



BRIEFING NOTE ON ADVANCE PURCHASE COMMITMENTS¹

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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 also describe the "deal-making" interactions which are common in pharmaceutical R&D markets.

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, governments 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 products. Both theory and evidence suggest pull-like policies can spur R&D investments and innovation, and we here 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 thus far 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 more difficult to put in place and 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 (CGD) indicate private sector interest in advanced purchase commitments across a variety of firm types. These 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 large 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.

We review and discuss critiques of advance purchase commitments, and then suggest a number of key issues on which further and more targeted analytic work by governments, industry and public health experts is needed. Priorities for further work include:

- 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;
- Considering the details of how the long-term price for products would best be set. The long-term price could be set in advance as a dollar amount per treatment, or determined by an agreed-upon formula related to the cost of production. A variety of hybrid options are also possible: for example, the long-term price could be structured such that sponsors and producers share the benefits of reducing the cost of production through a formula;
- For products that are at an early stage:
 - Considering the potential role of milestone payments through weighing the advantages and disadvantages of including milestone payments integrated within advance purchase commitments, through complementary push funding initiatives, or left to the private sector to organize as they see most useful;
 - Considering various mechanisms through which companies could be encouraged to sign onto advance purchase commitments at an early stage, so as to allow for some monitoring of R&D progress;
 - 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 PD-PPPs (Product Development Public Private Partnerships);
- 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.³

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, recently published a report recommending how advance purchase commitments for vaccines could be implemented.⁴ 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),⁵ who lay out the rationale for advance purchase commitments and discuss design issues; Berndt and Hurvitz (2005),⁶ who discuss some of the legal and economic practicalities of structuring advance

³ 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.

⁴ O. Barder, M. Kremer, R. Levine and the Advanced Market Commitment Working Group (2005) *Making Markets for Vaccines*, Washington, DC: Center for Global Development.

⁵ M. Kremer and R. Glennerster (2004) *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*, Princeton, NJ: Princeton University Press.

⁶ E. Berndt and J. Hurvitz (2005) "Vaccine advance-purchase agreements for low-income countries: Practical issues," *Health Affairs*, 24(3): 653-665.

purchase commitments; Berndt *et al.* (2005),⁷ who present a cost-effectiveness analysis of advance purchase commitments for the case of a malaria vaccine; Kettler and Towse (2002),⁸ who provide an overview of the pharmaceutical R&D landscape; Towse and Kettler (2005),⁹ who review design issues in advance purchase commitments; and Farlow (2005),¹⁰ Farlow *et al.* (2005),¹¹ and Maurer *et al.* (2004),¹² 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 widespread adoption of cheap, easy-to-use technologies that were developed in response to incentives provided by prospective sales in rich country markets. Vaccines are perhaps 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.¹³

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.¹⁴ 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.

⁷ 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," National Bureau of Economic Research (NBER) working paper #11288.

⁸ 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.

⁹ 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.

¹⁰ 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 WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH), available: <http://www.who.int/intellectualproperty/en>

¹¹ A. Farlow, D. Light, R. Mahoney, and R. Widdus (2005) "Concerns regarding the Center for Global Development Report 'Making Markets for Vaccines'," submission to the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH), available: <http://www.who.int/intellectualproperty/en>

¹² S. Maurer, A. Rai, and A. Sali (2004) "Finding cures for tropical diseases: Is open source an answer?" *PLoS Medicine*, 1(3): e56.

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

¹⁴ 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.

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, drug treatments, and diagnostics).
- In Section 3, we provide a taxonomy of firm types (biotechs, pharmaceutical firms, and emerging market suppliers) and overview the “deal-making” structure which characterizes the relationships among different firm types.
- 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 critically 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, criticisms that have been made of them, and design issues that would need to be addressed in any 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).¹⁵

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:¹⁶ 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*,¹⁷ 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 worldwide. 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 this and other candidate malaria vaccines through Phase II clinical trials and beyond.

2.1.2 Late-stage products

Late-stage products 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.¹⁸ 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.

¹⁵ A timeline of the clinical trials process within the pharmaceutical R&D pipeline is provided in Section 3, Figure 1.

¹⁶ BIO Ventures for Global Health (2005) available: <http://www.bvgh.org>

¹⁷ 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.

¹⁸ This discussion of candidate rotavirus vaccine summarizes the review of candidate rotavirus vaccines as presented in *Barder et al.* (2005).

2.1.3 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.¹⁹ 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, diagnostics 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.

¹⁹ M. Kremer and C. Snyder (2004) “Why is there no AIDS vaccine?” submitted.

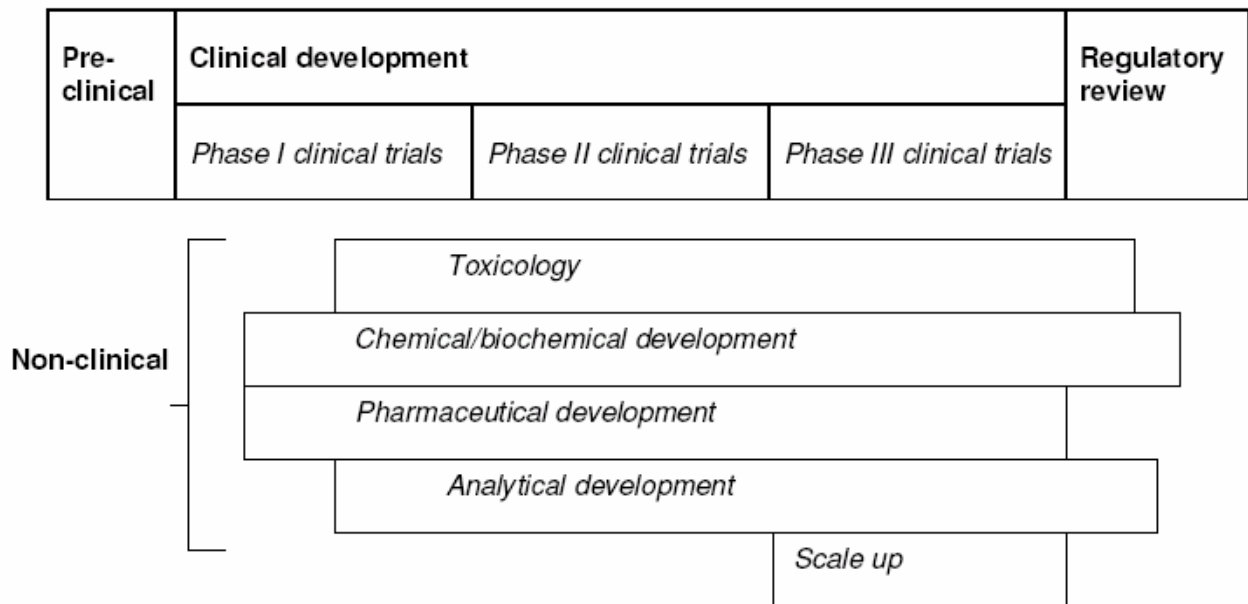
3 TAXONOMY OF FIRM TYPES

In this section, we provide a taxonomy of firm types, including biotechs, pharmaceutical firms, and emerging market suppliers, and review the “deal-making” relationships among various firm types.

We do not provide here an extensive discussion of particular firms and their specialties. Rather, our approach is to provide basic descriptions of the various firm types, and to then focus our discussion on how these firms interact with each other in existing pharmaceutical markets. As we will discuss, there is indicative evidence (for example, from the US Orphan Drug Act) that these types of firm interactions also arise in response to markets “created” by policies, implying an understanding of “deal-making” and firm interactions is relevant for thinking about the potential impact of advance purchase commitments.

We briefly describe the R&D process, highlighting the main issues relevant for our discussion. The business model of R&D-based pharmaceutical companies and biotechnology firms is to make investment decisions in the face of imperfect information. Development of vaccines and drugs can take in excess of 10 years. Candidate products move from basic research through clinical trials and regulatory approval, on to production and distribution. Even very promising candidates can fail at any point along this development pipeline. In part because of the failure risk of these investments, R&D costs are very high. Estimates of the total cost of bringing a new drug to the US market vary (in part depending on what is measured) from several hundred million dollars to more than \$1.5 billion dollars; one often-cited study that includes capitalized costs estimates the cost of bringing a new medicine through to the point of regulatory approval is more than \$800 million.²⁰

Figure 1. Sequencing of R&D activities in the pharmaceutical development pipeline



Source: Adapted from H. Kettler and A. Towse²¹

²⁰ 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.

²¹ Kettler and Towse (2002)

Figure 1 outlines many of the features of the pharmaceutical development pipeline which are relevant to our discussion in this paper.

Although the general structure presented in Figure 1 is applicable to both vaccines and drug treatments, it is worth briefly highlighting a few of the developmental differences between the two types of pharmaceuticals. Several of the points highlighted in Section 2.2 (for example, that side effects are traditionally a more critical issue with vaccines than with drug treatments) are relevant in R&D considerations as well. Clinical trials for vaccines typically include more people because they focus on those at risk rather than those with the disease and because of the greater need to identify any side effects in a “healthy “ population. A major additional issue from a developmental perspective is that vaccine development traditionally requires major investments (for example, in product-specific manufacturing plants) prior to regulatory approval – and hence, prior to the certainty of a marketable product and revenues has been ascertained. Data on R&D costs for vaccines is more limited than for pharmaceuticals. However, it is likely that on average vaccine development costs are at least as high as for drugs. There is a dearth of data on R&D costs for pharmaceuticals for neglected diseases in particular, but it is worth noting that the critical cost driver for drug development is thought to be patient numbers in clinical trials.²²

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 Genentech. Most biotechnology companies are wholly dependent on external sources of finance, such as venture capital funding.

3.2 Large pharmaceutical and vaccine firms

The traditional model of pharmaceutical and vaccine R&D was one of “in house” research, development, and manufacture by vertically integrated major pharmaceutical companies.²³ 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.²⁴ Many argue the rise of biotech companies in pharmaceutical R&D has been an institutional response to the technological opportunities created by new scientific advances (for example, in genetics and molecular biotechnology).²⁵

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. Several

²² A. Towse and D. Jamison (2003) “The R&D process for new drugs and vaccines: The case of neglected diseases,” Draft paper for the World Bank Technical Consultative Group on Health and Pharmaceuticals.

²³ 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.

²⁴ Kettler and Towse (2002)

²⁵ R. Henderson, L. Orsenigo, and G. Pisano (1997) “The pharmaceutical industry and the revolution in molecular biology: Interactions among scientific, institutional, and organizational change,” *Organizational Change*: 267-311.

studies suggest the “integrator” skills of pharmaceutical firms are key to successfully bringing products to market.²⁶

It is generally believed that biotech companies will be a permanent feature of the pharmaceutical R&D process, but that large pharmaceutical companies will continue to play a major (if not dominant) role because of their continued role in discovery as well as their competencies in the management of large-scale clinical trials, in the process of gaining regulatory approval, and in commercialization (including marketing and distribution).²⁷

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 (such as the work of the Serum Institute of India on meningitis A vaccine development in collaboration with the Meningitis Vaccine Project at PATH, the Program for Appropriate Technology in Health), 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.²⁸

3.4 “Deal-making” and relationships among various firm types²⁹

As noted above, with a few notable exceptions (such as Genentech and Amgen), biotechnology companies have not evolved into fully integrated firms but rather have maintained operations within the discovery and pre-clinical phases of pharmaceutical development. A general model of a common relationship between biotechnology companies and larger pharmaceutical firms is that biotechs advance candidate products through the “proof of concept” phase (say, through pre-clinical development or phase I trials), at which point promising candidate products are licensed out to pharmaceutical firms for further research and development. In recent decades licensing has become a critical part of the pharmaceutical R&D process.

From the perspective of a small biotech company, reasons to engage in such licensing deals include gaining from the resources (both financial and technical expertise) of larger firms in developing these products, gaining access to markets, and having opportunities for co-promotion in terms of marketing. From the perspective of a large pharmaceutical firm, licensing in is useful in addressing market pressures, as time to market is likely to be shorter with licensed-in products, and allows pharmaceutical firms to take advantage of the innovation and expertise biotech companies have developed in early-stage R&D. We highlight this “deal making” structure not to imply that a perfect market exists for these deals, but rather to describe the interactions of firms in existing markets. Inefficiencies may arise in the market for deals (among other reasons) in response to information asymmetries between biotechs and large pharmaceutical firms.³⁰

²⁶ R. Henderson and I. Cockburn (1994) “Measuring competence? Exploring firm effects in pharmaceutical research,” *Strategic Management Journal*, 15: 64-86; R. Henderson and I. Cockburn (1996) “Scale, scope, and spillovers: The determinants of research productivity in drug discovery,” *RAND Journal of Economics*, 27(1): 32-59.

²⁷ See the discussion in Kettler and Towse (2002).

²⁸ Mercer Management Consulting (2002) *Lessons Learned: New Procurement Strategies for Vaccines*, Final Report to the GAVI (Global Alliance for Vaccines and Immunizations) Board.

²⁹ The discussion in this sub-section draws on the following sources: Boston Consulting Group (BCG, 2004) “The gentle art of licensing: Rising to the productivity challenge in biopharma R&D,” *BCG Focus*, July; T.F. Dagi (2005) “Licensing and strategic business combinations for the small life sciences company: The VC perspective,” presentation at MIT Sloan School of Management, 12 April; and K.A. Theil (2004) “Goodbye Columbus! New NRDOs forego discovery,” *Nature Biotechnology*, 22(9): 1087-1092.

³⁰ See Berndt and Hurvitz (2005), who cite the work of Kalamas *et al.* (2002) and give some discussion of this topic. Kalamas, J., G. Pinkus, and K. Sachs (2002) “The new math for drug licensing,” *McKinsey Quarterly*, 4: 9-12.

Kettler and Marjanovic (2004) present some illustrative statistics on this market structure, summarizing the work of Ashton *et al.* (2001).³¹ According to a 2001 survey of the pharmaceutical and biotechnology sectors, biotechnology companies discovered 45 percent of the biomedical products on the market in that year (universities accounted for 10 percent, pharmaceutical firms for 45 percent), up from 5 percent in 1993. However, biotechnology companies brought only 20 percent of those products through the development process to market. From the perspective of pharmaceutical companies, more than 30 percent of the products in their pipelines were in-licensed or developed elsewhere with company sponsorship. Ashton *et al.* estimate that by 2005 more than 50 percent of pharmaceutical companies' revenues will be derived from products that are discovered, researched, and developed by an outside organization.

Licensing deals can involve cash payments (up front payments, milestone payments given upon accomplishment of certain pre-specified goals, structure and timing of royalties, *etc.*); management of trials as well as development processes; sub-licensing rights; and many others. Theil (2004) argues that most licensing executives agree the general "ingredients for success" in licensing deals are the reputation, network, and skills of a company's management team and expected revenues from the product.³²

One structure commonly found in biotech partnerships with large pharmaceutical firms is that of "milestone payments," or payments made by pharmaceutical firms or investors to biotechs at certain pre-defined landmarks in the R&D process. Figure 2 illustrates some common points at which milestone payments are made in the pharmaceutical R&D pipeline.

Figure 2. Common milestones in the pharmaceutical R&D pipeline



Source: Centre for Medicines Research International

Milestone payments play a variety of roles: for investors, they provide a rough set of metrics by which investors can judge the success of a biotech partnership; for biotechs, the fact that sponsors or pharmaceutical companies are willing to make milestone payments can serve to validate the biotech's candidate product.

³¹ Kettler, H. and S. Marjanovic (2004) "Engaging biotechnology companies in the development of innovative solutions for diseases of poverty," *Nature Reviews Drug Discovery*, 3 (February): 171-176. Statistics compiled from G. Ashton *et al.* (2001) *External collaboration and Licensing In Pharmaceutical R&D*, London: CMR International.

³² Theil (2004)

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

A number of factors contribute to low levels of R&D being 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 reduce the incentives for R&D on new products for these diseases.

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.³³ 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.³⁴

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. Kettler (2000) argues biotechs in particular responded to the incentives provided by the US Orphan Drug Act; Kettler and Marjanovic (2004) note that as of 2000, biotechnology companies had sponsored 70 percent of the more than 900 orphan-designated projects in the US, and 50 percent of all approved biotechnology products had orphan status.³⁵

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.³⁶ 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

³³ 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.

³⁴ Acemoglu and Linn (2004)

³⁵ H. Kettler (2000) “The biotechnology industry and orphan drug incentive: A win-win strategy for Europe?” *Journal of Commercial Biotechnology*, 7(1): 62-69; Kettler and Marjanovic (2004)

³⁶ A. Finkelstein (2004) “Static and dynamic effects of health policy: Evidence from the vaccine industry,” *Quarterly Journal of Economics*, 119(2): 527-564.

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 3, adapted from the CGD working group report, summarizes the advantages and challenges of various “pull” mechanisms.

In thinking about how to evaluate the relative appropriateness of various pull mechanism options, we can use the five design issues set out in Towse and Kettler (2005)³⁷:

- *Which mechanisms will be seen as credible to industry?* As we will discuss in the next section, spurring R&D investments into products which do not yet exist will require making credible, binding commitments to industry that “promises to pay” by sponsors will not be reneged on *ex post*.
- *How do we set the price?* The size of an incentive should be set to balance the twin goals of encouraging innovation but not encouraging excessive duplication of R&D efforts.
- *How do we get the quality we need?* The measures need to reward success. To do this the quality threshold must be set clearly in advance and meet the requirements of those tackling the disease in question.
- *Which mechanisms can be structured so as to foster competition and encourage improved follow-on products?* For the case of vaccines, it is widely believed that first generation vaccines will not be ideal, and that there should be a strong effort to provide incentives for subsequent innovation. In addition some types of pull mechanisms may disproportionately favor one type of firm (for example, large pharmaceutical firms), which may not be the optimal structure in terms of innovation incentives.
- *Which mechanisms can be structured to guarantee timely access to products, if and when they are developed, for individuals in poor countries?* A key concern from the perspective of improving public health in developing countries is not just providing incentives for innovation but also linking incentives to access to products once they are developed. From a sponsor’s point of view it is important to link rewards to desired products, rather than committing resources to products regardless of whether or not they are acceptable to the target populations and will actually be used.

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 undervalue the innovations in order to reduce the payments to the developer, and hence free up sponsor resources for other public health expenditures;
- “Wild card” or transferable patent extensions (whereby a company developing a product for a neglected disease is allowed 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

³⁷ Towse and Kettler (2005)

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;

- The value of 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) can vary over time, 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.

Figure 3. Alternative forms of “pull” incentives for commercial R&D³⁸

Approach	Description	Advantages	Risks and challenges
Advance market commitment <i>Example:</i> As proposed for vaccines by the Center for Global Development	Sponsor promises to fully or partially fund purchases of products meeting specified conditions	<ul style="list-style-type: none"> - Creates link between payment and product quality - Creates market for improvements - Ensures access in short- and long-run - Sponsors only pay if a desired product is developed 	<ul style="list-style-type: none"> - Promises must be credible - Must be designed to cover appropriate products
Patent buyouts <i>Example:</i> <i>Ex post</i> purchase, in 1839, by the French Government of Louis Jacques Mande Daguerre’s patent for photography process ³⁹	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"> - Allows competition among manufacturers - May reduce prices and thus increase access 	<ul style="list-style-type: none"> - Promises must be credible - Must be designed to cover appropriate products - No tight link between payments and product quality - Challenge of judging value of inventions - Likely to be winner takes all
Prizes <i>Example:</i> \$10 million X-prize for non-government human spaceflight ⁴⁰	Offer cash or other reward to whoever achieves a certain, pre-specified goal	<ul style="list-style-type: none"> - Immediate up-front payment—no need for long-term contract 	<ul style="list-style-type: none"> - Industry may not be enthusiastic about competing for prizes - Does not address access - Winner takes all – does not foster competition for subsequent improvements
Patent extensions on existing pharmaceuticals (“wildcard” or transferable patents) <i>Example:</i> Currently applied selectively by the US Food and Drug Administration through the pediatric exclusivity rule, under which drug companies receive an extra six months patent protection if they test their product on children	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"> - Attractive to larger pharmaceutical companies 	<ul style="list-style-type: none"> - Favors big companies and those with existing patents (unless transferable) - Places cost of development on users of drugs whose patent is extended; may impede access to that drug - Winner takes all – does not foster competition for subsequent improvements
Fast-track regulatory approval <i>Example:</i> Currently applied selectively by the US Food and Drug Administration (FDA)	Rewarding pharmaceutical companies by fast-tracking regulator approval for them or for other, more profitable medicines	<ul style="list-style-type: none"> - Benefits to pharmaceutical companies at little cost - Complement other approaches 	<ul style="list-style-type: none"> - Reward insufficiently large and insufficiently certain - Only benefits firms with other profitable products (unless transferable) - Unless carefully designed, would be comparable to winner takes all – and hence not foster competition for subsequent improvements

³⁸ Adapted from Barder *et al.* (2005) and Kremer and Glennerster (2004).

³⁹ See M. Kremer (1998) “Patent buyouts: A mechanism for encouraging innovation,” *Quarterly Journal of Economics*, 113(4): 1137-1167.

⁴⁰ See <http://www.xprizefoundation.com/> for more details. The X-prize was modeled after a long history of aviation prizes, and was intended to spur the first non-government human spaceflight. On 4 October 2004, ‘SpaceShipOne’ (the winning entry) became the first private manned spacecraft to exceed an altitude of 100 kilometers twice in as many weeks, thus claiming the \$10 million prize.

5 TAXONOMY OF ADVANCE PURCHASE CONTRACTS AND COMMITMENTS

The idea of advance purchase commitments, such as the CGD proposal, 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. In this section we seek to highlight the relevant differences between various types of advance contracts and commitments.

5.1 Defining what we mean by “advance contract”

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 purchase 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, such 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 as discussed in Section 4.1, 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 will only pay for useful products and, in addition, pay in proportion to how useful the product is.

5.1.1 “Advance contract” as a multi-year commitment 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, thus 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.

A strength of such bidding procedures is that they can address potential concerns over corruption in purchasing, but in some markets (such as here) such bidding procedures can create substantial problems. 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 (the financing arm of GAVI, the Global Alliance for Vaccines and Immunization) 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

necessarily 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 this constraint.

In the next sub-section (5.1.2), we will discuss how "advance contracts" can be applied to products which do not yet exist, but the establishment of long-term contracts would also be useful for currently available underutilized products. Long-term contracts could be designed as in the CGD-recommended structure, for example, in which donors would agree to pay a relatively high price for, say, the first hundred million people treated with a product like the Hib (*haemophilus influenzae* type b) 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 contract" 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.

We now review several types of advance contracts and attempt to highlight the relevant differences among them.

5.2 Advance purchase commitments

In advance purchase commitments, such as the CGD proposal, 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, average-revenue

pharmaceutical 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 4.

Figure 4. Example structure of an advance purchase commitment⁴¹

Advance market commitment	Example for malaria vaccine
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 4. 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.

As we discuss in Section 4.4 above, several design issues are therefore critical for advance purchase commitments. The CGD proposal summarised in Figure 4 sets out one framework seeking to tackle these design issues. 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

⁴¹ Barder *et al.* (2005)

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.

Donor funds are spent only if desired products are developed. If desired vaccines are developed, advance purchase commitments would be a very cost-effective expenditure from a public health perspective. 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.⁴²

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: namely, in the case of revenue guarantees sponsors shoulder more risk than they do in the case of advance purchase commitments. 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

⁴² Berndt *et al.* (2005)

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 because 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. Thus 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 non-binding 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 of an existing product, rather than to provide incentives for the development of a new product. 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 low-price 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 better 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). Critics argue the scientific uncertainty involved at early stages may make it more difficult to set the guaranteed price; specifically (as we will discuss in Section 6.3.6), critics argue there is a risk of 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 these challenges, 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.

It is difficult to comment on the applicability of advance purchase commitments to specific products other than vaccines, because doing so in a way that sufficiently covered the relevant issues would require substantial collaborative work among public health officials, experts familiar with the industry work in these areas, etc. – similar to the work of the Center for Global Development working group for the case of vaccines. We here simply attempt to highlight relevant issues which would need to be considered in applying advance purchase commitments to products other than vaccines; we feel that further speculation without a depth of analysis similar to that which has been undertaken for the case of vaccines would be inappropriate given the complexity of the issues involved. Overall, the key issue to bear in mind is the feasibility of designing contract terms which would be appropriate for the product.

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 need 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 resources into R&D.⁴³ 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 biotech, 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, biotech, 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 (see Figure 5).

⁴³ Rockefeller Foundation Microbicide Initiative (2002) *The Economics of Microbicide Development: A Case for Investment*, New York: Rockefeller Foundation.

Figure 5. Firms consulted by the Center for Global Development⁴⁴**Biotechnology companies**

Ardana
 Avant
 Human Genome Science
 Maxygen
 Mojave Therapeutics
 Nectin Therapeutics
 Targeted Genetics
 Vertex

Multinational vaccine manufacturers

Avantis-Pasteur
 Chiron
 GlaxoSmithKline Biologics
 Merck Vaccine Division
 Wyeth

Emerging supplier

Serum Institute of India, Ltd.

In general the consultations undertaken by CGD suggest that, for early-stage products, the response to the “market” created by advance purchase commitments may be very similar to the deal-making structure which arises in response to normal markets for pharmaceuticals, as discussed in Section 3.4. That is, 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 later, at the licensing-in phase, after further advances in the science perhaps led by biotech firms. This finding is supported by anecdotal evidence that biotechs responded more enthusiastically than large pharmaceutical companies to orphan drug incentives and to the BioShield incentives in the US.⁴⁵ For example, Kettler (2000) and Kettler and Marjanovic (2004) argue biotechs in particular responded to the incentives provided by the US Orphan Drug Act.⁴⁶ BIO Ventures for Global Health (a Bill and Melinda Gates Foundation-funded agency designed to encourage the involvement of biotech companies 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 depend on whether the commitment is for an early- or late-stage product. The general picture is that an advance-purchase commitment announced early in the R&D process 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. Resources made available through advance purchase commitments would flow back to biotechs through these licensing-in deals, or through other arrangements as preferred by the firms involved. Advance purchase commitments create an environment similar to the market structure which exists for other pharmaceutical products, and places the decision of how to divide research and development tasks in the hands of the private sector – which has much more information for any given product on the skills and complementary research that various biotech, pharmaceutical firms, and emerging suppliers bring to the table.

⁴⁴ Barder *et al.* (2005)

⁴⁵ Kettler (2000); G. Poland (2004), e-mail communication.

⁴⁶ Kettler (2000); Kettler and Marjanovic (2004)

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. 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. Finkelstein (2004) investigates the private sector response to changes in health policies such as the ACIP recommendations, and after controlling for underlying vaccine R&D trends as discussed previously finds a positive impact of these policies on private sector R&D activity on affected vaccines. For a number of reasons, Finkelstein's estimates may well be a lower bound on the R&D response that could be expected from an advance purchase commitment: firms may have attributed some probability to coverage prior to the policy changes; may not have expected the policy to be permanent; or may have taken this as indicative of a more general turn towards increased vaccination coverage rates which would have affected potential comparison groups of vaccines. Finkelstein's analysis, by its nature, applies to markets with existing products; this difference is key in understanding how the context of her analysis differs from the incentive effects one would expect from an advance purchase commitment. Incentives created in markets with existing products will in part reward developers of existing products, and hence only in part reward subsequent follow-on innovations. In markets where there is no existing product, more of the resources flow to potential new products and hence the ratio of innovation stimulated to expenditure is likely much higher.

While it is not completely clear how emerging market suppliers should be expected to respond to advance purchase commitments, 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.

Some have argued that milestone payments, as discussed in Section 3.4, should be integrated into advance purchase commitment frameworks as a way of encouraging the involvement of small biotech companies.⁴⁷ One advantage of milestone payments is that they could be calibrated to provide incentives for research avenues which seem to be under-explored: for example, if most firms are testing sporozoite malaria vaccines there could be a milestone payment for a merozoite candidate vaccine. However, milestone payments also raise a number of potential problems. Decisions would need to be made on what benchmarks would trigger milestone payments, whether multiple companies would be eligible for milestone payments after the first company had reached them, how funds should be split between milestone payments, for what purposes funds awarded through the milestone payments could be used, *etc.* In addition, there is a danger that milestones may cause firms to pursue technologies which have no hope of actually being useable simply because they want to be awarded the milestone payment. These and other concerns suggest that although milestone payments are a potentially valuable part of a package for advancing R&D, their potential problems would need to be carefully addressed.

There are several potential options for how milestone payments could be used: (1) as an explicit contractual part of advance purchase commitments; (2) as a part of complementary "push" funding; or (3) as an implicit part of implementing an advance purchase commitment, *i.e.* by allowing the private sector to use milestone payments on a company-by-company basis as they

⁴⁷ Farlow (2005), p.72.

see most useful. The third option would overcome many of the potential problems associated with milestone payments as discussed above. Independent investors or pharmaceutical firms could on their own decide to enter into agreements with biotech or other developers, and provide them with interim payments. Rather than having sponsors attempt to weigh the scientific and other factors involved with determining milestone markers, firms could establish milestone frameworks just as they do in other, existing markets (as discussed in Section 3.4).

6.3 Addressing criticisms of advance purchase commitments⁴⁸

In this section we discuss concerns about advance market commitments as outlined by Farlow *et al.* (2005), although we also seek to address the main points from an earlier critique (Farlow 2005) that are not picked up in this more recent paper.

We group together the main concerns into five broad categories:

- (1) Choosing efficient prices/quantities
- (2) Creating incentives for participation by a variety of firm types
- (3) Political risks and the time inconsistency problem
- (4) Higher costs of capital in the private sector
- (5) "Crowding out"

After reviewing in turn the five points listed above, we then consider in more detail the comparisons between a mixed model with both directly-financed R&D efforts and advance purchase commitments and the alternative model proposed by Farlow *et al.*, which relies solely on public or philanthropic-funded "push" financing of R&D.

6.3.1 Choosing efficient prices/quantities

Farlow *et al.* (2005) say there is "no rationale provided" for the proposed market size other than political expediency.

As discussed in Berndt *et al.* (2005) and Chapter 5 of the Center for Global Development working group report,⁴⁹ one reasonable approach to setting market size is based on looking at the realized revenues of new chemical entities which have been developed in response to rich-country markets, under the rationale that the expected net present values of these revenues must have been sufficient to spur investment. Specifically, the \$3.1 billion figure reflects the mean⁵⁰ net present value of revenues (in 2004 dollars) in a sample of recently developed new chemical entities, assuming an industry-wide real cost of capital of 8 percent and adjusted down by 10 percent as an adjustment for lower promotional/marketing expenditures.

Under the approach followed by Berndt *et al.* (2005) and the CGD report, there is no single "correct" market size; rather, sponsors will need to decide what level of commitment they are willing to make, based on the extent to which they believe larger or smaller commitments will elicit more or less R&D activity from different types of companies and so result in a vaccine more or less quickly, the likely technical difficulty of producing a vaccine, the size of alternative markets (e.g. for

⁴⁸ The discussion in this section draws on A. Towse (2005) "A review of IP and non-IP incentives for R&D for diseases of poverty: What type of innovation is required and how can we incentivise the private sector to deliver it?" Final report for the WHO Commission on Intellectual Property Rights, Innovation, and Public Health (CIPIH), 28 April; O. Barder, M. Kremer, and R. Levine (2005) "Answering concerns about *Making Markets for Vaccines*," submission to the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH), available: <http://www.who.int/intellectualproperty/en>

⁴⁹ Barder *et al.* (2005)

⁵⁰ It is the mean of the sample rather than developed country 'blockbuster' drugs as Farlow *et al.* (2005) suggest.

the military or travelers market), other potential sources of funding, and the point in the R&D development process that potential products have already progressed to. Although Farlow *et al.* focus on the difficulty of getting the price (and, by extension, the size of the commitment) “right,” it is worth noting that increases in the size of an advance purchase commitment will, in expectation, simply intensify the R&D efforts of industry and thus accelerate the development and distribution of a desired product.⁵¹ Moreover, while it is unlikely that the currently recommended size is exactly optimal in terms of balancing the goals of rewarding the first developer and providing incentives for follow-on products, it is quite clear that the level of market incentives that exists in absence of an advance purchase commitment is far too low.

6.3.2 *Creating incentives for participation by a variety of firm types*

Farlow *et al.* (2005) argue that biotechs and other small firms will find it difficult to compete for an advance purchase commitment because they do not have the resources to sustain a full development program. This statement runs contrary to what we observe in markets for diseases prevalent in rich countries, because (as discussed in Section 3.4) in these cases there is a market for deals between large and small companies at each stage of the R&D process. The existence of an advance purchase commitment simply means there is a *de facto* market for intermediate research outcomes, as a small company can sell promising leads in a neglected disease covered by an advance purchase commitment in the same way that a small company would sell leads in a major developed country therapeutic area such as cancer or heart disease. Farlow *et al.*'s argument on this point also runs contrary to the observed biotech response to incentives provided by policies such as the US Orphan Drug Act, as discussed previously. Finally, this argument runs counter to the support of biotechs as well as of the Serum Institute of India (an emerging supplier) for advance purchase commitments; for example, BIO Ventures for Global Health has been a strong supporter of advance purchase commitments. Unlike conventional funding directed by donors and philanthropists, this incentive is available to everyone equally; firms with innovative proposals need only find an investor willing to take the risk – they do not have to persuade the much more conservative policy-making community to take a chance. There is no reason to think that only large pharmaceutical firms will be able to compete for this market. Unlike push funding in which sponsors need to choose which scientific approaches they consider most likely to succeed, with advance purchase commitments sponsors need only specify what they are looking for in a desired product but not specify how the goal should be achieved.

Farlow *et al.* (2005) also argue advance purchase commitments will be unable to reward follow-on, higher quality products. Yet contract structures (including that proposed by the CGD working group) can be designed to encourage subsequent innovations through allowing demand to switch to superior products when they are available. Depending on the choice of price and quantity (which, combined, make up the market revenue guaranteed by the commitment), sponsors can choose how far they wish to create incentives for early discovery from first movers, and how much of the commitment they want to leave to reward any developers of subsequent improvements. Specifically, for any given net present value of the commitment, choosing a higher price for a lower quantity of products will provide incentives to speed of development of the first product. Spreading the commitment out over a higher quantity with a lower price will provide greater opportunity and therefore incentives for subsequent innovations to obtain some of the commitment value. Obviously any fixed amount of funding would have to balance achieving the multiple objectives of rewarding the first product which reaches the market and of rewarding follow-on innovation where the later product is of superior quality.

⁵¹ For an analysis of cost-effectiveness of advance purchase commitments under larger sized commitments, and in the case of accelerated development and distribution, see Berndt *et al.* (2005).

However, this issue of how to provide sufficient incentives for competition and follow-on products arises with any type of funding. An analogy for directly-funded “push” R&D is that sponsors will have to choose how much funding to allocate to support research leads which are likely to be successful in the short run but may be of only limited efficacy, and how much to allocate towards research leads which may take longer to advance but are more likely to be of high quality. The balance struck by the CGD proposal on how to balance the goals of rewarding the first product to market and rewarding follow-on products may not be precisely optimal, but it is important to note there are a number of options of how the contracts can be structured, and disagreeing with one particular choice in the example of the CGD draft contracts is not a reason to abandon the idea of pull or advance purchase commitments altogether.

It is difficult to imagine a scenario under which the existence of an advanced purchase commitment would *reduce* incentives for follow-on improvements below the incentives which exist in the absence of such a commitment, although clearly the design will impact the relative rewards for first and follow-on products. Of course, if donors wanted to make future commitments to provide additional incentives for the development of improved products they would be free to do so.

From the point of view of the sponsor, there may be a desire for some monitoring of R&D progress; in recognition of this, the CGD proposal suggests offering an early sign-on incentive, structured so as to encourage companies to sign on to the first stage of the contract within 36 months. Farlow *et al.* (2005) imply this structure is binding and argue it would “close the door” on later innovators. To the contrary, the proposed CGD framework would very easily allow for the addition of new developers to the framework agreement (see p. 98). However, the intention of the CGD proposal was simply to create incentives for companies to sign on early to the advance purchase commitments, and a variety of structures could be used to accomplish this goal – such as requiring sign-on prior to the start of Phase II clinical trials, or providing a bonus prize to successful developers who signed on early;

6.3.3 *Political risks and the time-inconsistency problem*

Farlow *et al.* (2005) write that an advanced purchase commitment is vulnerable to political risk in terms of sponsors reneging on their commitment. It is precisely because of the serious political risk and time inconsistency problem which Farlow *et al.* rightly identify that a legally binding structure is proposed (for example, in the CGD proposal) for advance purchase commitments. Recall (as discussed in Section 5.1.2) that a legal commitment was not needed in the case of the Meningitis C vaccine in the UK, but that because the UK government was a vaccine buyer with a good track record and reputation; there is no analogous case for vaccines needed primarily in poor countries.

6.3.4 *Higher costs of capital in the private sector*

Farlow (2005) argues that it is more efficient for the public sector to fund research up front than to incentivise the private sector since capital costs are lower in the public sector.⁵² Thus with long development periods and high costs of capital the out-of-pocket costs of research are dwarfed by “capital costs,” and hence using the public sector to fund public or private researchers on an up front “push” basis will be cheaper because it avoids these costs.

The reason the public sector has a lower cost of capital is because of its tax raising power. High-risk projects can be funded using low borrowing rates because if the projects fail, the agency undertaking them is subsidized by the rest of the public sector. The risk is still there, and is borne

⁵² Farlow (2005), p. 50

by taxpayers, but it is pooled and thus hidden. If the project fails the bondholders still receive a fixed stream of revenue in repayment but the tax burden on citizens rises. The social cost of the project depends on the actual risk rather than on the rate at which the borrowing takes place for the government. Thus, it is a false economy to think that the government should finance projects simply because its apparent cost of borrowing is cheaper. It is simply that the public sector can hide the true cost.

The logic of Farlow's position that governments should undertake investment projects since they have a lower capital cost implies that governments should not merely develop vaccines and drugs for malaria but also should develop pharmaceutical products for developed country markets and indeed undertake all investment. It is widely recognized that such a strategy of government undertaking large-scale investments in economic sectors where the private sector has substantial expertise runs the risk of introducing considerable inefficiencies. Indeed, in recognition of this the UK government has been moving out of those sectors of the economy where there is substantial private sector expertise and has been seeking ways to involve the private sector in bearing risk where it is better placed to respond efficiently to the incentives provided.⁵³

6.3.5 "Crowding out"

Farlow (2005) discusses the problem of "crowding out;" in other words, how would an advanced purchase commitment interact with other initiatives such as product development public-private partnership (PD-PPP) "push" funding?⁵⁴ Farlow argues that if a PD-PPP is working in a disease area then companies not working with the PD-PPP will view it as a competitor, and those working with the PD-PPP will in effect have some of their R&D costs met via PD-PPP "push" funding; he argues that in either case the genuinely new R&D stimulated by the advanced purchase commitment is less than might be expected – in one case because the incentive properties of the advanced purchase commitment are reduced due to fears that the PD-PPP will win the race, in the other case because the "push" measure was funding some of the R&D anyway.

In fact, an advance purchase commitment could as easily complement "push" funding as it could crowd it out. Researchers may be more likely to work on something that they believe can actually be translated into a useable product. Moreover, push funders would be free to negotiate clauses in their grant agreements under which companies that benefit from push funding would pay some share of royalties under a pull agreement to the push funder. The setting up of PD-PPPs for R&D into neglected diseases as "push" funders has improved product development pipelines in key disease areas, but these bodies need substantial additional funding if they are to take products through the development process. "Pull" funding such as via an advanced purchase commitment can offer a complementary way of engaging the private sector. Judicious use of push funding to support neglected research areas could spur competition under an advance purchase commitment.

The idea of push and pull financing structures as complementary is widely agreed for diseases prevalent in rich countries – in which case basic research is sponsored by institutions such as the US National Institutes of Health, while market incentives encourage firms to translate the results of basic R&D into useable products. Although the appropriate line between up-front public funding and private investment motivated by markets can always be debated, there is a general consensus that both are needed.

⁵³ For a discussion of appropriate risk allocation between the public and private sectors in the provision of publicly funded services see Appendix 2 of Comptroller and Auditor General (1999) "Examining the value for money of deals under the Private Finance Initiative," HC 739, Session 1998-99, National Audit Office, London: The Stationary Office.

⁵⁴ Farlow (2005), p. 53.

6.3.6 *The Farlow et al. alternative*

Farlow *et al.* (2005) propose an alternative model in which research on diseases primarily concentrated in developing countries is funded exclusively by the public sector and by philanthropies, with no role for programs to motivate private sector actors by the prospect of a market (as opposed to grants from funding agencies). Certainly, on *a priori* grounds there are arguments that research should be encouraged in part through the use of market incentives and the system of intellectual property rights; likewise, there are also arguments for a system in which research is entirely funded centrally with no market rewards. In practice, rich countries have chosen to use the former approach in combination with “push” funding, due to a recognition that there are complementary roles for the two approaches - with public research being necessary to create basic fundamental knowledge and private sector investment (motivated by a market) being critical to turn this basic R&D into useable products. To employ this mixed system of R&D for diseases concentrated in rich countries but have an entirely one-sided approach for the products primarily used in poor countries seems strange.

Many of Farlow *et al.*'s and Farlow's concerns focus around the asymmetry of information between donors and the companies working on the R&D. However, many of the problems discussed by Farlow *et al.* are also present (and in many cases, more problematic) in the alternative model Farlow and co-authors implicitly have in mind. Farlow *et al.* seem to imply that concerns over asymmetry of information are alleviated in their proposed model, but in fact these concerns may only be exacerbated. In models relying solely on publicly funded R&D, policy makers are forced to predict the future or choose among various scientific approaches in order to allocate R&D, whereas under advance purchase commitments firms are placed in the position of judging the relative promise of various research leads. The information asymmetry which exists between the donors and the research institutions in the case of a solely publicly-funded model is likely much greater than in the case of advance purchase commitments; for example, this is a problem faced by donors in relation to PD-PPPs where portfolio approaches similar to those used by venture capitalists in the private sector are being employed to manage the problem.⁵⁵ Farlow's preferred model is the Global HIV Vaccine Enterprise with its “open source” logic of sharing out tasks and sharing results. He also cites the discovery of the Human Genome as a collaborative effort, but the reality of that exercise was that competition from the private sector seeking commercial uses for genes stimulated the public-/foundation-financed activity to work much more intensely and more quickly. Overall, while Farlow critiques the potential failings of advanced purchase commitments he assumes away the underlying market failures in looking at the potential weaknesses of models solely relying on public sector “push” funding and non-IP based forms of collaboration such as “open source.” A primary benefit of advance purchase commitments is that they recognize the problem of information asymmetry and seek to ensure that decisions are made by those with the most information, and that incentives and information are aligned. Governments and donors decide what public policy priorities advance purchase commitments will be applied to based on the judged social value of the products, and scientists involved with the R&D and with money at stake decide which lines of research are most promising.

A related concern raised by Farlow (2005) is the issue of a “ratchet effect.”⁵⁶ We have discussed above (Section 6.1.1) concerns that scientific uncertainty will enable companies to press for price increases in early stage advance purchase commitments. This is to a large extent based on an argument that only a small number of firms will be able to compete under advance purchase

⁵⁵ See A. Towse, J. Mestre-Ferrandiz, and O. Renowden (2004) “Estimates of the medium-term financial resource needs for development of pharmaceuticals to combat ‘neglected diseases’,” Geneva: The Initiative on Public-Private Partnerships for Health, Global Forum for Health Research.

⁵⁶ Farlow (2005), p. 58.

commitments, and that these firms will then have strong bargaining power to raise the guaranteed price. It is worth clearly spelling out several issues related to this argument.

- Early in the R&D process, there will likely be a number of firms (for example, small biotechs) pursuing research leads and these firms are unlikely to have much bargaining power.
- Later in the R&D process, it may well be the case that there are a smaller number of firms who will be in a position to bring products to market, and these firms would have potential bargaining power with sponsors. However, these firms would have even more bargaining power under push programs than under pull programs. Under both push and pull programs, the companies may have access to markets outside of those targeted by the program, which will give them some incentive to bring the product to market. However, in the case of pull programs firms have a large additional incentive to move the product to market in order to receive their compensation, and purchasers are in a strong position to simply refuse to discuss contract revisions. In contrast, under push programs firms are rewarded up front and once the product is on the market will not receive as much additional compensation. These firms therefore have more ability, if they are so inclined, to hold out for push payments that more than cover their R&D costs before they agree to take the research forward.
- Finally, as previously discussed there is no reason to think that only a small number of firms would be seen as competing under an advance purchase commitment. Although it may be true that only a few firms have the capacity to bring a product fully through the development pipeline and commercialisation process, the capacity for deal-making and past responses of small biotechs to policy-generated incentives (such as the US Orphan Drug Act) suggest that an advance purchase commitment would nonetheless generate interest among firms other than large pharmaceutical firms. In particular, the available evidence suggests that there would not be a hold up problem because many biotechs would be involved in R&D. By late stage development there may only be a few firms which are able to take a product through the final stages to approval, but at that point the sponsor is in a strong bargaining position to resist efforts to increase the price beyond the guaranteed price.

Farlow (2005) also argues advance purchase commitments could stifle collaboration. Yet the structure of advance purchase commitments is similar to the incentive structure for drugs for diseases common in rich countries, and as discussed in Section 3.4 collaborative efforts do arise in response to these markets (for example, through licensing-in of products from biotech firms to large pharmaceutical companies) under the system of intellectual property rights that is currently in place. In addition, it is incorrect to assume that in the absence of an advance purchase commitment there would be widespread collaboration in these areas of R&D. Nonetheless, a legitimate concern is that 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 duplication of R&D activities is necessarily problematic.

The next section (Section 6.4) discusses areas where additional work is needed, including some areas that were outside the remit of the Center for Global Development working group. Some of the points we discuss in Section 6.4 are argued by Farlow *et al.* and Farlow to be too difficult to solve; to the contrary, we argue these issues can be feasibly addressed, but that further work is needed.

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

As noted above, there are a number of key issues on which further and more targeted analytic work by governments, industry and public health experts is needed. Priorities for further work include:

- 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;
- Considering the details of how the long-term price for products would best be set. The long-term price could be set in advance as a dollar amount per treatment, or determined by an agreed-upon formula related to the cost of production. A variety of hybrid options are also possible: for example, the long-term price could be structured such that sponsors and producers share the benefits of reducing the cost of production through a formula;
- For products that are at an early stage:
 - Considering the potential role of milestone payments through weighing the advantages and disadvantages of including milestone payments integrated within advance purchase commitments, through complementary push funding initiatives, or left to the private sector to organize as they see most useful;
 - Considering various mechanisms through which companies could be encouraged to sign onto advance purchase commitments at an early stage, so as to allow for some monitoring of R&D progress;
 - 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 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.