



## **BRIEFING NOTE ON ADVANCE PURCHASE COMMITMENTS**

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## EXECUTIVE SUMMARY

Together, malaria, HIV, and tuberculosis kill 5 million people each year, almost all of them in poor countries. Yet research and development (R&D) on health technologies for these and other diseases concentrated in poor countries remains minimal. One proposal to incentivise private sector investment in R&D for these diseases is for sponsors to undertake 'advance purchase commitments' for desired products, and we here discuss issues relevant to such proposals.

We first present a taxonomy of products to which advance purchase contracts could be applied (early-stage R&D, late-stage R&D, and existing products; vaccines, diagnostics and drug treatments) as well as a taxonomy of firm types (biotechs, pharmaceutical firms, and emerging market suppliers).

We then discuss issues relevant to R&D on diseases concentrated in poor countries. The markets for diseases concentrated in poor countries are small not only due to the poverty of the relevant populations, but also due to several severe market failures. Most notably, firms face a threat that once R&D costs have been sunk, government and other large purchasers of products for poor countries will bargain down prices to levels which do not allow firms to recoup their R&D investments.

In markets for diseases prevalent in rich countries, direct 'push' R&D financing and 'pull' market incentives combine to spur innovation; several push initiatives are in place for diseases concentrated in poor countries, but there is a lack of complementary pull incentives to encourage the transformation of basic research into useable product. Both theory and evidence suggest pull-like policies can spur R&D investments and innovation, and we critically review of number of possible structures for pull incentive mechanisms.

We then provide a taxonomy of various advance contracting arrangements, and discuss the principle ways in which advance purchase commitments differ from other advance contracting arrangements. A primary difference is that, unlike other unbinding "promises to purchase," advance purchase commitments are enforceable by contract law and thus should be much more effective at mobilizing additional R&D investments in products which do not yet exist.

Drawing on these discussions, we then review the potential for advance purchase commitments – including which products they may be most appropriate for, how different firms may be expected to respond, and what design issues are most critical in the implementation of advance purchase commitments.

In terms of types of products, the critical design issues with advance purchase commitments seem to be most easily dealt with in the case of vaccines and this is where most thinking has taken place; however, the approach is potentially applicable to drug treatments and diagnostics as well. In terms of the timing of when to introduce advance purchase commitments there is recognition of their value for late-stage products but concern that scientific uncertainty may make contracts for early-stage products harder to put in place and to manage over time. On the other hand, there are strong arguments that advance purchase commitments would be useful for early-stage products. For any given size of commitment (in terms of the amount of money and end product purchases), announcing earlier rather than later will align incentives earlier, and accelerate R&D efforts towards the end goal of a useable product which is suitable for use in poor countries.

Consultations undertaken by the Center for Global Development indicate private sector interest in advanced purchase commitments. They suggest that for products at an early stage an advance-

purchase commitment may initially motivate biotechs and potentially the venture capitalists which provide their funding, while some larger multinational pharmaceutical firms may get involved only after further advances in the science, perhaps led by biotech firms. This finding is supported by anecdotal evidence that biotechs responded more enthusiastically than big pharmaceutical companies to orphan drug incentives and to the BioShield incentives in the US. Biotechs would be more willing to invest because they would be more confident that they would attract interest from pharmaceutical companies for the products they develop. There is considerable evidence that firms respond to market signals by adjusting their R&D to reflect the size of the potential market.

There are several critical issues that need to be considered when thinking about whether and how to move ahead with advance purchase commitments for vaccines or other products. Further and more targeted analytic work by governments, industry and public health experts is needed on several key topics. Priorities for further work include:

- Strengthening the financing for the purchase of existing health products, and strengthening health systems in developing countries to increase coverage of vaccines and other health technologies;
- Developing advance market commitments with producers of late stage products that will be available in the near future, using the commitment to negotiate on price, timing of supply, and characteristics of the products and their presentation;
- For products that are at an early stage:
  - Considering the specific issues with respect to individual diseases (such as the likely demand from high-income and middle-income markets)
  - Validating estimates of the market size needed to induce private sector investment in R&D, using alternative datasets for market revenues;
  - Working closely with industry and the public health community to develop the contractual framework, including addressing the various design choices highlighted here;
  - Developing technical specifications for each product, in collaboration with developing country health specialists and the scientific community;
  - Considering what adaptations, if any, should be made to mechanisms for funding R&D in the context of an advance market commitment, in particular ensuring complementarity with the important and push incentives provided by structures such as Product Development Public-Private Partnership (or PD-PPPs).
- Considering how this approach might be extended to other diseases that affect the developing world, such as schistosomiasis or leishmaniasis;
- Considering whether this approach could be applied to drug treatments, including microbicides, and diagnostic tests.

## 1 INTRODUCTION

### 1.1 Purpose of this note

Together, malaria, HIV, and tuberculosis kill 5 million people each year, almost all of them in poor countries. Yet research and development (R&D) on health technologies for these and other diseases concentrated in poor countries remains minimal. One commonly cited estimate is that whilst half of all global health R&D in 1992 was undertaken by private industry, less than 5 percent was spent on diseases specific to poor countries.<sup>1</sup>

One proposal to incentivise private sector investment in diseases concentrated in poor countries is for sponsors to undertake 'advance purchase commitments' for desired products. In November 2004, Chancellor of the Exchequer Gordon Brown announced that the UK government, working in cooperation with other donors, would be willing to enter into an advance purchase commitment for a malaria vaccine as a way of establishing a market sufficient to incentivise greater industry investment in the development and launch of a malaria vaccine. The Chancellor also announced that the UK will explore the potential use of advance purchase commitments for HIV vaccines.

This note is targeted towards a generalist 'access to medicines' audience, rather than to 'pull mechanisms' specialists. It is intended as a communication tool, to help enable donors and practitioners entering into discussions on advance purchase commitments to identify areas requiring further work by DFID. In particular, it seeks to set out:

- A taxonomy of product types, giving an explanation of economic and development characteristics of different product types (e.g. drugs versus vaccines, late stage R&D versus early stage R&D products);
- A taxonomy of firm types (e.g. biotechnology companies, large R&D-based pharmaceutical companies, and emerging market suppliers); and
- A taxonomy of advance purchasing contracts and commitments. 'Advance purchase commitments' and 'advance contracting' are used by a variety of commentators to refer to a range of different mechanisms. This note identifies and clarifies the differences between various advance contracting schemes as well as other 'pull' mechanisms and discusses design issues.

It then draws on these taxonomies to discuss issues related to advance purchase commitments – including which products they may be most appropriate for, how different firms may be expected to respond, and which implementation issues are most critical.

A working group convened by the Center for Global Development (CGD), with the support of the Bill & Melinda Gates Foundation, developed a report recommending how advance purchase commitments for vaccines could be implemented.<sup>2</sup> In this note we will reference the CGD proposal as the benchmark structure of an advance purchase commitment, and will draw on the analysis set out in that report. We also draw from Kremer and Glennerster (2004),<sup>3</sup> who lay out the rationale for advance purchase commitments and discuss design issues; Berndt and Hurvitz (forthcoming),<sup>4</sup> who discuss some of the legal and economic practicalities of structuring advance purchase commitments; Berndt *et al.* (2005),<sup>5</sup> who present a cost-effectiveness analysis of advance purchase commitments for the case of a malaria vaccine; Kettler and Towse (2002),<sup>6</sup> who provide an overview of the pharmaceutical R&D landscape; Towse and Kettler (2005),<sup>7</sup> who review design issues in advance purchase commitments; and Farlow (2005)<sup>8</sup> and Maurer *et al.* (2004),<sup>9</sup> who set out criticisms of advance purchase commitments.

## 1.2 Why new health technologies are needed for poor countries, in addition to improved distribution of existing products

Many lives in poor countries could be saved with improved access to existing health technologies. For example, three million people die every year of diseases preventable with existing vaccines.

However, the need for accelerated development of new health technologies targeted to and appropriate for the epidemiological conditions and health systems of poor countries cannot be understated. In recent decades much of the improved health in poor countries has been due to the wide-spread adoption of cheap, easy-to-use technologies that were developed in response to incentives provided by prospective sales in rich country markets. Vaccines are the best example: 74 percent of the world's children now receive a standard package of cheap, off-patent vaccines through the World Health Organization's (WHO) Expanded Programme on Immunization (EPI). These vaccines save some 3 million lives per year – almost 10,000 lives a day – and protect millions more from illness and permanent disability.<sup>10</sup>

Poor countries have benefited enormously from such products, but this has been, for the most part, a fortunate byproduct. Little public or private sector R&D is targeted towards developing new health technologies for diseases concentrated in poor countries. Of the 1,233 drugs licensed worldwide between 1975 and 1997, only 13 were for tropical diseases; of these 13, five came from veterinary research, two were modifications of existing medicines, and two were produced for the US military – only four were developed by commercial pharmaceutical firms specifically for tropical diseases of humans.<sup>11</sup> Even for diseases that are major health issues in rich countries, R&D on these diseases may not result in products that easily spill over to the epidemiological conditions and health systems of poor countries. For example, in the case of HIV most R&D is focused on the strain of the virus common in rich countries, and is on drug treatments rather than vaccines – treatments which are more difficult than vaccines to deliver in poor countries with weak health care infrastructures.

## 1.3 Overview

In this report, we review several topics related to advance purchase commitments as relevant to health products for diseases concentrated in poor countries:

- In Section 2, we provide a taxonomy of products to which advance purchase contracts could be applied. We discuss one classification based on stage of development (early-stage R&D, late-stage R&D, and existing products) and a second classification based on therapeutic category (vaccines, diagnostics and drug treatments).
- In Section 3, we provide a taxonomy of firm types (biotechs, pharmaceutical firms, and emerging market suppliers).
- In Section 4, we provide a background on R&D as related to diseases concentrated in poor countries. We review relevant market failures (both static and dynamic), discuss the complementary roles of 'push' and 'pull' incentives, discuss precedents which suggest pull-like incentives can spur R&D investments and innovation, and review various structures through which pull incentives can be implemented.
- In Section 5, we provide a taxonomy of various advance contracting arrangements, and discuss the principle ways in which advance purchase commitments differ from other advance contracting arrangements.
- Finally, in Section 6 we discuss the potential for advance purchase commitments – including which products they may be most appropriate for, how different firms (biotechs, pharmaceutical firms, emerging market suppliers) may be expected to respond, and what design issues are most critical in the implementation of advance purchase commitments.

## 2 TAXONOMY OF PRODUCT TYPES

In this section we provide a taxonomy of product types, classified first by stage of development and second by therapeutic category.

### 2.1 Taxonomy of products by stage of development

#### 2.1.1 *Early-stage products*

Early-stage products can be defined as those for which scientific progress and extensive testing of numerous candidates is needed (say, pre-Phase III clinical trials).

An example of an early stage product is a vaccine for malaria. There are around fourteen candidate malaria vaccines currently registered as being in development:<sup>12</sup> two in Phase II trials, four in Phase I trials, and eight pre-clinical.

In October 2004, Phase IIb trial results were released for a candidate malaria vaccine which had been under development at GlaxoSmithKline (GSK) Biologicals for more than fifteen years, and which came “off the shelf” with the support of a Product Development Public-Private Partnership (PD-PPP) called MVI (the Malaria Vaccine Initiative, mostly funded by the Bill & Melinda Gates Foundation) and the Mozambique Ministry of Health. The phase IIb trial study, published in *The Lancet*,<sup>13</sup> found that the vaccine’s efficacy against severe malaria disease was 58 percent, and argued the results of the trial “demonstrate the feasibility of an efficacious vaccine against malaria.” Although promising, substantial additional work is needed before this vaccine or others would be ready for widespread use. For example, this vaccine has not yet been tested in infants – a critical issue if the vaccine is to be added to the existing schedule of EPI vaccines that reach around three-quarters of infants around the world. The GSK vaccine is also currently a three-dose vaccine, but a one-dose vaccine would be much more useful in poor countries. Other candidate malaria vaccines may be as effective or more so. Additional resources are needed to pull these candidate vaccines through Phase II clinical trials and beyond.

#### 2.1.1. *Late-stage products*

Late-stage vaccines can be defined as those in late stage clinical trials (say, Phase III or later), the final stages of regulatory approval and for which production capacity is being established.

An example of a late-stage product is a vaccine for rotavirus.<sup>14</sup> An oral vaccine, developed by the US-based biotech Avant Immunotherapeutics and licensed to GSK Biologicals, has undergone Phase III trials in Latin America; is in Phase II trials in South Africa, Singapore, and Bangladesh; and was recently licensed for use in Mexico. A second oral vaccine, developed by Merck & Co., is now in Phase III trials in Central and South America. Biovirx has also recently indicated it will pursue licensing for a rotavirus vaccine that had previously sold in the US market but was withdrawn for fears of adverse effects. Development of other rotavirus vaccines - at the Lanzhou Institute in China, Bharat Pharmaceuticals in India, Bio-Farma in Indonesia, and the US National Institutes of Health – is in progress but several years behind.

#### 2.1.2. *Existing products*

Existing products are those which have obtained regulatory approval and are on the market.

An example of an existing product is Coartem, an artemisinin-based combination therapy (ACT) anti-malarial. Artemisinin had been used for centuries in traditional Chinese medicines; in 1994, Novartis licensed worldwide marketing rights to Coartem outside China, and following clinical trials Novartis was awarded regulatory approval in 1998.

## 2.2 Taxonomy of products by therapeutic category

### 2.2.1 Vaccines

Vaccines require little training or expensive equipment to implement, and hence are easier to deliver (relative to drug treatments) in poor countries with weak health-care infrastructures. Vaccines do not require diagnosis for use, can be taken in a few doses instead of in longer-term regimens, and rarely have major side effects. This is because regulators rarely, if ever, approve vaccines that have major side-effects as vaccines are given to healthy people – many of whom would never get the disease in absence of a vaccination program. Hence, vaccines can be prescribed and distributed by health care workers with limited training. Resistance rarely develops against vaccines.

Existing institutions such as the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) already have credibility in determining the safety and efficacy of vaccines.

There is a notable lack of vaccines for the diseases which carry the heaviest disease burdens in poor countries, including both well-known diseases such as HIV and malaria as well as lesser-known diseases such as schistosomiasis and lymphatic filariasis.

### 2.2.2 Drug treatments

As with vaccines, existing institutions such as the US FDA and the EMA already have credibility in determining the safety and efficacy of drug treatments. Characteristics of drug treatments relevant for our discussion are perhaps most easily presented through contrasts with the case of vaccines:

- Diagnosis is required in most cases, as well as repeat prescribing or follow-up to ensure the disease has been tackled. Thus drug treatments often require more health care infrastructure than vaccines;
- In contrast to vaccines, since drug treatments are taken by sick people regulators are often willing to approve drugs with significant side effects. For example, a drug with potentially dangerous side-effects might not be worth taking to cope with an ordinary case of malaria, but might be appropriate to fight drug-resistant cerebral malaria where the alternative is death;
- Resistance is more likely to develop to drug treatments than to vaccines. For this reason, new drug treatments (for example, for malaria or tuberculosis) are sometimes restricted to patients who have strains of diseases resistant to mainstream treatment;
- Market distortions, while important in drug markets, may not be quite as severe as for vaccines. Drugs have more vocal interest groups to lobby for their development and funding because the benefits of drugs are more concentrated. For a number of reasons pharmaceutical manufacturers will typically find it easier to obtain revenue from consumers by selling drugs rather than vaccines.<sup>15</sup> For these and other reasons, some drug treatments already exist for many diseases concentrated in poor countries – such as Coartem for malaria.

One example of a drug treatment targeted towards poor countries is microbicides – that is, products that prevent the sexual transmission of HIV and other sexually transmitted diseases when applied topically (in the form of a gel, cream, suppository, film, or as a sponge or ring that releases the active ingredient over time).

### *2.2.3 Diagnostics*

Diagnostics appropriate for use in poor countries are also needed for many diseases. Often diagnostics which are standard in developed countries (for example, for HIV) are not widely available in poor countries because of the high cost of testing equipment and supplies, or because they cannot be used in a typical clinical setting in a poor country.

### **3 TAXONOMY OF FIRM TYPES**

In this section, we provide a taxonomy of firm types, including biotechs, pharmaceutical firms, and emerging market suppliers. We do not describe the R&D process in detail, but this is a lengthy process, usually taking in excess of 10 years for drugs and vaccines and estimated to cost more than \$800m (including capitalised costs) for drugs<sup>16</sup>.

#### **3.1 Biotechnology companies**

Smaller biotechnology companies (biotechs) usually focus on early stage research. If initial tests at these companies are promising, their work is then usually either licensed to, or purchased by, larger pharmaceutical companies for the later stages of development, marketing, and manufacturing. Some biotech companies develop and sell their own products in specialist areas, but few seek or expect to become large vertically integrated pharmaceutical companies, as happened in the cases of Amgen and Genetech.

#### **3.2 Pharmaceutical firms**

The traditional model of pharmaceutical R&D was one of “in house” research, development, and manufacture by vertically integrated major pharmaceutical companies.<sup>17</sup> Although most major companies continue to undertake activity in each of these areas, in recent decades this model has been fundamentally changed in large part due to the rise of biotechs and the shift of large pharmaceutical companies towards subcontracting of some of their development and manufacturing activities.<sup>18</sup>

In this new, current model of R&D, a primary role of large pharmaceutical firms is that of an “integrator” in the drug discovery process – playing the central (although not exclusive) role in coordinating discovery activities and in bringing the products through development and to the market. The R&D market place varies by therapeutic category and by product, leading to more short-term, project-specific contracting between biotechs and large pharmaceutical firms.

#### **3.3 Emerging market suppliers**

Since 1992, the number and scale of World Health Organization (WHO)-prequalified producers in low- and middle-income countries, often called ‘emerging market suppliers,’ has increased. With notable exceptions, their production is largely limited to older products – in part because emerging suppliers often have a large cost advantage but typically lack significant R&D or process development capability.<sup>19</sup>

## **4 BACKGROUND ON R&D FOR DISEASES CONCENTRATED IN POOR COUNTRIES**

A number of factors contribute to the low levels of R&D targeted towards diseases concentrated in poor countries. In this section we review some of the relevant issues as a background to our discussion of advance purchase commitments in the next section.

### **4.1 Market failures for products needed by poor countries**

Biotechnology and pharmaceutical firms have little incentive to undertake R&D on diseases concentrated in poor countries. One reason is that the potential consumers (patients and their governments) are poor. This requires assistance from the richer countries. But there are also two main market distortions that also reduce the incentives for R&D on new products.

First, the scientific and technological advances generated by R&D on these diseases spill over to many nations, so none of the many small countries that would benefit from (for example) a malaria vaccine has an incentive to encourage R&D by unilaterally offering to fund R&D directly or to pay higher prices for new products. A coordinated response is required, but even then the incentives for each country to defect would be high unless they were bound into a contract. Second, governments and other institutions that buy health technologies for these diseases face a “time-inconsistency” problem. Once pharmaceutical companies have made the R&D investments necessary to develop health technologies, governments and aid institutions often use their powers as dominant purchasers and arbiters of intellectual property rights to keep prices close to marginal cost in the interest of increasing access to life-saving products from limited budgets. Because, however, the largest part of the industry’s expenditures lies in the initial R&D cost, prices that cover the (typically modest) variable costs of production will not enable companies to recover their R&D investment, thereby deterring industry from investing in such R&D in the first place. Contracting mechanisms that overcome this problem are required if private sector investment is sought.

As we will discuss, although the goals of creating incentives for R&D on new pharmaceuticals (which requires high prices) and ensuring wide access to pharmaceuticals once developed (where low prices enable budgets to go further) are often pitted against each other, well-designed incentive mechanisms can de-couple these goals and promote both effectively.

### **4.2 New technologies are a combination of “push” and “pull,” but there is a lack of market incentives for diseases concentrated in poor countries**

For diseases prevalent in rich countries, a combination of “push” (reducing R&D cost and generating scientific leads) and “pull” (demand for the products that flow from the R&D) measures help to provide incentives for private sector R&D. Push funding from institutions such as the US National Institutes of Health and the Wellcome Trust supports basic scientific research and some clinical development, while the prospect of profits in rich country markets provide pull incentives for private sector firms to transfer basic research into useable products.

Applying the same principle to vaccines and drugs for poor countries would suggest using push programs for basic research and for clinical development and pull programs to encourage biotech and pharmaceutical firms to turn this research into needed health technologies. For diseases concentrated in poor countries, push funding is being provided from a number of institutions, notably Product Development Public Private Partnerships (PD-PPPs) such as the Malaria Vaccine Initiative (MVI) and the International Aids Vaccine Initiative (IAVI), but there is a dearth of complementary pull incentives to encourage private sector R&D into health technologies for these diseases.

While more push funding is needed, some of which is used to fund private sector R&D, a major stumbling block remains the lack of a market pull incentive to turn basic R&D into useable products.

### 4.3 Precedents for “pull” market incentives

A sizeable academic literature as well as several historical precedents suggests market based pull incentives are effective in stimulating R&D investments and innovation in developed country markets.<sup>20</sup> Specific to the pharmaceutical industry, Acemoglu and Linn (2004) analyze the effect of expected market size on the entry of new drugs through examining variations in market size for pharmaceuticals linked to demographic changes, and find that a 1 percent increase in the potential market size for a drug category leads to a 4-6 percent increase in the number of new drugs in that category.

Several historical examples reinforce the view that policies increasing the value of markets for pharmaceuticals can encourage R&D. For example, the US Orphan Drug Act, which went into effect in 1983, created a number of financial incentives for pharmaceutical companies to develop drugs for rare diseases like Huntington’s, ALS (Lou Gehrig’s disease), and muscular dystrophy – diseases which affect fewer than 200,000 people in the USA and therefore have a limited market. The primary attraction for companies is a promise of seven years of market exclusivity. Although before/after comparisons are difficult to make, over 200 orphan drugs have been developed since 1983, while fewer than ten were introduced in the decade preceding passage of the act.

Another set of precedents for the case of vaccines are the recommendations from the US Advisory Committee on Immunization Practices (ACIP). ACIP’s recommendations typically set policy for immunization requirements in the US, and hence if a vaccine is recommended by ACIP the producers of that vaccine are assured of a reasonably large market. Finkelstein (2004) investigates the private sector response to health policies such as the ACIP recommendations that, in attempting to increase immunization rates, also increased the expected profits from new vaccines. Her work estimates the change in investment in vaccines against those diseases, using changes in investment for vaccines against carefully-selected diseases that were not affected by the policies to control for underlying secular trends in R&D in the vaccine market, and finds a strong positive impact of these policies on private sector R&D activity on affected vaccines.

### 4.4 Types of “pull” market incentive mechanisms

In practice, pull programs that reward successful R&D on needed global health products could take a variety of forms. Given the current huge disparities between private and social returns to R&D on diseases concentrated in poor countries, any program that committed to compensate private developers of needed products would likely be an improvement on the status quo. However, as we discuss further in Section 5, advance purchase commitments may be particularly well suited to encouraging R&D on neglected diseases.

Figure 1, adapted from the CGD working group report, summarises the advantages and challenges of various “pull” mechanisms.

**Figure 1. Alternative forms of “pull” incentives for commercial R&D<sup>21</sup>**

Approach	Description	Advantages	Risks and challenges
<b>Advance market commitment</b>	Sponsor promises to fully or partially fund purchases of products meeting specified conditions	<ul style="list-style-type: none"> <li>• Creates link between payment and product quality</li> <li>• Creates market for improvements</li> <li>• Ensures access in short- and long-run</li> <li>• Sponsors only pay if a desired product is developed</li> </ul>	<ul style="list-style-type: none"> <li>• Promises must be credible</li> <li>• Must be designed to cover appropriate products</li> </ul>
<b>Patent buyouts</b>	Sponsor offers to buy patent rights to a product meeting specified conditions, then puts the patent in the public domain and encourages competition in manufacturing the product	<ul style="list-style-type: none"> <li>• Allows competition among manufacturers</li> <li>• May reduce prices and thus increase access</li> </ul>	<ul style="list-style-type: none"> <li>• Promises must be credible</li> <li>• Must be designed to cover appropriate products</li> <li>• No tight link between payments and product quality</li> <li>• Challenge of judging value of inventions</li> <li>• Likely to be winner takes all</li> </ul>
<b>Prizes</b>	Offer cash or other reward to whoever achieves a certain, pre-specified goal	<ul style="list-style-type: none"> <li>• Immediate up-front payment—no need for long-term contract</li> </ul>	<ul style="list-style-type: none"> <li>• Industry may not be enthusiastic about competing for prizes</li> <li>• Does not address access</li> <li>• Winner takes all – does not foster competition for subsequent improvements.</li> </ul>
<b>Patent extensions on existing pharmaceuticals (“wildcard” or transferable patents)</b>	Give a manufacturer the right to extend the patent on any product in an industrial market, or allow a manufacturer to extend the customary time period that a patent is protected	<ul style="list-style-type: none"> <li>• Attractive to larger pharmaceutical companies</li> </ul>	<ul style="list-style-type: none"> <li>• Favors big companies and those with existing patents (unless transferable)</li> <li>• Places cost of development on users of drugs whose patent is extended; may impede access to that drug</li> <li>• Winner takes all – does not foster competition for subsequent improvements.</li> </ul>
<b>Fast-track regulatory approval</b>	Rewarding pharmaceutical companies by fast-tracking regulator approval for them or for other, more profitable medicines.	<ul style="list-style-type: none"> <li>• Benefits to pharmaceutical companies at little cost</li> <li>• Complement other approaches</li> </ul>	<ul style="list-style-type: none"> <li>• Reward insufficiently large and insufficiently certain</li> <li>• Only benefits firms with other profitable products (unless transferable)</li> <li>• Unless carefully designed, would be comparable to winner takes all – and hence not foster competition for subsequent improvements.</li> </ul>

For example:

- With “prize” or best entry tournament proposals (which effectively give an advance revenue or purchase commitment), it may be difficult to avoid a winner-take-all framework while maintaining credibility. For example, if committees evaluate the value of innovations *ex post*, they will be tempted to “low ball” the developer;
- “Wild card” or transferable patent extensions (whereby a company developing a product for a neglected disease can get a patent extension on an unrelated best-selling product in rich country markets to enable it to get a return on its R&D) place the cost of developing products for poor countries on rich country patients and / or third party payers who are buying the existing products whose patent is extended; this would be economically equivalent to putting high taxes on a narrow base, which can be an inefficient way of raising revenue, and if there are significant out-of-pocket payments by patients would also raise equity concerns;

- Transferable “fast track” licensing approval (whereby a company developing a product for a neglected disease can get fast track regulatory approval for an unrelated product in developed country markets to enable it to get a return on its R&D). The value of a “fast track” can vary over time, however, creating a substantial amount of uncertainty for companies. Moreover, if there are positive health impacts of fast track approvals then, arguably, they should be used for all products, and not held out as a reward; if there are negative health impacts then fast track approvals are inappropriate and should not be used.

## 5 TAXONOMY OF ADVANCE PURCHASE CONTRACTS AND COMMITMENTS

### 5.1 Defining what we mean by “advance purchase”

The idea of advance purchase commitments may seem similar in flavor to some things that are already being done in practice. For example, in 2001 Novartis signed a memorandum of understanding with the World Health Organization (WHO) to agree to provide the artemisinin-based anti-malarial treatment Coartem at cost for ten years to the public agencies of malaria-endemic countries through the WHO.

For the purposes of this discussion, we wish to distinguish between two distinct meanings of “advance contracts:”

- First is an “advance contract” in terms of a multi-year commitment to purchase;
- Second is an “advance contract” in terms of a commitment to purchase a product which does not yet exist.

As we will discuss, increasing the use of “advance” multi-year commitments to purchase existing products would be very valuable and can be useful in expanding access to existing products. Although applying the concept of multi-year commitments to “advance” products which do not yet exist may seem a sensible means of procurement, the critical issue is that in order to encourage needed R&D investments commitments must be made contractually binding. In the case of non-existent products, commitments must be credible enough to spur substantial R&D over long periods of time to generate candidate products which may or may not survive the product development pipeline and eventually make it to market. Hence, due to time inconsistency problems, in the case of non-existent products issues of credibility in commitments are *critical*. As we will discuss, care needs to be taken in how to construct contracts which are legally binding, yet only pay for useful products and pay in proportion to how useful the product it.

#### 5.1.1 “Advance purchase” as multi-year commitments to purchase

For the first meaning of “advance contract,” consider the case of UNICEF - the primary purchaser of vaccines for poor countries. At present, UNICEF’s usual procurement awards (under which UNICEF and manufacturers agree to the commercial terms for products, such as prices, delivery schedules and packing requirements) have a duration of 1-2 years. This creates uncertainty that can lead either to vaccine shortages or to unused capacity. UNICEF also provides the vaccine industry with forecasts for vaccine requirements (in 3-4 year increments), but these are only indicative (that is, they do not form an enforceable contract). The lack of long-term contracts makes it difficult for potential suppliers to invest in long-term productive capacity, which would increase supply and lower unit costs enabling the manufacturer to get higher profits and UNICEF to pay lower prices. The result of the present arrangements is higher prices for developing countries, lower usage and, occasionally, supply constraints.<sup>22</sup>

The establishment of long-term contracts would be useful both for currently available underutilized products, and for products which do not yet exist. Long-term contracts could be designed as in the CGD recommended structure, in which donors would agree to pay a relatively high price for, say, the first hundred million people treated with a new product like the rotavirus vaccine, in exchange for a commitment by the manufacturer to supply additional treatments to poor countries at a modest markup over production cost. The firm would be contractually obligated to meet demand, as long as it was given sufficient notice. If poor countries knew that they would have reliable access to products at a modest markup, they would be more likely to adopt those products. Both

manufacturers and public health would be better served by this type of long-run contract than by the existing system of short-run contracts.

### 5.1.2 *“Advance purchase” as committing to buy products which do not yet exist*

For the second meaning of “advance contract,” consider the UK effort to stimulate the development of a vaccine for meningococcal C. Beginning in 1994, the Department of Health recorded a marked increase in group C cases of meningococcal disease, an uncommon but very serious bacterial infection that can cause inflammation of membranes surrounding the brain as well as septicemia. Realizing that the small market size for the meningococcal C vaccine in the UK could limit interest in R&D for new products, the Department attempted to stimulate commercial activity through a variety of incentives, including an indication that it would buy any effective vaccines that were offered -- though it did not offer a legal guarantee. New vaccines were subsequently developed and pediatric vaccination in the UK has been routine since late 1999. In this case, the high level of public concern about the disease coupled with the good procurement record of the Health Department created sufficient credibility that the vaccine would be purchased to stimulate private research. But the circumstances that enabled the UK government to do this are not replicated in the case of neglected diseases. In order to induce manufacturers to invest in R&D in cases where development is likely to take many years to reach fruition and where government and international priorities could easily shift, it will be vital to make contractually binding commitments.

Although efforts to improve demand forecasts and engage international organizations such as UNICEF in longer-term purchasing contracts are critical, they are different from efforts which seek to spur R&D on products which do not yet exist. In attempting to stimulate R&D on non-existent products, the credibility of purchase contracts is especially critical.

## 5.2 **Advance purchase commitments**

In advance purchase commitments, sponsors commit – in advance of product development and licensure – to fully or partially finance purchases of health technologies for poor countries at a pre-specified price. A financially (and otherwise) credible program sponsor or coalition of sponsors would sign a contract underwriting a guaranteed price for the supplier. Poor countries would decide whether to buy a product at a low and affordable price (say, \$1 per treatment), and sponsors would guarantee to top-up to a guaranteed price (say, \$15 per treatment) – thus providing market returns for the developer which are comparable to other products. Once the full number of treatments has been purchased at the guaranteed price, the supplier would, in return, be committed to selling further treatments at an affordable price in the long term. The sponsors could retain the right to seek alternative suppliers at the end of the guaranteed price contract period. Although not part of the contract, there would be nothing to stop the original sponsors or other donors from covering the \$1 price on behalf of poor countries at the time of purchase.

The advance purchase commitment structure as recommended in the CGD report is presented in Figure 2.

**Figure 2. Example structure of an advance purchase commitment<sup>23</sup>**

<b>Advance market commitment</b>	<b>Example for malaria vaccine</b>
Legally binding contracts, enforceable by law	Offer made by a group of sponsors
Total market value approximately equal to sales revenues earned by average new medicines	Total market size of \$3 billion (net present value, 2004 dollars)
Sponsors under-write a specific price	\$15 per treatment (e.g. \$5 per dose for 3 doses)
Price guarantee applies to a maximum number of treatments	Guarantee for first 200 million treatments
Treatments sold in eligible countries	Vaccine Fund eligible countries
In return, the developer guarantees to sell subsequent treatments at a low price	\$1 per treatment
Recipient country makes a co-payment for the products they buy (or asks a donor to do so)	\$1.00 paid by recipient \$14.00 paid by sponsors
Successful developers receive \$15 per treatment sold.	
Subsequent products are also eligible for the guaranteed price, if superior to existing products – as developing countries can switch their demand to these subsequent, superior products.	
An Independent Adjudication Committee oversees the arrangement.	

For firms, this type of advance purchase arrangement would reduce economic uncertainty and give investors confidence about the returns they can expect if the relevant scientific challenges are overcome. Advance purchase commitments would not eliminate all risk to developers – the scientific challenge and risks, as in markets for diseases in rich countries, would be considerable and the risk of failure high - but advance purchase commitments would greatly reduce the risks specific to markets for diseases concentrated in poor countries.

If structured correctly, advance purchase commitments can also facilitate access to these technologies if and when they are developed. Consider the structure presented in Figure 2. In the short-term, access is facilitated through donor purchasers at the higher, pre-specified purchase price. In the long-term, financially sustainable access to these technologies is facilitated through the contract provision which requires developers to commit to drop the price to a low level (close to marginal cost) after all high-price purchases have been made.

Advance purchase commitments could potentially lead to duplication of R&D activities if companies are competing for the contract. However, it is often appropriate to pursue many different leads simultaneously in searching for solutions to important problems. Even when a task may seem mechanical and well-defined, it may be useful to have multiple, competing teams – each with their own ideas on how to execute the project (as in the example of efforts to sequence the human genetic code). It is not clear therefore that this is a problem. Nonetheless, it is possible to construct theoretical examples in which advance purchase commitments could lead to excessive duplication of research.

Several design issues are critical for advance purchase commitments. Commitments would need to cover the case in which more than one vaccine is developed, the rules for which should be set with several objectives in mind: first, fashioning incentives to appropriately reward development of the initial vaccine; second, creating incentives to improve on the original vaccine; and third, delivering the best available vaccines to patients. For example, from the standpoint of society as a whole, it is not a good use of resources to encourage development of second products that are different but not superior in use.

A key issue with advance purchase commitments is that the contracts must be credible. Legal precedents suggest that such contracts are enforceable by contract law and existing legal institutions. The sponsors must have credible financial backing – such as developed country governments and well-endowed foundations.

### 5.3 Revenue (price and quantity) guarantees

An advance contract mechanism closely related to that of advance purchase commitments is a revenue (or price and quantity) guarantee. That is, rather than simply committing to a guaranteed minimum price for a desired product, sponsors could commit to how many treatments would be bought from each supplier at this price.

In a revenue guarantee scheme, manufacturers of qualifying products would be guaranteed all – or, if there are multiple qualifying products, a portion – of the sponsor's financial commitment, regardless of whether the products are actually used. This has the benefit of reducing the demand risk for manufacturers, which is an important benefit for pharmaceutical companies in light of the existing deficiencies in the forecasting and procurement systems in many poor countries.

Arguably, however, a purchase commitment should pay for a product only if there is demand for that product. This requires manufacturers, sponsors and recipient countries to work together to take the steps necessary to ensure that the product is delivered to those who need it – thus ensuring that sponsors do not find themselves legally obliged to purchase a product that nobody wants.

The critical issue is who bears risk. Credibility in commitment is necessary given the time inconsistency problem. That is, the contract cannot allow sponsors to renege. On the other hand, companies have to deliver high-quality products that countries want to use. We can note that a “front loaded” pricing structure (whereby the price guarantee starts very high and comes down slowly so earlier volume sales generate higher profits) can provide some insulation against quantity risk.

### 5.4 Advance Development and Introduction Plans (ADIPs)

For late-stage vaccines (those in Phase III trials and beyond), the Global Alliance for Vaccines and Immunization (GAVI) has suggested that public-private partnerships in the form of Advanced Development and Introduction Plans (ADIPs) can reduce the time lag between adoption of new vaccines in developed and developing countries by reducing demand uncertainty. ADIPs have been developed for the rotavirus and pneumococcal vaccines, and aim to speed uptake of vaccines by encouraging early communication between firms and major purchasers. They are intended to predict both demand and supply for a late-stage vaccine, generate practical plans for vaccine delivery in developing countries, and assess the impact and cost-effectiveness of early introduction.

While the institutional framework of ADIPs can address demand uncertainty by creating demand forecasts and advocating for early introduction, they in themselves are not able to resolve the major market failures for vaccines as ADIPs are not involved with contractual arrangements.

Critically relevant for this discussion, ADIPs are only applicable for vaccines that *have been developed, typically in response to rich country markets*. ADIPs have a valuable role to play in closing the gap between when vaccines are introduced in rich countries and when they are made available to poor countries, but are unable to be used for products such as a malaria vaccine which would not be developed in response to rich country markets. While ADIPs can accelerate access to existing vaccines developed in response to rich country markets, different and more substantive

incentives are needed to spur investments into vaccines for diseases concentrated in poor countries.

### 5.5 The case of Coartem

As previously mentioned, another example of an advance purchase arrangement is the memorandum of understanding signed by Novartis and the WHO in 2001. Here, Novartis agreed to provide the artemisinin-based anti-malarial treatment Coartem at cost for ten years to the public agencies of malaria-endemic countries through the WHO.

This case illustrates both the benefits and potential pitfalls of nonbinding long-term agreements. It is possible that production capacity has been scaled up faster than might have been the case in the absence of the agreement. However, Novartis' recent announcement that production would fall nearly one million doses short of the 2.4 million promised for 2005 shows the weakness of agreements that are not legally binding.

It should also be noted that in this case as well as in the case of ADIPs, the mechanism was intended to ensure faster supply to an existing product, rather than provide incentives for the development of a new one. The commercial counterpart of Coartem had been approved for use before the introduction of the memorandum of understanding. In addition, Novartis' willingness to enter into this agreement should not be taken as an indication of industry's willingness to enter into similar long-term agreements in the future with other products. Some features of artemisinin-based treatments, such as the fourteen-month lead time needed to produce the raw ingredient and its short two-year shelf life, may make the demand forecasts provided by the WHO particularly valuable in this case. It is also worth noting that in this case, since agreement was *ex post*, after the product was developed, the agreement involved Novartis supplying at manufacturing cost. This supports our earlier discussion suggesting that buyers have strong incentives to negotiate such agreements *ex post*. If suppliers foresee this happening, the commercial rationale for investing large amounts in R&D will be weak. Hence the potential benefits of advance purchase commitments.

## 6 THE POTENTIAL FOR ADVANCE PURCHASE COMMITMENTS

### 6.1 Which R&D incentive structures for which products?

#### 6.1.1 *Should incentives be announced early or late in the R&D process?*

Some critics argue advance purchase commitments are more well-suited for late-stage products (such as a rotavirus vaccine, which is very close to market) than for early-stage products (such as a malaria vaccine, for which extensive R&D is still required). This is because of the scientific uncertainty involved at early stages which may make it harder to set the guaranteed price and risk a “ratchet effect”, whereby companies complain if the price is too low given the scientific challenges and the specification of the product required, but not if it is high. On the other hand, there are strong arguments that advance purchase commitments would be useful for early-stage products. For any given size of commitment (in terms of the amount of money and end product purchases), announcing earlier rather than later will align incentives earlier, and accelerate R&D efforts towards the end goal of a useable product which is suitable for use in poor countries. If the price is seen as “high” then greater R&D effort will be stimulated. This should bring forward the launch of a new product and /or increase the likelihood of follow-on products with better performance being available soon after the launch of the first product. Both of these effects would increase the health gain generated by the contract commitment.

#### 6.1.2 *What products – vaccine, drugs, diagnostics?*

To date, most work on advance purchase commitments has been applied to vaccines – in part due to a number of other challenges which arise in thinking about their application to drug treatments. Because of this, it is likely that the critical design issues involved with advance purchase commitments can most easily be dealt with for the case of vaccines.

Advance purchase commitments may well be able to be applied to diagnostics, but we are not aware of work exploring this option. Applying advance purchase commitments to drug treatments would require additional consideration of a number of issues, such as:

- The degree of out-of-pocket purchase of the drug, which will reduce the size of the price guarantee needed. The number of drug doses needed for the contract depends on a multitude of decisions by individual patients and health care providers;
- How the emergence of any side-effects will be dealt with. These may not be known for several years after the launch of the drug. As a result, a purchase commitment for drugs may have to specify the purchase price associated with a particular group of side-effects;
- As some drugs already exist for most diseases, the specification of any commitment for a drug would need to be very carefully defined to avoid the risk of creating an incentive to develop new therapies that are only slightly better than existing ones and so not worth the price guarantee. For example, consider the case of artemisinin-based combination therapies (ACTs). ACTs already exist, and the available evidence suggests they are currently very effective. Advance purchase commitments for ACTs may create inefficient incentives to develop new ACTs that are only slightly better than existing products;
- Because drug resistance is more likely to develop than vaccine resistance, it may make sense for new drugs (for malaria or tuberculosis, for example) to be initially restricted to patients who have strains of diseases resistant to mainstream treatment. Thus, a program providing a price guarantee but requiring use to give the company a return could potentially cause a counterproductive shift toward their widespread early use.

It seems likely that these problems could be addressed through careful program design, but these issues would have to be carefully thought through.

Consider the case of microbicides. The R&D incentives for microbicides are small: the market for microbicides, particularly for first-generation products, is expected to be too small – and the market for second generation products may still not be large enough to incentivise industry to invest their own resource into R&D.<sup>24</sup> Several microbicides are currently in clinical trials, funded with PD-PPP or other public support.

In thinking about whether advance purchase commitments could be usefully applied to microbicides, it is important to think about whether appropriate contracts could be designed. The benefits of microbicides heavily depend on consistent use, and as with many drugs it is difficult to estimate the “doses” needed. Depending on their form, microbicides may also be susceptible to resistance. There is a wide range of possible desired product characteristics (for example, vaginal versus rectal, contraceptive versus non-contraceptive, *etc.*), and it may be difficult to anticipate in advance the product characteristics that will in practice make a microbicide most attractive for use by women. For these and other reasons, designing contractual requirements for an advance purchase commitment for microbicides will require additional work. It may be particularly important to link rewards for developers to actual use.

## **6.2 Which firms would be expected to respond to advance purchase commitments?**

In general, market incentives such as those provided by advance-purchase commitments allow biotechs, pharmaceutical firms, and emerging market suppliers to create whatever R&D structures they believe will be most effective. Rather than having sponsors dictate which R&D set-ups (or divisions of labor) between pharmaceutical firms, biotechs, and emerging market suppliers would be most effective, this open structure allows the firms (which have much more information) to make these decisions and arrangements themselves.

The only way to know for certain how firms would react is to implement an advance-purchase commitment and observe what happens. In the meantime, the CGD working group conducted structured consultations for the case of vaccines with informed individuals inside and outside of industry, including representatives of biotech firms (of various sizes and orientations), multinational vaccine manufacturers, and emerging market suppliers.

The consultations suggest that for products at an early stage an advance-purchase commitment may initially motivate biotechs and potentially the venture capitalists which provide their funding, while some larger multinational pharmaceutical firms may get involved only after further advances in the science, perhaps led by biotech firms. This finding is supported by anecdotal evidence that biotechs responded more enthusiastically than big pharmaceutical companies to orphan drug incentives and to the BioShield incentives in the US.<sup>25</sup> BIO Ventures for Global Health (a Bill and Melinda Gates Foundation-funded agency designed to get biotech companies involved in neglected disease research) is a strong supporter of advance-purchase commitments.

The expected response to an advance-purchase commitment from either biotechs or pharmaceutical firms may therefore depend on whether the commitment is for an early- or late-stage product. The general picture is that an advance-purchase commitment is likely to generate a response from biotechs and other early-stage researchers. Biotechs would be more willing to invest because they would be more confident that they would attract interest from pharmaceutical companies for the products they develop. As we noted above, there is considerable evidence that firms respond to market signals by adjusting their R&D to reflect the size of the potential market.

The emerging market vaccine supplier consulted by CGD particularly welcomed the proposal. Although they lack the financial backing of large pharmaceutical companies, emerging market suppliers bring considerable expertise in developing country diseases, and might have a comparative advantage, for example, in managing clinical trials in developing countries. One advantage of the open framework of an advance-purchase commitment is that any firm capable of producing innovations can benefit, and it might well be that the developing country innovators are among the beneficiaries.

### 6.3 What are the critical issues to think about with advance purchase commitments?

Towse and Kettler (2005)<sup>26</sup> set out five design issues that need to be addressed in developing an advance purchase commitment:

- Establishing credibility;
- Setting the price;
- The quality specification;
- Dealing with improved follow-on products;
- Ensuring the products get used.

In this report, we have set out for illustrative purposes how the CGD advance purchase commitment proposal would seek to tackle these issues, and discussed the relevant topics which should be considered. The work done to date suggests that advance purchase commitments offer an opportunity to funnel the energy of the private sector into developing products needed by the world's poorest countries. If no products are developed, no donor funds would be spent. If successful, millions of lives would be saved at a very low cost. For the case of a malaria vaccine, the CGD report estimates that a purchase commitment of \$3.1 billion (comparable to the average revenue for existing commercial products) would cost an estimated \$15 per life-year saved – very cost effective compared to other health or development expenditures.<sup>27</sup>

Critically, advance purchase commitments do not require donors to cut back current expenditures on other health services – such as increasing coverage of existing health technologies, including insecticide-treated bed nets for malaria. Thus commitments to purchase needed products can be made without reducing the resources available today to buy existing health technologies and without reducing “push” funding for R&D on new technologies through (for example) product development public-private partnerships (PD-PPP).

There are several critical issues that need to be considered when thinking about whether and how to move ahead with advance purchase commitments for vaccines or other products. Further and more targeted analytic work by governments, industry and public health experts is needed on several key topics.

Priorities for further work include:

- Strengthening the financing for the purchase of existing health products, and strengthening health systems in developing countries to increase coverage of vaccines and other health technologies;
- Developing advance market commitments with producers of late stage products that will be available in the near future, using the commitment to negotiate on price, timing of supply, and characteristics of the products and their presentation;
- For products that are at an early stage:
  - Considering the specific issues with respect to individual diseases (such as the likely demand from high-income and middle-income markets)

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- Validating estimates of the market size needed to induce private sector investment in R&D, using alternative datasets for market revenues;
  - Working closely with industry and the public health community to develop the contractual framework, including addressing the various design choices highlighted here;
  - Developing technical specifications for each product, in collaboration with developing country health specialists and the scientific community;
  - Considering what adaptations, if any, should be made to mechanisms for funding R&D in the context of an advance market commitment, in particular ensuring complementarity with the important and push incentives provided by the PD-PPPs.
- Considering how this approach might be extended to other diseases that affect the developing world, such as schistosomiasis or leishmaniasis;
  - Considering whether this approach could be applied to drug treatments, including microbicides, and diagnostic tests.

## ENDNOTES

<sup>1</sup> World Health Organization (WHO) (1996) *Investing in Health Research and Development: Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options*, Geneva, WHO.

<sup>2</sup> O. Barder, M. Kremer, R. Levine and the Advanced Market Commitment Working Group (2005) *Making Markets for Vaccines*, Washington, DC: Center for Global Development.

<sup>3</sup> M. Kremer and R. Glennerster (2004) *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*, Princeton, NJ: Princeton University Press.

<sup>4</sup> E. Berndt and J. Hurvitz (forthcoming) "Vaccine advance-purchase agreements for low-income countries Practical issues," *Health Affairs*.

<sup>5</sup> E. Berndt, R. Glennerster, M. Kremer, J. Lee, R. Levine, G. Weisäcker, and H. Williams (2005) "Advance purchase commitments for a malaria vaccine: Estimating costs and effectiveness," mimeo, MIT.

<sup>6</sup> H. Kettler and A. Towse (2002) *Public Private Partnerships for Research and Development: Medicines and Vaccines for Diseases of Poverty*, London: Office of Health Economics.

<sup>7</sup> A. Towse and H. Kettler (2005) "Advance price or purchase commitments to create markets for treatments for diseases of poverty: Lessons from three policies," *Bulletin of the World Health Organization*, 83:301-307.

<sup>8</sup> A. Farlow (2005) "The global HIV vaccine enterprise, malaria vaccines, and purchase commitments: What is the fit? A response to 'Making Markets' and 'Strong Medicine'," submission to the Commission on Intellectual Property Rights, Innovation and Public Health, available: <http://www.who.int/intellectualproperty/en>

<sup>9</sup> S. Maurer, A. Rai, and A. Sali (2004) "Finding cures for tropical diseases: Is open source an answer?" *PLoS Medicine*, 1(3): e56.

<sup>10</sup> R. Kim-Farley and the Expanded Programme on Immunization Team (1992) "Global immunization," *Annual Review of Public Health*, 13: 223-237.

<sup>11</sup> B. Pecoul, P. Chirac, P. Trouiller, and J. Pinel (1999) "Access to essential drugs in poor countries: A lost battle?" *Journal of the American Medical Association*, 281(4): 361-367.

<sup>12</sup> BIO Ventures for Global Health (2005) available: <http://www.bvgh.org>

<sup>13</sup> P.L. Alonso *et al.* (2004) "Efficacy of the RTS, S/AS02A vaccine against plasmodium falciparum infection and disease in young African children: Randomised controlled trial," *Lancet*, 364(9443): 1411-1420.

<sup>14</sup> This discussion of candidate rotavirus vaccine summarizes the review of candidate rotavirus vaccines as presented in Barder *et al.* (2005). O. Barder, M. Kremer, R. Levine and the Advanced Market Commitment Working Group (2005) *Making Markets for Vaccines*, Washington, DC: Center for Global Development.

<sup>15</sup> M. Kremer and C. Snyder (2004) "Why is there no AIDS vaccine?" submitted.

<sup>16</sup> J. DiMasi, R. Hansen, and H. Grabowski (2003) "The price of innovation: new estimates of drug development costs," *Journal of Health Economics*, 22:151-85.

<sup>17</sup> L. Galambos and J.L. Sturchi (1998) "Pharmaceutical firms and the transition to biotechnology: A study in strategic innovation," *Harvard Business School Business History Review*, 72: 250-278.

<sup>18</sup> H. Kettler and A. Towse (2002) *Public Private Partnerships for Research and Development: Medicines and Vaccines for Diseases of Poverty*, London: Office of Health Economics.

<sup>19</sup> Mercer Management Consulting (2002) *Lessons Learned: New Procurement Strategies for Vaccines*, Final Report to the GAVI (Global Alliance for Vaccines and Immunizations) Board.

<sup>20</sup> A long academic literature relating back to Schmookler (1966) and Griliches (1957) finds technological change to be closely linked to expected market size. More recently, Vernon and Grabowski (2000), Scott Morton (1999), Reiffen and Ward (2002), and Acemoglu and Linn (2004) have provided evidence of this trend specific to the pharmaceutical industry. J. Schmookler (1966) *Innovation and Economic Growth*, Cambridge, MA: Harvard University Press; Z. Griliches (1957) "Hybrid corn: An exploration in the economics of technological change," *Econometrica*, 25: 501-522; J. Vernon and H. Grabowski (2000) "The distribution of sales revenues from pharmaceutical innovation," *Pharmoeconomics*, 18(1): 21-32; F. Scott-Morton (1999) "Entry decisions into the generic pharmaceutical industry," *RAND Journal of Economics*, 30(3): 421-440; D. Reiffen and M. Ward (2002) "Generic drug dynamics," mimeo, University of Texas at Arlington; D. Acemoglu and J. Linn (2004) "Market size in innovation: Theory and evidence from the pharmaceutical industry," *Quarterly Journal of Economics*, 119(3): 1049-1090.

<sup>21</sup> O. Barder, M. Kremer, R. Levine and the Advanced Market Commitment Working Group (2005) *Making Markets for Vaccines*, Washington, DC: Center for Global Development.

<sup>22</sup> UNICEF is aware of this concern, but is currently constrained in its ability to sign multi-year purchase agreements because its funding streams are typically guaranteed annually. In a recent procurement, the Vaccine Fund was able to give UNICEF multi-year funding "in trust" to support a multi-year contract. This arrangement involved setting aside money for future payments, which is not an efficient use of funds. Donors and UNICEF need to work together to establish whether there is some way to enable UNICEF to enter into long-term contracts, either by amending the rules governing UNICEF's financial position, or whether there are other possible financing mechanisms such as underwriting agreements or promissory notes that would overcome the constraint.

<sup>23</sup> O. Barder, M. Kremer, R. Levine and the Advanced Market Commitment Working Group (2005) *Making Markets for Vaccines*, Washington, DC: Center for Global Development.

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<sup>24</sup> Rockefeller Foundation Microbicide Initiative (2002) *The Economics of Microbicide Development: A Case for Investment*, New York: Rockefeller Foundation.

<sup>25</sup> H. Kettler (2004) "The biotechnology industry and orphan drug incentive: A win-win strategy for Europe?" *Journal of Commercial Biotechnology*, 7(1): 62-69; G. Poland (2004), e-mail communication.

<sup>26</sup> A. Towse and H. Kettler (2005) "Advance price or purchase commitments to create markets for treatments for diseases of poverty: Lessons from three policies," *Bulletin of the World Health Organization*, 83:301-307.

<sup>27</sup> E. Berndt, R. Glennerster, M. Kremer, J. Lee, R. Levine, G. Weisäcker, and H. Williams (2005) "Advance purchase commitments for a malaria vaccine: Estimating costs and effectiveness," mimeo, MIT.