicted in 1970 that Korea would become one of the major developers and suppliers of hepatitis B vaccine by 1990? How could the computation spreadsheets take into account costs in developing countries?

The Working Group did not have as much contact with developing country industry as it would have liked. However, one advantage of the proposed mechanism is that it is open to any and all vaccine developers. It is not necessary for Governments making the commitment to know in advance which developer is likely to succeed in developing the vaccine.

The computation spreadsheets are not dependent on estimated costs of R&D or vaccine production.

5. Given the known failure risk of biotechnology firms, how does an AdvancedMarkets agreement involving these firms have credibility given the long lead times for vaccine development? Will the existence of an AdvancedMarkets agreement on the books of a biotech firm raise or lower its value to potential investors?

The requirements on firms in advance of a vaccine being available are very small (little more than identifying who they are and providing limited information regarding their progress). Signing an AdvancedMarkets agreement is optional for the firm it gives them the right to enforce the sponsors commitment and to obtain information and feedback from the IAC. The AdvancedMarkets commitment is essentially a call option for the firm: it is difficult to see how it could reduce the perceived value of a company to potential investors.

The Working Group considered the possibility of interim pull awards, similar to milestone payments, for developers that meet certain interim achievements short of obtaining approval-- e.g., commencing a Phase III trial for a product with endpoints that are consistent with the qualifying specifications. There types of payments are typical in agreements between biotechnology and pharmaceutical companies and would, therefore, be familiar to the venture capitalists and the capital markets. These types of interim pull payments would be particularly attractive to smaller biotechnology firms and could be easily worked into the AdvancedMarkets agreements.

6. How does the IAC distinguish a me too product? What if the only differences between the first and second products are that a) the second product is offered at a substantially lower price and b) the second product is produced in a country where the patents had not been filed for the first product and there were many developing countries that are potential users of the second product in which the patents for the first product also had not been filed?

A second or subsequent product would only be eligible for the guaranteed price if it is superior to the first product. A product that is manufactured at a lower cost, or that is not covered by IP protection, would not qualify unless it were also more effective than existing qualified products. However, depending on how the rules are established for a given AdvancedMarkets contract, an innovative product that is equally effective as an existing product could qualify if its cost of manufacture were significantly lower than the existing product. Although manufacturing costs will not be an issue with respect to qualified product that for so long as it is subject to the price guarantee, as the guarantee is fixed in advance, the AdvancedMarkets contracts are also designed to ensure that product will continue to be available to developing countries at reasonable prices once the guarantee is exhausted. Manufacturing costs are obviously an important component of the ongoing price of a product.

7. Appendix C: Draft Term Sheet for Guaranty Agreement specifies that The Designated Supplier shall own all right, title and interest in and to the Approved Vaccine. How can the agreement do this? Arent patent rights (and other IP rights) granted by sovereign governments and arent patents rights protected or voided in the courts of sovereign governments? What if the inventor chooses not to obtain patent protection (as mentioned above) in various countries of interest?

Contracts can re-assign intellectual property rights; the purpose of this clause is to make it clear that this contract does not do so. The developer will keep its IP rights (unless it defaults on its long term obligation to supply the vaccine at a low price, in which case it grants a license to permit others to manufacture and supply product for indigenous use in developing countries). It is entirely up to a developer to decide whether an where to obtain patent protection; it can decide not to obtain or enforce patent protection if it wishes.

8. The Consultation Draft notes on p. 56 that the price would be per course and not per dose. To what extent is the cost of development and of production of a vaccine dependent on the

number of doses required to achieve the desired level of protection? The proposed strategy is said to be justified because it will encourage developers to produce single-dose, long-acting vaccines. But what if the science does not allow this and yet the vaccine costs more than $5 per dose to produce (a three-dose vaccine course where the AdvancedMarkets agreement had laid out $15 for a course). To what extent has the Working Group debated the issue of a procurement mechanism seeking to drive an R&D effort?

The contract is intended to give developers the incentive to create a low cost vaccine that meets the technical specification, if at all possible. If a developer produces a vaccine that is more expensive than $15 per course, they are unlikely to want to avail themselves of the AdvancedMarkets mechanism (as this guarantees the price at $15). They would be in the same position as they are now, of seeking to negotiate an agreement with recipient countries and donors. The AdvancedMarkets commitment makes them no worse off than they would be in the absence of the commitment. The Working Group attached importance to ensuring that the procurement mechanism should create the best possible incentives for developers to target their R&D on optimal products, characteristics and presentations.

9. How will liability issues be handled for the individuals involved, for example, as members of the IAC? Will the suppliers agree to hold these parties harmless in all jurisdictions for all causes? What if the suppliers are the ones to sue the IAC?

As noted in Section 5(c) of the Framework Agreement, the donors would be responsible for indemnifying the members of the IAC. The donors could purchase an insurance policy or, depending on the legal status of the donors, enter into an indemnification agreement. In either case, the indemnification obligation would need to be irrevocable to ensure the independence of the IAC.

10. The issues with respect to legal aegis are illustrated by Appendix B, Draft Term Sheet for Framework Agreement. For example the Representations and Warranties section is indicated TBD (to be determined). It is in the Warranties that the signatories verify that they have the right and authority to make the commitments contained in the Agreement. What legal entity(ies) will have these rights and authorities? Governing Law is shown as New York. Will Cuba, for example, be able to participate in the program?

The nature of the representations and warranties will be determined, in part, by the identity of the donors that are participating. The representations and warranties that a government makes will be different than those that a private foundation would make. In addition, certain governments may not be able to make credible future commitments based on their budget authority. The particulars of the representations and warranties, as well as the need for other provisions to ensure the enforceability of the pull commitment, will need to be worked out on a case-by-case basis.

Governing law would obviously be determined, in part, by the identity of the donors. New York law was selected for purposes of the form contracts, because it has a well established body of contract and commercial law and because its choice of law rules expressly provide that the selection of NY law in a contract involving more than $500,000 provides the necessary contacts to the State for choice of law purposes.

11. the current strategy seems to lock out developing country companies for some time when in fact they may be the major sources of innovation in the future for health products for the poor in their countries: consider Cuba. Is it possible to arrange for these groups to participate from the start? As currently constructed, the program seems to discriminate against developing country producers in favor of large developed country developers/manufacturers.

On the contrary, the Working Group envisions an open contract that is available to any supplier that produces an eligible vaccine, including those from developing country companies. One contrast with other interventions is that sponsors do not pick which companies to support in advance.

12. more attention needs to be paid to issues concerning the legal aegis under which this program would be conducted. Vaccine regulation and IP are sovereign nation issues. (I use the term "sovereign" to include International Organizations such as WHO and the World Bank which must operate in accord with various treaties that have legal force. Foundations must operate according to the laws of the countries in which they are based.) A good beginning would be to specify the exact legal status of the IAC even though that specification may lead to complex political considerations.

As noted above, the specific choice of law will likely depend upon the identity of the donors. However, the contracts do not affect the local regulation of intellectual property or vaccines. A vaccine must be qualified under the contract to be eligible for the price guarantee, but the vaccine must also be qualified for use in a developing country under the laws of that country and purchased by that country in order for the supplier to receive a payment under the contract. As discussed, the contracts do not alter the applicable intellectual property regimes; a license would be granted, which is a matter of contract, if and only if the supplier obtained certain minimum payments under the contract with respect to a product and then failed to meet the ongoing requirements of such product in the qualifying countries, which license, in any event, would be limited to indigenous use in the developing countries.

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17 December 2004, 03h06

This posting was submitted by: "Ernst R. Berndt" eberndt@mit.edu

I read with interest Andrew Farlows review of Strong Medicine from the Lancet, which was posted on this discussion forum, as well as the message he subsequently posted here concerning the costs of research.

Dr Farlow appears to misunderstand both the ideas in the Kremer & Glennerster book, and the practical proposals in the CGD Working Group report.

Scientific progress in medicine has, in the past century, been made through a combination of publicly funded research, collaborative work between the public and private sector, and through investment by research-based pharmaceutical and biotech companies. Very few medicines have ever been developed without a contribution from both public and private sectors. But a critical part of the puzzle is missing for diseases that mainly afflict the poor: the expected market return is insufficient to provide an incentive for private firms to invest in bringing the product to market through clinical trials, regulatory approval and investment in production capacity. In short, our arrangements for funding R&D are more generous for rich country diseases than for the diseases of the poor.

Dr Farlow is simply wrong to say that the proposal in Strong Medicine favors large pharmaceutical firms it is deliberately neutral, allowing any company, small or large, North or South, biotech or pharmaceutical, to benefit from the contract. He is wrong to say that the proposal depends on a particular model of scientific progress one benefit of this incentive is that it rewards scientific advances however they are achieved. He is also wrong to say that it is uncharitable to the many people who devote their lives to scientific research on the contrary, it takes the position that these efforts should be rewarded by society as much as the efforts of those who research into other diseases. He is wrong to say that it would require centralized

control of global public research the proposal requires relatively little prescription on the part of governments. He is wrong to say that those who support advance purchase commitments do so to the exclusion of supporting up-front finance of public research and public-private partnerships. All these policies are important, complementary components of an end-to-end strategy for supporting the development of new vaccines.

Dr Farlow points out, in his later posting on this forum, that the private sector faces capital costs which will need to be repaid through the vaccine purchase. Are we to conclude that, because in general, the public sector cost of capital is lower than private sector financing costs, the public sector should therefore finance all investments? Why would this be true for medicines but not for other goods and services? For as long as the private sector makes R&D investments financed through the private market, ultimately customers will have to pay the cost of capital one way or another - but by putting in place an advance purchase commitment, the overall risk, and hence the cost of capital that will need to be repaid, is lower.

It is of course possible for people to believe sincerely that society's arrangements for funding medical R&D are all wrong, and that instead of competition between firms, we should have collaboration; instead of patents, we should have open access; instead of making consumers pay for R&D through the purchase price, governments should fund R&D directly; and that instead of lending from private capital markets, governments should exploit their lower cost of capital to fund investments. These arguments would apply equally to research into breast cancer and arthritis, and other diseases of rich countries, as they would into AIDS and malaria. But for now, society's preference remains that R&D should be a mixture of public and private funding. While this is the case, don't the diseases of the poor deserve the same overall package of incentives for research as the diseases of the rich?

Ernst R. Berndt

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17 December 2004, 06h47

This posting was submitted by: Jeff Williams <jwkckid1@ix.netcom.com> John and all,

Thank you for you brief answers to some of the questions posed.

I must say that our members along with myself have a concern in IAC relying on WHO to carry out IAC's responsibilities, if that was your meaning? WHO as far as I know is not well suited to do such, and with recent UN scandals being uncovered and spreading in scope, it would be very unlikely that WHO will escape future scrutiny.

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17 December 2004, 11h47

This posting was submitted by: Mary Moran

Dear Charles

Thanks for this alert - as you noted, SciDevNet is an interesting site.

There's just a couple of points in the article that I'd like to comment on, as it helps to be quite clear as to what we're saying. The SciDevNet article noted that around 1/3 of industry projects were "undertaken by pharmaceutical companies as profit-driven projects, which are often more

expensive". What our analysis showed, though, was that around 1/3 were undertaken by industry under the in-house commercial model (rather than in partnerships) - but this does not necessarily mean they were profit-driven, with CoArtem being a good example.

Also, I'd hesitate to say that Orphan Drug has been ineffective overall, since it's had a substantial impact on Western Orphans, where the market dynamics are quite different - its really in the neglected disease area where it's ineffective.

But these are minor points! Merry Xmas to all.

Mary

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17 December 2004, 15h37

This posting was submitted by: "Hurvitz, John" jhurvitz@cov.com

The Working Group had explored the possibility that the WHO prequalification process could be relied on to ensure that qualifying product met certain safety and efficacy requirements and that its manufacture was in compliance with relevant standards. My understanding is that the WHO already performs these functions. The one question was whether the WHO process could be tied to the minimum safety and efficacy standards established in the advanced purchase contracts.

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17 December 2004, 17h01

This posting was submitted by: "Charles Clift" cliftc@who.int

Posted by the Secretariat on behalf of Kevin Outterson.

A few thoughts on US orphan drug incentives and TIPRs.

Orphan drugs
Undoubtably, orphan drug incentives in the US have subsidized increasing amounts of R&D. In recent years, the US tax expenditure budget for orphan drug research has increased dramatically, and now stands at over $300 million per year. In addition, the ODA grants 7 years exclusivity to orphan drugs, delaying generic entry and permitting the collection of additional patent rents (I am not aware of a dollar figure for the incremental value of this 'subsidy' but it may well be more than the $300 mm annual figure for the tax credits).

A more interesting question is whether the subsidies are efficient, whether the program is a success. Proponents point to the many drugs which have received OD designation as evidence of success. Some of these widely-used drugs such as AZT, Epo, and Taxol. Skeptics would ask how did these extremely popular drugs ever qualify for 'orphan' status. The answer lies in the US definition of orphan drug. For purposes of the US Tax Code, an orphan drug is designed to treat a condition afflicting 250,000 or fewer US residents (it is a one-time test). Companies slice up definitions of diseases into narrow clinical categories in order to get under the 250,000 limit; they

also underestimate the ultimate market potential of drugs. Even if the drug treats 10 orphan conditions (ie, 10 different types of cancer) with a total market of 2 million Americans, it could qualify as an orphan drug for 10 conditions. ! This is a far cry from the paradigm case of orphan drug research usually touted to Congress. The large number of OD designations, and the eventual combined markets for these drugs suggest that perhaps the system is being gamed to garner additional incentives for ordinary R&D, rather than really focusing the additional subsidies on truly orphan conditions. The question should be asked whether the output level of truly orphan R&D could have been bought more cheaply with NIH funding, AdvancedMarkets contracts, or some other funding mechanism. (The US experience with pediatric exclusivity also raises this same question).

The US-centric definition of orphan drug may be helpful in global neglected diseases: the incidence of Chagas disease amongst Americans might well qualify for OD designation, despite the millions of persons in South and Central America with the disease. In a sense, the US tax code already features an open-ended subsidy for US-based global neglected disease R&D, so long as the incidence is relatively rare in the US. Malaria and TB should qualify (with slicing), together with all of the other neglected tropical infectious diseases. This is an opportunity which does not require additional legislation.

TIPRs
A current bill in the US Congress (S. 666, Biological, Chemical, and Radiological Weapons Countermeasures Research Act) grants a transferable 2 year extension for certain categories of war on terror research. (http://thomas.loc.gov/ Search for s.666). A host of questions ensue:

1. A company qualifies for a TIPR if it patents an 'eligible countermeasure' which is contracted to the US government for use. Existing drugs could qualify, and drugs could well have earned this designation while having many broader uses. Given US experience with both orphan drugs and pediatric exclusivity, the definition of the trigger for being awarded a TIPR will be critical. Too broad a definition will dilute the efficiency of the process. Prizes and APCs face similar issues.

2. The 2 year extension is transferrable only within the firm: thus a 2 year extension is more valuable to big PhRMA (think Lipitor) than other companies. The proposed law limits the extension to firms with gross assets under $750mm (locking big PhRMA out), and limits trading. Making the extensions fully tradeable would maximize their value.

3. Either way, the value of the extensions declines as more are issued, but there is no system to prioritize which inventions were more valuable. A modest 'me-too' drug, if certified quickly, could give a company 2 more years of market exclusivity for a valuable drug. A truly innovative first in class drug, approved a few years later, might generate much smaller rewards from the TIPR. The connection in the patent system between the value of the invention and the patent rents is severed. This strikes me as a very bad idea.

4. Very little reliable evidence exists that demonstrates that current R&D incentives for these drugs are sub-optimal. Billions would be 'spent' under this plan, money that could have been (perhaps) better allocated to other R&D (or to uses other than R&D). Where is the data to support this allocation?

5. In addition to TIPR, the proposed law also expands many other appropriation techniques for 'eligible countermeasures' such as data exclusivity (from 5 to 10 years), orphan drug exclusivity (from 7 to 10), additional tax breaks, and expanded Hatch-Waxman 'restoration' provisions.

6. I am troubled that the costs of these subsidies are spread in such a non-transparent and un-accountable fashion. Some of the costs are borne out of general federal tax revenue (tax expenditures - not subject to an appropriations process); others are borne very indirectly by all health care payors and patients in the form of higher drug costs due to delayed generic entry.

With TIPRs, the costs will be carried very remotely by others (people with high blood lipids, and their payors). This will not show up as a line item on anyone's bill.

The more transparent and accountable method would be to simply pay full value for the government contracts. In the proposed TIPR legislation, an 'eligible countermeasure' must also have a signed procurement contract with the government. If so, that contract is the appropriate place to fund the subsidy.

I am sure that other questions can be raised, but I just wanted to move the discussion along. I look forward to seeing the LSE report.

Kevin Outterson

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17 December 2004, 17h57

This posting was submitted by: "Kevin Outterson"

From the FDA Cumulative List of Orphan Drug Designations (2004):

Generic Name:
rofecoxib

Indication Designated:
Treatment of juvenile rheumatoid arthritis

Trade Name (if present):
VIOXX

Sponsor and Address
MERCK & Co., Inc.
126 East Lincoln Ave.

Date Designated:
3/16/2004

Rahway NJ 07065 !

Marketing Exculsivity Date:

Kevin Outterson

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18 December 2004, 08h29

This posting was submitted by: Jeff Williams jwkckid1@ix.netcom.com

Ernst and all,

I as I am sure most logical folks would agree that the diseases of the rich are the same as those of the poor. Disease has no sense of economic status. However it is unlikely that the costs of treating disease can be structured to be affordable to the poor without significant dedication from the rich to recognize that the poor are as important to treat equally as the rich...

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20 December 2004, 09h49

This posting was submitted by: "Sunil Deepak" sunil.deepak@aifo.it

The diseases of the rich (developed) countries are not the same as the diseases of the poor countries. Even inside countries like India, Mozambique or Brazil, diseases like leprosy affect much more the poor than the better off. Probably lot of factors including living conditions, nutrition, vaccination, etc. come into play. Costs of the drugs is a crucial, though not the only factor influencing the access to health services for the poor.

Regards, Sunil Deepak

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20 December 2004, 09h52

This posting was submitted by: Harvey Bale

Regarding the last posting I saw from the CIPIH on orphan drug legislation, mentioning Vioxx, I wonder whether Professor Outterson would like to confirm his logical system. It seems to be as follows:

1) The FDA and a number of other reputable national regulatory officials approved Vioxx -- a COX-2 inhibitor; subsequently, the originating company received orphan drug approval for a certain seriously debilitating juvenile indication

2) However, following approval of Vioxx by such agencies, in much wider use in populations the drug was found to have certain serious adverse effects on a number of individuals and the company decided to withdraw the product from the market rather than seek additional warnings on its approved labelling from regulatory authorities

4) Therefore, and rather strangely I suggest, this sequence somehow has something to do with the system of orphan drug incentives that have been in place in the United States, Europe, Japan, Singapore and elsewhere for a number of years, yielding many new useful medicines for cystic fibrosis, etc. What novel logical system is the good professor from West Virginia using? I.e, what do scientific issues involved in the very nature of drug development and approval have to do with orphan drug incentives? Normal logic suggests that the answer is: "nothing at all." But he, perhaps, has a "new math" logical system that he is expounding.

Dr. Harvey E. Bale

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20 December 2004, 21h37

This posting was submitted by: "Charles Clift" cliftc@who.int

Dear All

We are posting this on behalf of Professor Outterson for a particular reason.

That is, I would like to draw participants' attention to the following guidelines for the discussion posted on our website:

"The principles of moderation will be that all views should be posted, except when they are personally or otherwise abusive, completely off the subject, or may otherwise be thought to transgress the conventions of reasonable debate. We hope discussions will be constructive and amicable, and draw, wherever possible, on evidence."

There is a danger that these rules will be transgressed. Harvey Bale said:

"What novel logical system is the good professor from West Virginia using? I.e, what do scientific issues involved in the very nature of drug development and approval have to do with orphan drug incentives? Normal logic suggests that the answer is: "nothing at all." But he, perhaps, has a "new math" logical system that he is expounding."

In response, Kevin Outterson says:

"I look forward to comments on these thoughts, but I do ask Dr. Bale to resist the temptation to resort to ad hominem attacks in the future."

In retrospect, these comments transgress the guidelines. In future the moderators will be stricter about posting submissions that contain even a hint of personal attacks. Please take note and abide by the rules, which are surely in all our best interests.

Charles Clift
Secretary CIPIH

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Dr. Bale,

The point in my brief posting was to give an example of an orphan drug designation which did not fit the "paradigm case" of orphan drugs (Vioxx was listed as an US orphan drug in March 2004).

The larger policy issue (discussed in my posting earlier that day, appended at the bottom, below) was that we needed to evaluate the efficiency of incentives such as orphan drug designations, pediatric testing and TIPRs.
To take the example of Vioxx, what did it cost to discover that Vioxx was indicated for the pediatric disorder? What was the public cost, in terms of the R&D tax incentives and the longer market exclusivity for Vioxx? Can we do a cost-benefit analysis of this, and make a reasoned guess as to whether the incentive was efficient? Or perhaps another funding mechanism would have been better?

These are important questions; ones that should be studied. My prior posting outlined some preliminary thoughts. I look forward to comments on these thoughts, but I do ask Dr. Bale to resist the temptation to resort to ad hominem attacks in the future.

Kevin Outterson

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21 December 2004, 19h40

This posting was submitted by: "Richard Mahoney"

Dear John,

Thank you for taking the time to respond to my questions. In the interest of transparency, it would be nice to know which members of the Working Group asked you to respond and which Working Group members provided guidance. This is important not for purposes of identifying the individuals but for knowing which organizations are taking the lead in this venture. Also, it is important to know if these individuals represented the full Working Group and thus your responses would represent a consensus. Proposals representing the potential allocation of billions of dollars should be debated with the greatest level of transparency. I believe the Global Fund to Fight AIDS, Malaria and TB has done very well along this line.

If the IAC is not an independent legal body, it would derive its legitimacy only through the legally established organizations that create it. Thus, one wonders how those organizations will deal with changing events, for example, without becoming directly involved in the operations of the IAC. The IAC could not, in my view, be intellectually and operationally independent. The founding organizations could and should be involved in its operations, which means, de facto, it is not independent. They are paying for it; their reputations are at stake; and they have vital policy and financial interests that they must be able to exercise.

Your sentence, "This is a failsafe mechanism to ensure that donors are not committed to buying a vaccine which, though it meets the technical specification, is for some unforeseen reason not suitable." only supports the intent of my question, i.e. recipient countries would indeed have a veto power over the program and thus could use that power for a wide range of purposes. Also, it shows that the procurement guarantee is not a guarantee, but simply a statement of intent dependent on the views, wishes and financial resources of recipient countries.

With respect to your comment about how AdvancedMarkets commitments would impact the priorities of donors, I would observe that the lives of millions of HIV infected children in Africa could be saved with the purchase now of antiretrovirals and yet the important 3X5 initiative languishes. As other commentators have noted, an AdvancedMarkets commitment could give leaders the chance of appearing that they had done something.

Your sentence, "These types of interim pull payments would be particularly attractive to smaller biotechnology firms and could be easily worked into the AdvancedMarkets agreements." seems not to take into account the extraordinarily complicated way in which vaccine R&D takes place. Milestones are built into donor contracts, venture capital investment agreements, and even internally within companies. If the AdvancedMarkets agreements were to incorporate additional milestones, the complexity of the overall agreement, in at least some cases, would be extraordinary and would require great expertise in vaccine R&D on the side of the AdvancedMarkets program. For example, who would adjudicate whether a milestone had been reached when there was disagreement?

With respect to IP, I don't see how the AdvancedMarkets agreements can say anything about patents without the concurrence, in the first place, of the private company(ies) that holds the patents or may obtain the patents. Therefore, statements ensuring that certain actions will not be taken in the future have no meaning unless they are agreed to at the beginning. The IAC or whatever entity that would sign the agreement would not have the authority to do anything about patents. (Even sovereign nations could not make the commitment unless they revised the way in which their courts worked.) As I noted before, patents are granted by sovereign nations and patents are adjudicated by the courts of sovereign nations. (An exception could be if the

establishment of the IAC was carried out through an international treaty wherein the member countries agreed to pass over to the IAC their sovereignty with respect to patents.)

It is very interesting to learn that donors are willing to accept liability for the proposed arrangements.

Your answer with respect to Representations and Warranties indicates that this most important matter will be worked out in the future.

With respect to your answer concerning the legal aegis of the IAC, can you say what individual (title and affiliation) would sign an AdvancedMarkets agreement on behalf of the AdvancedMarkets program? Or would it be all the legally established organizations that had set up the IAC?

The establishment of a pull mechanism that would cause excellent research-based pharmaceutical companies to raise the priority of vaccines needed by the poor would be a wonderful achievement. I very much hope the key questions can be answered satisfactorily and that eventually we can have such a mechanism.

It seems to me that the first order of priority with respect to vaccines should be to fund fully the existing product procurement/donation mechanisms run by foundations, companies, non-governmental organizations, and international bodies. These actions could save hundreds of thousands of lives today. With respect to vaccines, the first priorities should include funding fully the requirements for a) hepatitis B vaccine, b) haemophilus influenzae vaccine, c) rotavirus vaccine, d) HPV vaccine (when that product soon enters the market), e) a cholera vaccine emergency supply, and f) the conjugated typhoid vaccine emerging from research at NIH, IVI, Vietnam, and elsewhere. In addition, priorities should include preparing arrangements to buy a) the malaria vaccine of GSK developed with MVI (if further testing confirms the promise), b) the meningitis C vaccine being developed by a consortium under WHO and PATH, and c) a pneumococcal vaccine against the important strains in developing countries. Shining success in these efforts will be essential in proving to the private sector that the public sector is committed to providing vaccines to the poor.

In addition, there should be full funding of the delivery mechanisms for these vaccines. Indeed, the absence of any provisions within the AdvancedMarkets proposal to address the need for funds to distribute the vaccines seems to be another unresolved problem. It would seem unwise to establish a multi-billion dollar AdvancedMarkets scheme without also having in place an "AdvancedDistribution" scheme.

An open and transparent debate of the issues can only serve to improve the outcome. I admire the efforts and devotion of the Working Group. But much further work is needed, in my opinion.

Richard T. Mahoney

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22 December 09h25

This posting was submitted by: Eric Dierker

I worry with this posting on the slightest suggestion that ideas and thoughts follow protocal and open and transparent methodology. Ideas on making things work can be one man and one continuous thought. The open and transparent process should be a methodology employeed in

the adoption and implementation of ideas not necessarily vice versa.
I particularly support the idea, as laid out in this letter, of focusing on a particular disease and a vaccine. Then using the approach of applying all, sociological, economic, political and scientific problem solving techniques to arrive at solutions. Creation of a "one size fits all" solution will established norms to hurdles yet to be encountered. Working groups and tasks forces are a fine model for vetting out good concepts and making them work in an everchanging dynamic environment which include governments and free enterprise and indeed religious and moral questions. We must never operate in a vacuum of either openness or closeness. The best technical answers will never reach application without approval of those they are designed to help.

Sincerely,
Dr. Eric Hugh Dierker
