Making Markets for Vaccines

A practical plan

Consultation Draft

Report of the Working Group

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This report does not necessarily represent the views of the organizations to which they are affiliated.

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Summary

Vaccines are a very effective way to tackle poverty

Immunization is one of the safest and most cost-effective ways to reduce disease and prevent death. It is safe and cheap, and requires relatively little contact between the health system and the patient. As well as preventing death and illness, immunization also contributes to greater attendance in school, increased productivity, enhanced lifetime earnings and economic growth.

Immunization has been one of the great successes in global health. In 1974, about five percent of the world's children had access to vaccines. As a spin-off from the successful effort to eradicate smallpox, a global effort was launched in the 1980s to get six vaccines for serious childhood diseases to the world's children. Thanks to this effort, and the investments by both developing country governments and donors, three-quarters of all children are now immunized, saving about 3 million lives a year, and preventing long term illness and disability in millions more.

New vaccines take too long to reach poor countries

In the past, new vaccines have been introduced in the developing world through the gradual adoption of vaccines from the developed world. This has been true of nearly all of today's basic immunizations, including diphtheria, tetanus, pertussis,[1] measles and polio. These products, which were primarily developed for rich countries, have made an enormous impact on the developing world.

However, after a new vaccine has been introduced in rich countries, there has been a considerable delay before they are widely and cheaply available in poor countries. As a result of these delays, millions of children have died from diseases against which they could have been vaccinated.

Developing countries need different vaccines from developed countries

In the future, developing countries will not be able to count on hand-me-down vaccines from the developed world to tackle the diseases that affect them most. The most devastating diseases in developing countries are rare, or do not occur at all, in developed countries. Communicable diseases make up 56 percent of the disease burden in developing countries, but account for just 6

[1] Whooping cough

percent of diseases in developed countries. In cases in which the same disease affects both rich and poor countries, the particular strains of the disease often differ, requiring different vaccines. There are also differences in the way vaccines can be stored and distributed in different countries, and developing countries specifically need vaccines that can be produced and distributed cheaply.

There is insufficient R&D into vaccines for developing countries.

The market for vaccines for diseases of developing countries is neither sufficiently big, nor sufficiently predictable, to offer returns on investment in expensive research and product development. Commercial biotech and pharmaceutical companies, which are accountable to their investors and shareholders, have to target their research and development on innovations that can yield a commercial return, and typically that means medicines for the larger markets of the rich industrialized world.

Many individuals and companies in the biotech and pharmaceutical industry are deeply committed to developing products for global health. But the relative market size is inevitably reflected in product pipelines: only an estimated 10 percent of global research and development expenditure is targeted toward diseases affecting 90 percent of the world's population. Three of the developing world's leading killers – AIDS, tuberculosis and malaria – do not have an effective vaccine, yet together they kill nearly five million people each year.

Significant scientific barriers impede the development of vaccines for these diseases. But without the prospect of a profitable market, there is little chance that sufficient resources and priority will be given to basic scientific research, and then bringing the medicines through the expensive process of trials, regulatory approval and production.

Much is already being done to promote vaccine development

Developing country governments, donors, international public health professionals, and the vaccine industry recognize these problems, and have been working together to develop solutions. The pharmaceutical industry recognizes global needs for vaccines and drugs. Donors have created product development partnerships such as the Malaria Vaccine Initiative and the Aeras Global TB Fund to subsidize the cost of basic research and clinical trials for early-stage products. Partnerships such as the Accelerated Development and Introduction Plans for Rotavirus and Pneumococcus disease have been created to support the epidemiological work and market-building that will lead to greater demand and more credible demand forecasts for new vaccines.

The Global Alliance for Vaccines and Immunization (GAVI) and the Vaccine Fund are working to improve the adequacy and sustainability of funding for the purchase of existing vaccines. Manufacturers in developing countries, which have lower cost structures, are building the capability to supply low-priced products in the long-term.

An AdvancedMarkets commitment to promote the development of new vaccines

All these steps are having a positive impact on the structure of the vaccine market. But the fundamental rewards associated with developing country vaccines have not changed. It is inevitable that priority will be given in basic research, clinical testing, production, marketing and distribution to those products for which the market is larger and more certain.

This report examines a proposal which aims to solve the problem of inadequate market incentives for research into vaccines for diseases of developing countries. Donors would make a legally binding commitment to pay for a new vaccine if and when one is developed. This commitment, which we have called an AdvancedMarkets commitment, would create a larger market, with more certainty, which would attract firms to develop new products. It would imitate the market conditions that stimulate research for diseases of developed countries, and so bring the same market forces to bear on diseases of developing countries. It would create incentives for more firms to identify and pursue promising avenues of research and to compete to bring these to market as quickly as possible.

There would be benefits to all stakeholders.

An AdvancedMarkets commitment would be beneficial for donors, for industry and for developing countries.

For **donors**, there would be no cost unless the policy succeeds and a vaccine is developed. Donors would make a legally binding commitment, but this would have no impact on their budget until a vaccine is developed. Until then, development budgets would not need to be diverted from existing priorities. If and when a vaccine is available, donors will want to use aid to ensure that it is bought and distributed, because this would be a highly cost-effective way of reducing poverty. By making a commitment to spend aid in this way in the future, donors can influence the research priorities of the private sector today. In effect, the AdvancedMarkets commitment would greatly increase the productivity of aid by making it more predictable.

For **industry**, the AdvancedMarkets commitment would significantly extend the range of profitable markets in which firms can operate. It would enable firms to develop life-saving vaccines without the risk that they might be compelled by governments (or public opinion) to supply them at a price that is too low to recover their investment; and it removes the risk of compulsory licensing. That would enable firms to invest with confidence today in vaccines for diseases that mainly affect developing countries. An AdvancedMarkets commitment would enable firms to do something that is good for the world, not as an act of charity or only for reasons of corporate social responsibility, but as a straightforward economic investment.

Most importantly, for the **people of developing countries** the proposal offers the prospect of earlier development of vaccines that would save lives and reduce the burden of disease; and it would ensure that, once those medicines have been developed, they would be available rapidly and affordably to the people who need them.

AdvancedMarkets eliminates the trade-off between access and innovation

Some people want to see medicines available at the lowest possible price, so that everyone who needs them can afford to use them. Some want industry to make a sufficient return on medicines to enable and encourage them to go on developing important new products. Many people have some sympathy with both points of view. The AdvancedMarkets commitment would resolve this trade-off both by ensuring that poor people get access to a vaccine they need, and by providing a return to the developer to encourage further innovation.

AdvancedMarkets builds on well-established principles.

In rich countries, firms are able to invest in research and development for new medicines because they are confident that, if they succeed, they will be able to recover their costs through sales. This creates an incentive to support research and development into products that people are willing to buy, and to bring those products to market as quickly as possible. The AdvancedMarkets commitment would extend this principle to new markets, for which products are not currently being developed commercially because the consumers in those markets are too poor to pay the higher prices themselves. And it would do so in a way that not only encourages research and investment, but ensures that, if a vaccine is developed, it will be made available quickly to people who need it.

There are many precedents for using long-term procurement contracts for public purchase of goods or services that require investment. Governments enter into long-term contracts every day,

to secure better value for money for taxpayers, and more reliable services than if they were limited to short-term contracts.

But while the idea is built on familiar foundations, it is innovative because the commitment to buy would be made in advance of the product being available. By making this commitment in a legally binding form, donors will influence firms' investment decisions, and so accelerate the development of critical vaccines.

Practical proposals for AdvancedMarkets

The Working Group was established to consider whether this idea would work, and how it could be implemented in practice. It worked with experts in contract law to develop practical proposals for binding long-term advance contracts. It worked with academic experts on incentives and pricing to design various rewards that would stimulate investments under different market conditions. And it consulted decision-makers in the pharmaceutical and biotech industry, experts in global health, and donors on the feasibility and potential impact of such tools. Drawing on this expertise, the Working Group undertook its own analysis of the financial, commercial and legal parameters within which a commitment might be made.

The conclusion of the Working Group is that AdvancedMarkets would be likely to accelerate development and delivery of new vaccines and that it could be implemented in practice. This report sets out in detail how a commitment could be designed: how it would be constructed in law, the main principles of the contract, and how sponsors could make the necessary funding commitments. The analysis shows that a commitment large enough to be likely to stimulate a response from the industry would also be very good value for money for the donors.

The Working Group does not believe that AdvancedMarkets is a silver bullet that would, by itself, ensure the provision of new vaccines. It would need to be implemented in conjunction with other significant improvements in the system through which vaccines are procured and delivered. It would not replace the need for subsidies for basic research. However, if properly implemented, AdvancedMarkets has the potential to change significantly the market dynamics for new product development and accelerate the development and availability of vitally important new vaccines for neglected diseases.

Summary of Working Group conclusions

- An AdvancedMarkets commitment would **complement public and philanthropic funding of research** by helping to overcome market-related constraints that prevent new vaccines from being created and supplied for the developing world.
- The proposal would be effective both for products that are at a **late stage** of development (*i.e.* close to licensing) and for products that are at an **early stage**.
- **It can be implemented in practice**. It is based on sound and familiar legal principles. The contracts should be legally binding, to increase certainty. The rules of the system would need to be transparent and binding from the outset, including price, eligibility criteria and dispute resolution procedures.
- AdvancedMarkets could be implemented within **existing regulatory and procurement systems** for the poorest countries of the developing world vaccines.
- The proposal would **increase industry's willingness to invest in research and development in vaccines and drugs for diseases of the developing world**.
- The credibility and effectiveness of an AdvancedMarkets commitment would be enhanced if it were accompanied by **continuing efforts to scale up vaccination delivery systems in developing countries**, to improve demand forecasts and to extend long term procurement for existing vaccines; these measures would increase market confidence in future demand for vaccines, as well as being desirable in their own right.
- The **systems of budgetary control and commitment of potential sponsors do not impose insurmountable constraints** on making a legally binding commitment. Both public and private funders could make the necessary commitment within existing budgetary and commitment processes.
- **A commitment could be large enough to provide an incentive to industry and still represent a very good deal for a sponsor.** A contract that created an expected revenue stream broadly comparable to that of existing commercial products would result in a cost-per-life-saved that represents very good value by comparison with other health interventions.
- Public health funders, the industry and the public private partnerships should work together to agree the **details of pilot AdvancedMarkets commitments** in at least one early stage and one late stage product; and to become partners in the development and launch of this important new approach.

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Chapter 1: About vaccines

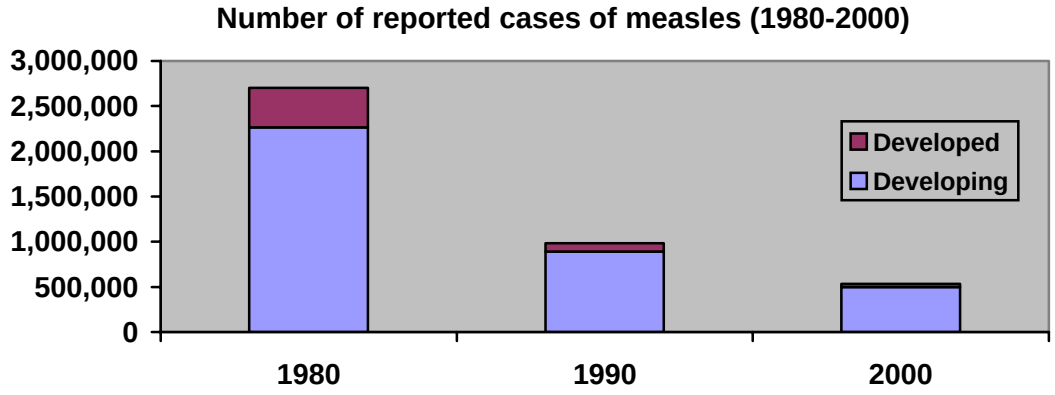
1.1 Vaccines and Global Health

1.1.1 Vaccines have transformed the world's health

Technological innovations have transformed health conditions in the past fifty years, in both rich and poor countries. In the industrialized world, for example, basic childhood immunization[2] at high levels has almost eliminated many diseases that once crippled, severely sickened or killed thousands of young children each year.

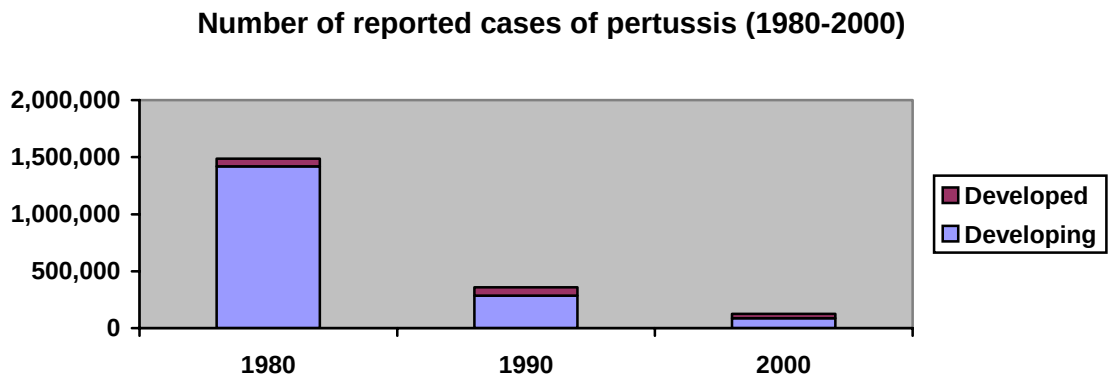
Those same vaccines – originally developed for the US and Europe – were subsequently purchased and used in the developing world, typically at low prices after manufacturing capacity had been built up. Even with much lower levels of use than in developed nations, these products had an enormous health impact in the developing world.

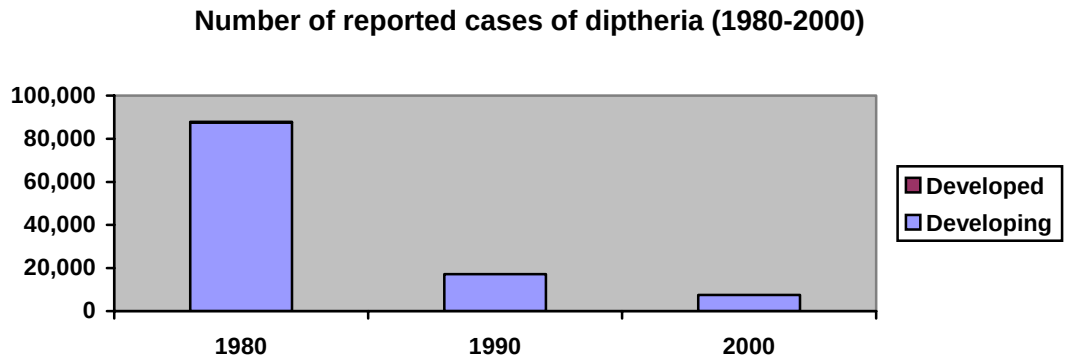
Figure 1.1. Decline in number of reported cases with introduction of basic childhood immunizations in developed and developing countries – selected examples[3]



[2] Against diphtheria-tetanus-pertussis (DTP combinations), measles-mumps-rubella (MMR), and polio

[3] Source: WHO Immunization Profiles for "Developed" and "Developing" country blocks





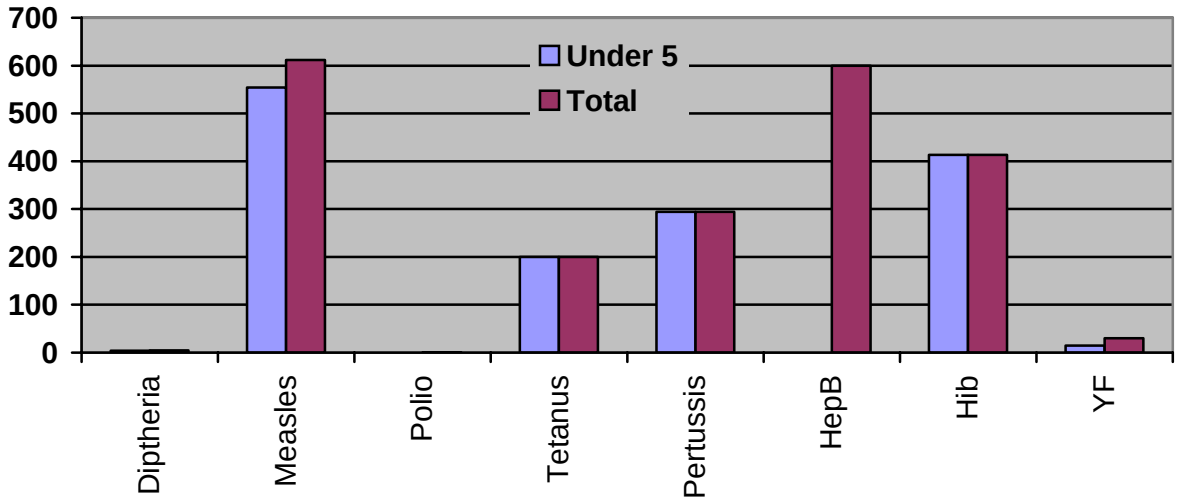
1.1.2 Millions die of vaccine-preventable diseases

About three million people a year die of diseases that can be prevented with existing vaccines, such a measles, Hepatitis B and tetanus. People die of vaccine-preventable diseases partly because around a quarter of children, almost all of whom are in developing countries, do not have access to basic immunization services. Furthermore, the children who are immunized do not always get vaccines against some high-risk diseases, not because there is no vaccine on the market but because there is a delay before newer vaccines are made available at low cost in developing countries. In a repeat of the pattern for earlier vaccines, those that protect against hepatitis B and Hib[4] are only now becoming affordable in developing countries, more than a decade after they were first used in North America, Europe and Australia.

The result is that more than 1½ million children die each year of vaccine-preventable diseases. As the graph below shows, the main vaccine-preventable causes of death in under-5s are measles, Hib-related diseases, pertussis and tetanus.

[4] *Haemophilus influenzae B* – a major cause of childhood pneumonia and bacterial meningitis

Figure 1.2: Annual deaths from vaccine preventable diseases (thousands per year)[5]



1.1.3 New vaccines are needed for the developing world

The full spectrum of currently available vaccines, even if they were comprehensively used, would not solve a number of the major health problems facing the developing world.

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AIDS, tuberculosis and malaria account for about 5 million deaths a year; there is no available vaccine for any of these, and the science is at an early stage. Pneumococcus is estimated to kill 1.1 million people a year, and rotavirus 0.8 million; for these diseases, vaccines are being developed. Even once they have been licensed for use, experience suggests that it will be many years before they are widely available in developing countries at an affordable price. The form of the disease they protect against may not be the form that is most common in developing countries. Other diseases affecting the developing world for which no vaccine is available include shigella, schistosomiasis, leishmaniasis, chagas disease and dengue. [6]

Public health matters partly because it is possible to reduce death rates, and improve the quality of life for millions of people. But it is also important because improving life expectancy has a direct impact on economic development. Economists estimate that increased life expectancy

[5]WHO (2004). Figures are for 2002

[6] CVI Forum (July 1999) p6.

makes a significant contribution to economic growth.[7] One study of the US found that over half of the growth of real income in the first half of the 20th Century was attributable to declining mortality.[8] In other words, reducing the burden of disease will make a direct contribution not only to achieving the health-related Millennium Development Goals, but more generally to the lives and prosperity of the developing world.

New vaccines offer one of the most significant opportunities to improve global health. Vaccination is cost-effective and safe and has been proven to work. It can actually save money for health services, by reducing the burden of disease. As well as ensuring that vaccines are available at an affordable price for diseases that can already be prevented, research and scientific innovation to produce new products are needed to make the next leap forward in improving global health.

1.2 The development of vaccines

1.2.1 Pharmaceutical development is a risky investment decision

Research and development based pharmaceutical companies and biotechnology firms are in a risky business. Their business model – and their competitive edge – is based on placing smart bets on science in the face of imperfect market information. Vaccine development can take 7-20 years for basic research, clinical testing, regulatory approval, production and distribution. There are high investment costs - estimated to be more than $800m for a new medicine, up to the point of regulatory approval.[9] (Vaccines may cost more than this average.) There are costly regulatory hurdles with uncertain outcomes and high costs of production, marketing and distribution.

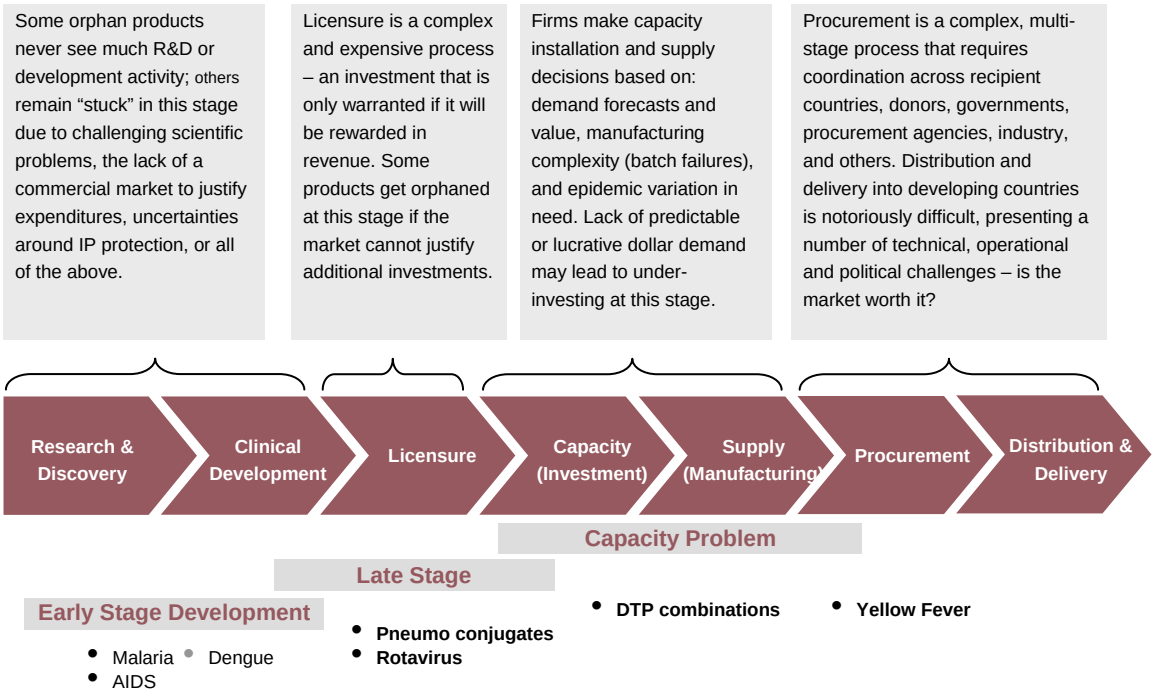
These are uncertain investments – for every ten candidate products which enter development only one will achieve product registration and far fewer will become “blockbusters” that earn a significant return for the company. Each successful product has to recover not only the costs of its own design and development, but also the costs of the candidates that were not successful. The development of new products is, in effect, a series of bets placed on emerging scientific

[7] Bloom, Canning and Malaney (2000); Bloom & Canning (2000). These studies estimate that an increase in life expectancy of 5 years adds 0.3 to 0.5 percentage points to annual economic growth.
[8] Nordhaus (2003).
[9] DiMasi, Hansen & Grabowski (2003)

pathways, based on a hard-nosed analysis of the competitive landscape and some reasonable estimates of the eventual market size and willingness to pay.

Despite these uncertainties, the market for medicines in the developed world does succeed in generating important new products. Effective and innovative drugs and vaccines are invented, tested, licensed, and produced. The functioning of the market for industrialized countries depends critically on patents, which enable the manufacturer, for a limited time, to limit competition; this means that manufacturers are able to charge consumers a price which is high enough not only to cover the cost of production but also the costs of research and development. As figure 1.3 below shows, market considerations play an important part in each stage of the process as possible medicines move from investment in basic research, through to trials, licensing, production and supply. By offering the opportunity to charge temporarily higher prices for the medicines, patents acts as a pull mechanism, providing pharmaceutical companies with sufficient incentive to make risky investments, some of which will eventually result in life-saving medicines of enormous social value.

Figure 1.3. Vaccine development pipeline



1.2.2 Costs of vaccine development

A recent study[10] looked at 68 randomly selected new drugs from ten pharmaceutical firms to estimate the average pre-tax cost of new drug development, up to the point of licensing. Costs of compounds that were abandoned during tested were included. The average estimated cost was $802 million (in 2000 dollars). However, vaccines are likely to cost more than the average for medicines as a whole, as they are technically more complex to design, and the costs of testing and production are significantly higher than for drugs.

It is also possible to estimate the market size needed to make a new vaccine viable. An earlier study[11] looked at 118 new pharmaceuticals introduced into the United States between 1990 and 1994. Based on this analysis, it is estimated[12] that the total market size (in net present value) of an average commercial product is about $2.5 billion (in 2004 dollars); with an upper quartile of around $3 billion.

The total vaccine market is very small as a share of pharmaceuticals as a whole. Vaccine revenues amount to only 1.5 percent of global pharmaceutical sales,[13] and global sales of all vaccines combined are roughly equivalent to annual sales of a single blockbuster drug such as Lipitor or Prilosec.[14]

1.3 The market for vaccines in developing countries

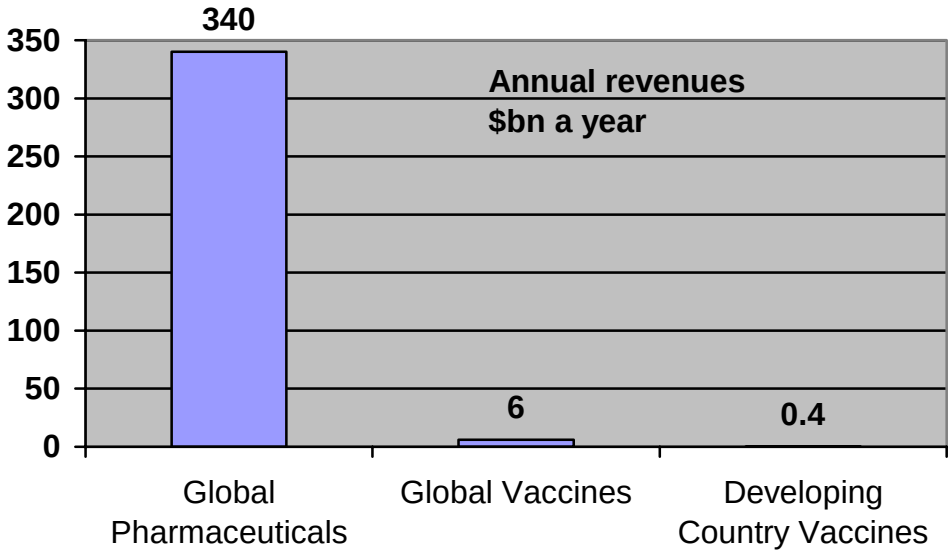
1.3.1 The market for vaccines in developing countries is small

Total spending on health in least-developed countries is approximately $17 a person a year (of which about $6 is from the Government budget). For other low-income countries, the average is about $36 a person a year. [15] (By comparison, the figure for high-income countries is $2263 a year). The global market for vaccines is about $6 billion a year. Developing country markets account for about half of total vaccine sales by volume, but only account for about 5 percent – or

[10] DiMasi, Hansen & Grabowski (2003)
[11] Grabowski, Vernon & diMasi (2002)
[12] Berndt, Bruce, Kremer & Weizsacker (2003)
[13] Batson (2001), quoted in IOM (2004) p 107
[14] Marketletter (2002) quoted in IOM (2004) p 108
[15] WHO (2003b)

less - of total revenue from the sales of vaccines. This creates a total market size of around $300-$400 million a year.[16]

Figure 1.4 Market sizes for pharmaceutical categories



Spending on vaccines used in developing countries has increased a little in recent years with the establishment of GAVI and the Vaccine Fund; but the developing country market value is clearly very small relative to the market in rich countries and relative to other pharmaceuticals.

1.3.2 The need to improve public procurement

The arrangements for buying medicines for developing countries add to the risks faced by companies investing in vaccines for developing countries.

Most vaccines are bought by public health authorities or on their behalf by procurement agencies such as UNICEF. Once a vaccine has been developed, governments have every reason to use their role as dominant purchasers, regulators and arbiters of intellectual property to negotiate the lowest possible price. Given the very small funds available for health, achieving a low price is essential to enable the authorities to buy medicines for as many people as possible.

But there is a trade-off between the short-term need to get vaccines to many people, and the long-term need to ensure that firms are able to meet the costs of research and provide returns to

[16] Mercer Management Consulting (2002)

shareholders. Buying vaccines at very low prices means that the firm receives little more than cost of production, and that is not enough to recover the costs of the original research and development. But pharmaceutical firms know when they are planning their future research that, once a medicine is available, governments will be able to negotiate the price down; and that the company will come under pressure from public opinion to make essential medicines available as cheaply as possible. In extreme cases, they may face compulsory licensing. If the firm does not anticipate being able to recover their development costs at this price, it makes it much less attractive for the industry to invest in developing the medicine in the first place.[17]

As well as driving the price down, centralized public procurement adds to the risk for firms that are developing medicines for these markets. Firms are at greater risk of unpredictable decisions by governments or regulators that would eliminate their entire market; and there is more uncertainty about the willingness or ability of governments to buy and deliver medicines through a less advanced health system.

This is not to deny that collective public procurement is better than private or decentralized purchasing. The point is that there may be ways to do public procurement better, to reduce the total costs over the medium term and reduce risks for firms, which could then stimulate more rapid product development and availability.

1.3.3 Hand-me-downs have been quite effective in the past

Given the small value of the market developing countries, it is not surprising that these countries have depended largely on hand-me-down medicines that were originally invented for industrialized countries.

The use of these vaccines has made a huge impact on global health. Smallpox used to kill five million people a year; thanks to the world's first vaccine, it was eradicated in 1979. Fifty years ago, polio was the leading cause of paralysis, crippling thousands of children and adults. The eradication of polio through vaccination is tantalizingly close, though it will require continued focus and commitment from policymakers. Two-thirds of developing countries have eliminated neo-natal tetanus. In one year alone (from June 2001), mass measles campaigns in eight African

[17] Economists call this a problem of "time inconsistency" because the best policy to pursue change is over time, in a way that can be anticipated at the outset. Predicting a future change in policy, economic actors adjust their behavior today. It is typically solved by some form of institutional pre-commitment which prevents the authorities from "re-optimizing" in the later phase. AdvancedMarkets would provide such a commitment in this case.

countries vaccinated more than 20 million children and prevented more than 140,000 deaths; measles vaccinations are now preventing ¼ million deaths a year.[18] As a result of vaccinations, millions of lives are saved every year; and millions more protected from disease and disability.

However, while overall vaccination rates are now about 70 percent, this average masks considerable variations across regions. In sub-Saharan Africa, for example, immunization rates are about 55%. Fewer than a quarter of Nigerians are vaccinated.[19]

In the cases in which vaccines have been introduced in developing countries, there has been a considerable delay – typically 10 to 15 years or more – following their adoption in developed countries. For example, during the 1990s, the use of a vaccine for Haemophilus influenzae type b (a strain that causes some forms of pneumonia and meningitis) almost eliminated Hib-related diseases in developed countries. But the vaccine has been too expensive for use in most low-income countries. As a result, an estimated 4.5 million unvaccinated children died from Hib-related diseases – mainly pneumonia – over the same 10-year period. [20]

1.3.4 Hand-me-downs will not meet the needs of developing countries in future

Not only is there typically a significant delay before new vaccines are made available in developing countries, but it is likely that new vaccines that are critically important for the developing world may not be developed at all. The reason is that the health needs of children in developed and developing countries are diverging. Fifteen years ago, a child born almost anywhere in the world received more or less the same basic vaccines – DTwP (diptheria, tetanus and whole-cell pertussis – whooping cough), OPV (oral polio vaccine), and BCG (tuberculosis). Today, a child born in the rich world uses different, enhanced (and more expensive) vaccines than children born in the developing world.[21]

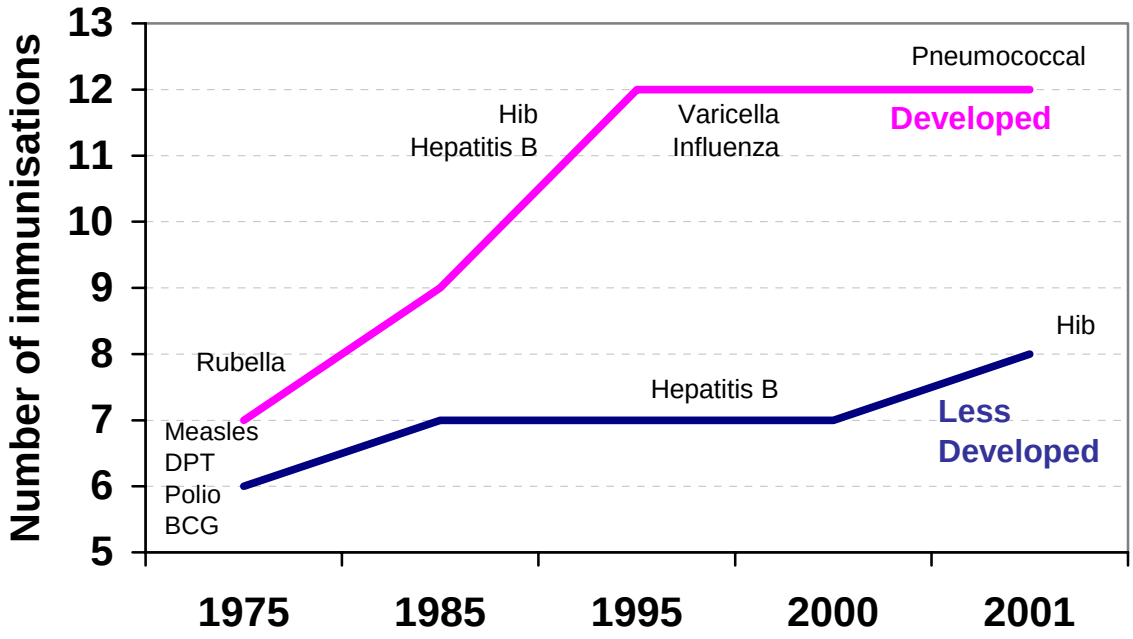
[18] http://www.measlesinitiative.org/facts2.asp

[19] WHO (2002)

[20] WHO (2002)

[21] DTwP coverage in OECD countries has fallen from 90 percent to 34 percent as they now use DtaP (diphtheria, tetanus and acellular pertussis) – a more costly product that is thought to have a marginally better safety record and a more reliable production profile.

Figure 1.5: Vaccination gap between children in rich and poor countries[22]



The priority diseases for rich countries and poor countries are now diverging. HIV/AIDS is the number one killer in the low-income countries but is not even one of the top 10 for high-income countries. Diarrhoeal diseases, malaria and other childhood diseases also appear on the developing world's top 10 causes of death, but are nowhere on the list for rich countries. As the table below shows, communicable diseases are the cause of 56 percent of the disease burden in low-income countries, and just 6 percent of diseases in high-income countries.

Second, the target product characteristics are also different: heat stability, safety and affordability continue to be major concerns for the developing world, while the developed world is driving toward absolutely risk-free vaccines at almost any cost.

This means that the developing world's previous source of affordable vaccines – residual supply from the developed world, at tiered prices – is no longer a reliable model. It also means that new products are developed with the rich – not the poor – world in mind, so diseases unique to the developing world are left behind.

[22] Batson (2001)

Table1.1. 2002 Global Burden of Disease, Disaggregated by Cause

Cause	Percent of Total World Disease Burden	Percent of Total Disease Burden in High-income Countries*	Percent of Total Disease Burden in Low-income Countries*
Communicable, maternal, & perinatal diseases	**41.0**	**6.2**	**56.4**
Infectious and parasitic diseases	*23.9*	*2.5*	*34.1*
HIV/AIDS	5.8	0.6	7.6
Tuberculosis	2.4	0.1	3.0
Malaria	3.0	0.0	4.9
Respiratory infections	*6.1*	*1.2*	*8.4*
Other	*11.1*	*2.5*	*13.9*
Noncommunicable conditions	**46.7**	**84.7**	**32.6**
Malignant neoplasms (cancers)	5.1	14.7	2.4
Cardiovascular diseases	9.9	15.3	7.3
Other	31.7	54.7	22.8
Injuries	**12.2**	**9.1**	**11.0**

Country classifications as in the 2003 World Bank World Development Indicators, based on World Bank estimates of 2001 gross national income (GNI) per capita. Data for upper- and lower-middle income countries not shown. *Source*: 2002 WHO Global Burden of Disease Data, as used in the 2003 WHO *World Health Report.* Figures are DALYs – see Chapter 5 for definition.

1.3.5 A new model of vaccine development is needed

In summary, this analysis shows that:

- hand-me-down vaccines have made a huge contribution to improving the health of people in developing countries;
- these vaccines have been available only after a significant delay; we need to find ways to ensure that new vaccines reach developing countries at affordable prices more quickly;

- the needs of developing countries and developed countries are diverging. This means that developing countries cannot depend in the future on obtaining new vaccines as a spin-off from the development of vaccines for the larger developed-country markets;
- the market size for vaccines in developing countries is not large enough to provide a market incentive for pharmaceutical companies to develop new vaccines specifically for diseases that occur mainly in these countries, because the people who need the vaccines do not have enough money to buy them; and
- collective procurement, aimed at getting medicines to as many people as possible, has huge short-term benefits. But it needs to be managed in way that balances the aim of minimizing short term costs with the need to stimulate development of new products.

The prospects for vaccines in developing countries are not promising. The total resources committed to developing vaccines against the three major global infectious diseases (HIV/AIDS, TB and malaria) is far less than $1 billion per year, compared to $60-100 billion spent on diseases of rich countries. Less than 10 percent of the worldwide expenditure on health research and development is devoted to the major health problems of 90 percent of the population – a phenomenon often referred to as the "10-90 gap." This disparity is reflected in the number and type of drugs that make it to market: among 1,223 new chemical entities brought to market from 1975 to 1997, only 13 (1 percent) were specifically for tropical diseases; of these, only 4 may be considered direct results of research and development activities of the pharmaceutical industry targeted at new human products.[23]

This trend is alarming because the importance of the development of new vaccines for the most significant health problems in the developing world can hardly be overstated. In general, vaccines are particularly well-suited to the needs of developing countries. They are a very cheap way to save lives. They do not require costly screening, diagnosis or follow-up, and can be delivered by para-professionals; so they are well suited to the needs of the developing world, where health systems tend to be weak. **In short, vaccines represent the best hope for large-scale and rapid improvements in health status in the developing world.**

[23] Pecoul *et al* (1999) p. 364. Two of 13 are updated versions of previous products; 2 are the result of military research; and 5 come from veterinary research.

Chapter 2: Promoting vaccine development

Chapter 1 concluded that the current market structure does not provide sufficient incentive for firms to develop vaccines for developing countries and that the hand-me-down model will no longer meet the needs of developing countries. It set out the evidence of the effect of this on the product pipeline: the current arrangements are not likely to produce the new vaccines that would have immense impact on developing countries. This chapter summarizes possible policy responses to this situation.

2.1 The difference between push and pull

Some interventions in the vaccine market subsidize the costs of research, development or production, for example through grants or public equity investments, research and development tax credits, and the establishment of public research labs. These are sometimes called “push” programs. Other policies creates incentives for investment by increasing the rewards for success, for example by increasing the price paid for a final product, offering sales tax credits, or guaranteeing patent extensions or exchanges. These have been called “pull” programs. Roughly, the difference between push and pull is the difference between funding inputs and paying for outputs.

Nearly all drugs and vaccines on the shelves of pharmacies in the industrialized world are the result of a combination of push from publicly subsidized research and pull from the market. These two factors combine to reduce the risks faced by commercial pharmaceutical firms in the early stages – before the establishment of a clear scientific pathway toward an effective product – and to then provide incentives for private investment in the costly stages of clinical development. In the pharmaceutical marketplace in wealthy countries, the firms that scout out and procure promising scientific innovations, and then invest sufficiently to get to market soonest, can be rewarded with a large enough share of a lucrative market both to offset the large investment in research and development and to provide a return on investment to shareholders.

2.2 Push programs

2.2.1 Public programs

Push programs for global health challenges are increasingly common. Funding of vaccine research through the US National Institutes of Health (NIH) is perhaps the most common form of push support. Most of this funding is in the form of grants to academic institutions and health-

related agencies; roughly two-thirds is for basic research and one-third is to support clinical trials.

2.2.2 Public-private partnerships

Alongside government funding, product development partnerships have been established to provide direct support for basic research and clinical trials in particular disease areas. These include the Malaria Vaccine Initiative (MVI), the International AIDS Vaccine Initiative (IAVI), and the Aeras Global TB Fund (Aeras). MVI focuses largely on push funding; it has spent more than $43 million on malaria vaccine R&D since 1999 and now supports 20 vaccine candidates in various stages of pre- or clinical development.[24] In 2004, a trial supported by MVI and GSK in Mozambique found that a malaria vaccine candidate protected a significant percentage of children against uncomplicated malaria, infection, and severe forms of the disease for at least six months.

Similarly, IAVI is focused mainly on providing financial and technical support for product development – according to IAVI's strategic plan, they will use 75 percent of their budget ($340 million donated to date) to support promising vaccine candidates; as of March 2004, IAVI was supporting 8 product development partnerships in Phase 1 trials or further.[25] The Aeras Global TB Foundation received a grant of $82.9 million from the Bill and Melinda Gates Foundation in February 2004 to support research of promising TB vaccines in three main areas: clinical trials of two promising vaccine candidates; improving the effectiveness of animal models to indicate efficacy in humans; and basic research on early-stage "next generation" candidates.[26]

However, the resources allocated to push funding are small. Total global funding for research and development for a malaria vaccine is about $65 million a year – much less than the amount needed to advance a single vaccine through the product development process.[27]

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[24] This is approximately 15 percent of total public sector malaria vaccine R&D expenditures from 1999 to 2003. The NIH (NIAID) accounts for more than 50 percent of the total; other funders include the European Community, WHO's Special Programme for Research and Training in Tropical Diseases (TDR), the US Agency for International Development (USAID), and the US Department of Defense. See the MVI website www.malariavaccine.org for details.

[25] See IAVI website www.iavi.org for details

[26] See the Aeras website on http://www.aeras.org/spotlight/gates829.html for details.

[27] Malaria Vaccine R&D: The Case for Greater Resources; Malaria Vaccine Initiative (http://www.path.org/)

Push mechanisms are clearly very important, particularly to stimulate the primary scientific research on which eventual solutions are likely to be based. But push funding poses a challenge for policy-makers, because funds are limited, which leaves many promising avenues of scientific research unexplored; and because it requires the funders to "pick winners" who will receive the scarce resources. As candidate vaccines progress towards large scale trials, regulatory approval and production, the process becomes more expensive, and the money available for push funding is not enough to bring the candidates through the pipeline. Only if there is a prospect of profitable sales will vaccine suppliers be able to invest enough to bring the products to market.

2.3 Pull programs

2.3.1 What are pull programs?

Pull programs are arrangements designed to create a market, or increase the certainty of a market, and so improve the likelihood of a return on investment. They pay for output – in this case, the actual creation of a new medicine or vaccine - rather than input.

The patent system is an example of such an incentive. Patents provide firms with more likelihood of being able to make a return on their investment (by granting temporary market exclusivity). This increases the incentive to invest in research and development, and leads to increased numbers of inventions and products being brought to market.

Box 2.1 Market Size and Product Development

Common sense, together with observation of real-world behaviour, suggest that firms will invest more in the R&D for products that promise larger revenues (net of R&D costs) and profits than in products that would yield a smaller volume and or unit price once they reach market.

Several recent studies have documented the impact of market size on pharmaceutical innovation (Vernon and Grabowski 2000, Morton 1999, Reiffan and Ward 2002). For example, Acemoglu and Linn (2003) analyzed the effect of variations in market size for pharmaceuticals linked to demographic changes. They find that, other things being equal, 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.

There are reasons to believe that complementing push programs with demand-based programs may be an efficient way to stimulate the development of new medicines, as they require less knowledge on the part of policy-makers about the likelihood of success of particular approaches while creating stronger internal incentives within pharmaceutical and biotech companies to identify and pursue the most promising avenues of research.

2.3.2 Examples of pull mechanisms in health

The Working Group looked at a number of examples of market enhancement for products that might otherwise not be commercially attractive. Although none of the programs described below has all the elements of the AdvancedMarkets commitment recommended in this report, they do illustrate important aspects and – crucially – the likely impact on firms' investment decisions.

US Orphan Drug Act

The US Orphan Drug Act (ODA) of 1983 uses market exclusivity and other mechanisms to enhance the market, and thereby stimulate research and development on neglected products in the US. It gives firms special incentives to develop drugs for diseases afflicting fewer than 200, 000 Americans.[28]

In the Orphan Drug Act, Congress approved the following incentives:

- Seven years marketing exclusivity upon Food and Drug Administration (FDA) approval; the FDA cannot approve another drug for the same indication without the sponsor's consent for seven years. A 1992 amendment provided that if a drug demonstrates clinical superiority and efficacy (with regard to prevention, diagnosis, or treatment of the disease), the new drug can then be authorized for the same rare disease;
- Tax credit for related clinical research, up to 50 percent of clinical testing expenses; and
- Grant support for investigation of rare disease treatment.

The Act has been successful: according to the FDA, more than 200 drugs and biological products for rare diseases have been brought to market since 1983, in contrast to fewer than 10 in the previous decade.[29] The primary feature of the Orphan Drug Act that is attractive to pharmaceutical companies is believed to be the promise of a period of market exclusivity.[30]

Advance contracts for Meningitis C vaccine in the UK

In the UK, the establishment of a more certain and commercially attractive market stimulated the development of a meningitis C vaccine.

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[28] For example, these diseases include Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome and muscular dystrophy.

[29] Lichtenberg and Waldfogel (2003)

[30] Henkel (1999)

Beginning in 1994, officials in the UK Department of Health noticed an increase in the notifications and laboratory confirmed cases of meningococcal disease. While some of the increase was the result of improvements in reporting, there had also been a disproportionate increase in group C cases, particularly in older teenagers. The Department conducted talks with all major pharmaceutical manufacturers in 1994 to understand the status of research on a vaccine for meningitis C. They found that a product was in the early stages of development.

In 1996 the UK announced that a tender would be issued for a meningitis conjugate vaccine and a tender for 18 million doses of vaccine was duly issued in 1999. Three companies responded to the tender and negotiations were conducted with each company separately. Clinical trial support and help by way of expedited regulatory reviews shortened the time to market for the companies in the UK, and through the Mutual Recognition Process in other European countries. The guaranteed purchase was negotiated with each company participating in the tender; the first to market would receive the lion's share of the purchase.

The first vaccine was licensed in October 1999 by Wyeth Lederle, who received a contract for approximately 10 million doses. This was followed by contracts for Chiron (5 million doses) and Baxter (3 million doses) in March and July 2000, respectively. The price was approximately $21 a dose. In subsequent tenders, in which only the annual birth cohort was vaccinated (approximately 240,000 births at three doses per infant), prices went down substantially and fluctuated around US$12-$18 a dose. The combination of accelerated approval and guaranteed purchase was successful in bringing forward the development of a conjugate meningococcal vaccine.[31]

Pull through Government procurement guidelines

Vaccines for Children (VFC), a US Government program established in 1994, provides vaccines to needy children free of charge. The Advisory Committee on Immunization Practices (ACIP), experts selected by the Department of Health and Human Services (HHS), makes recommendations to HHS regarding which vaccines should be administered in the US. In practice, the recommendations typically set policy for immunization requirements and determine which vaccines will be available under the VFC. Thus, if a vaccine is recommended by ACIP, producers of that vaccine are assured a reasonably large market. Vaccine prices are typically

[31] Details of the procurement of a meningococcal C vaccine were provided in private communications by Angeline Nanni, formerly with Baxter and now with the GAVI's Pneumo ADIP, and with David Salisbury, Principal Medical Officer of UK's Department of Health.

negotiated after the ACIP recommendation, so once ACIP has issued a recommendation, a vaccine producer is in a strong position to set the price close to the vaccine's social value. In this way, the ACIP system creates some of the characteristics of a pull program.

Similarly, an analysis of the private response to the 1993 Medicare policy to cover influenza vaccinations without co-payments or deductibles, which substantially enlarged the expected market for flu vaccines, offers evidence that this policy was successful in inducing research investments in the private sector.[32] The best flu vaccines in existence at the time had an efficacy rate of 58 percent, and the 1993 flu policy helped stimulate the research responsible for the approval (in 2003) of the first new flu vaccines since 1978, as well as the first intranasal flu vaccine, FluMist, which has an 85 percent efficacy rate in healthy adults. The annual potential benefits from the 1993 flu policy (in particular, the combination of greater efficacy and wider use of the new vaccine) were estimated to range from $4.3 to $9.5 billion.[33]

Project Bioshield

Project Bioshield legislation uses market enhancement mechanisms to stimulate development of bioterror countermeasures for 57 diagnostics, vaccines and therapeutic products prioritized by the Defense Science Board in the US. In 2003, Congress passed:

- a spending authority of nearly $6 billion for the procurement of qualifying countermeasures available in five years;[34]
- increased authority to NIH and NIAID to award R&D grants and contracts, and to hire technical experts; and
- FDA emergency-use authorization, *e.g.*, to waive licensing requirements if a product is needed in an emergency where alternatives are not available.

A drawback in the design of Project Bioshield is that the spending authority has been established without committing to a price for a particular product. This means that the producer is not guaranteed a larger market: once a product has been developed, the US Government would still have an incentive to bargain for a low price. Moreover, the budgetary authority expires after five years, even though it is likely to take longer to develop new products. Accordingly, the reaction

[32] Finkelstein (2003), Finkelstein (2004)

[33] A caveat is that sales of this intranasal flu vaccine have been lower than expected, likely at least in part due to a high pricing strategy by the manufacturer.

[34] Note this is not guaranteed purchase of any particular product but a guarantee of funds available for qualified products.

of industry has been mixed. In interviews with pharmaceutical and biotech companies, the Working Group found support for the need for explicit market creation, but a widespread feeling that the proposals in the legislation had not gone far enough to achieve this.

Congress is now considering the Biological, Chemical, and Radiological Weapons Countermeasures Research Act, dubbed BioShield II, which is expected to include tax credits, intellectual property incentives, and liability protection. One option that is being considered is that BioShield II might offer companies a two-year "wild-card" extension on an unrelated patent, as a reward for developing an anti-bioterrorism product.

Enhancing incentives by demonstrating demand

One way to increase firms' assessment of the possible returns on investment for future global health products is to demonstrate that products that are available today are actually bought in significant quantities. The existence of GAVI and the Vaccine Fund, which have committed to spend $750 million on purchasing existing vaccines, may encourage some manufacturers to look again at developing country markets. There is some evidence that this additional expenditure on vaccines is encouraging firms to be more interested in selling existing vaccines to the developing world. The *Washington Post* reported recently that as a result of the efforts of the Vaccine Fund "now when UNICEF puts out a tender for hepatitis B vaccine, for example, there are twelve firms ready to bid, up from three in 2000" [35].

Given the volatility of aid flows and the unpredictability of foreign assistance priorities, however, increased current expenditure on existing vaccines, while extremely valuable, will not be sufficient to provide assurance needed for developers of early-stage products.[36]

2.4 Types of incentives

The table below[37] summarizes a number of different types of possible mechanisms which fall into the broad definition of pull programs.

[35] "Opening the Gates" by Sebastian Mallaby in the Washington Post, April 5, 2004.

[36] It is not clear that, for example, a future malaria vaccine, will receive a reasonable price either 10 years from now when a vaccine might be developed, or in the 10 years following that, when a developer would need to recoup R&D expenditure.

[37] This table draws on Glass, Batson & Levine (2001) and Kremer & Glennerster (2004)

Table 2.1 Alternative pull approaches

Approach	Description	Advantages	Risks & Challenges
Commitment to product purchases ("Advance contracting")	Sponsor promises to fully or partially fund vaccines meeting specified conditions	• Creates link between payments and product quality • Addresses time inconsistency • Ensures rapid access to new vaccines	• Promises must be credible • Must be designed to cover appropriate products
Patent buyouts	Sponsor offers to buy patent rights to a vaccine meeting specified conditions, then puts the patent in the public domain and encourages competition in manufacturing the vaccine	• Addresses time inconsistency problems; • Allows competition among manufacturers • May reduce prices and thus increase access	• Promises must be credible • Manufacturer may have effective monopoly because vaccines are difficult to produce • No tight link between payments and product quality
Strengthened intellectual property right (IPR) protection	Public sector makes commitment to enforce IPRs	• Provides some additional incentive for industry	• Difficult to implement • Difficult to enforce • Does not solve time inconsistency problem of monopsonist buyer • Monopoly pricing may impede access • Politically unpopular
Tax credits for vaccine sales	Government offers a tax credit on vaccine sales to manufacturers	• Provides some additional incentive for industry to invest • Familiar policy tool • Money only spent when product is produced	• Only of benefit to those with a tax liability
Prizes	Offer cash or other reward to whoever achieves a certain, pre-specified goal	• Immediate up-front payment – no need for long term contract	• Industry may not be enthusiastic about competing for prizes • Does not address access
Best entry tournaments	Offer cash or other reward to whoever progresses farthest towards a specific research goal by a given date	• Credible that reward will be paid • Easy to implement	• Industry may not be enthusiastic about competing for prizes • May have to pay without getting result. • Does not address access
Patent extensions on existing pharmaceuticals	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	• Captures attention of the larger pharmaceutical companies	• Favors big companies and those with existing patents • Unfairly and inefficiently puts costs of developing new vaccines on users of other drugs • Very difficult to implement

2.5 Push and pull can complement each other

One attractive characteristic of pull mechanisms is that they do not require public spending until and unless they succeed. Thus, for example, a commitment to purchase a vaccine if and when it is developed does not require outlays of public spending until the vaccine is available for use.

This means, in turn, that there need not be a trade-off between push and pull policies. It is affordable and desirable to continue to fund scientific research and vaccine development through push mechanisms, while at the same time stimulating private sector research by making a purchase commitment which increases the expected market size.

Applied together, push and pull mechanisms may succeed in replicating the risk and reward structure that stimulates new product development in the developed world.

Chapter 3: An outline proposal

3.1 Rationale

The preceding analysis found that:

- vaccination is one of the most effective interventions to reduce premature death, improve quality of life, and accelerate growth and prosperity in developing countries. It is safe, reliable and cost effective. Over the last 50 years, vaccines that were primarily created for developed country markets have had a dramatic effect on health in developing countries.

- New vaccines typically do not reach developing countries for ten years or more after they are widely available in developed countries.

- In the future, developing countries cannot rely on spin-offs of new vaccines from rich markets because the disease burden is increasingly different. The market for a vaccine for diseases such as malaria, tuberculosis or HIV/AIDS is not big enough to attract sufficient levels of private sector investment in research and development on a scale to bring forward vaccines with the urgency that is required, and perhaps not at all.

- Direct funding of research and development in neglected diseases is beneficial, but is not on sufficient scale significantly to overcome the market reality. In order to harness the energy and expertise of biotech and pharmaceutical companies, and the funding of private sector investors, there has to be a more reliable prospect of a bigger market to make the investment worthwhile.

3.2 Outline of an AdvancedMarkets commitment

The Working Group has explored the options for introducing a version of contracting in advance. It has worked with experts in public policy, law, economics, health and scientific research; it has consulted potential sponsors and firms in the pharmaceutical and biotech sectors, both in developed countries and emerging markets. The aim has been to determine whether it would be possible, in practice, for sponsors to make a commitment that would be effective in accelerating the development of new vaccines. The Working Group concluded that such a scheme is indeed practical. The rest of this report discusses that finding in detail. This chapter

outlines the main features of how a scheme could work, and summarizes the benefits for the main stakeholders. The remaining chapters consider the practical implications of introducing such a program.

3.2.1 Recommended elements of a commitment

There are many possible designs of an advance purchase commitment. The Working Group identified the main features that it considers would be desirable, to achieve a balance of the interests of sponsors, suppliers and developing countries, and to create a well-targeted incentive framework. The approach aims broadly to reproduce the incentives to develop medicines for industrialized countries.

- A group of sponsors would work in partnership with the industry to specify the **technical specification** – in terms of outputs – required of a new vaccine.

- The program would set a **minimum price guarantee**, which would be applied up to a fixed number of treatments. The guaranteed price would be legally committed at the outset, at a level that is higher than current prices paid for vaccines for developing countries, in order to make it worthwhile for firms to accelerate investment in research and development; but well below the social value of the vaccine, so that the eventual vaccine purchases under the program would represent a good value for the money for the sponsors.

- To implement the minimum price guarantee, sponsors would **guarantee to make co-payments** on products meeting the specification; this would permit eligible countries to buy vaccines at affordable prices. (For example, the price might be fixed at $15 per treatment, of which the developing country might pay $1.) The co-payment made by the developing country government could also be funded by donors.

- The price guarantee and co-payment mechanism would be a **legally binding commitment.**

- The arrangements would be overseen by an **independent adjudication committee** and enforceable in law.

- The price guarantee would apply to a **maximum number of treatments** (*e.g.* the first 200 million treatments), and this number would also be specified at the outset.

- In return for taking up the guaranteed price on the first treatments sold, the producer would be obliged to commit to produce and sell **further treatments in eligible countries at a fixed, low price**. This two-stage pricing would ensure that the producer received a fair return on their investment but that, once this return had been achieved, developing countries would have continued access to the vaccine at lower prices.

- The program would not guarantee to buy a particular quantity of treatments: the **number of treatments sold would depend on the willingness of the developing countries**, assisted by donors, to buy them. This in turn would depend on the effectiveness of the vaccine and the alternatives available.

3.3 The expected benefits of an AdvancedMarkets commitment

The aim of AdvancedMarkets is to mimic the market conditions that stimulate research and development into medicines for rich country markets. Those incentives would promote the creation of products to benefit consumers who are too poor to pay for medicines themselves.

Chapters 6 and 7 consider the proposal in more detail from the perspective of industry and sponsors respectively.

3.3.1 Advantages for sponsors

For **sponsors**, an AdvancedMarkets commitment would be a cost-effective way to support development.

- It would accelerate the development of essential new medicines, which would in turn provide one of the most cost-effective ways to help countries to lift themselves out of poverty.
- There would only be an expenditure cost if the program succeeds. If no vaccine is developed, there is no cost to the sponsors.[38] If a vaccine is developed, sponsors are

[38] Apart from the modest cost for the institutional arrangements – that is, the cost of the Independent Adjudication Committee.

committed to buying it at a price that guarantees that it is a cost-effective way of saving lives and improving livelihoods.

- AdvancedMarkets is a form of payment-by-results. Expenditure is linked to clearly defined and measurable benefits.
- It would enable sponsors to harness the resources and expertise of the private sector while remaining at arms length from its decision-making. Sponsors do not need to identify promising avenues of scientific research or monitor the effectiveness with which research is being pursued. They can allow competition among firms to encourage them to find ways to deliver social benefits quickly.
- The co-payment mechanism and the absence of a quantity guarantee eliminate the risk that sponsors will be legally committed to paying for a product that nobody wants or needs.
- There is no opportunity cost to making the commitment. Because no cash expenditure from public funds is needed until and unless a vaccine is developed,[39] sponsors can, in the meantime, continue with their existing strategies for accelerating the development of new essential medicines. Indeed, AdvancedMarkets should enhance the effectiveness of those complementary interventions because it will align the incentives of private sector partners with the objectives of those programs.
- AdvancedMarkets is a way to increase the productivity of donor expenditure by making spending predictable. It is does not call upon donors to spend more than they otherwise would; but it does increase the value of that spending.
- AdvancedMarkets allows donors to target their spending on global public goods.

3.3.2 Advantages for industry

For **the biotech and pharmaceutical industry**, an AdvancedMarkets commitment also has significant benefits.

- The commitment would extend the overall size of the market in which firms operate. At present, firms are largely limited to producing medicines for rich-country markets; the AdvancedMarkets commitment would open up whole new markets and create demand for new products, enabling firms to expand the scope of their business and providing a new path for growth.

[39] Apart from the small institutional costs of the adjudication committee

- The commitment greatly reduces the risk that, if a global health product is invented, it will be subject to compulsory licensing, or that the firm will be forced to sell it at cost, either because of pressure of public opinion or because of the purchasing power of public procurement.
- AdvancedMarkets reproduces market structures with which firms are already familiar, since it replicates developed country markets in which they operate. Firms will be rewarded if they are able to bring a product to market that consumers want to buy. They are used to managing the risk that products from other firms will reach the market quicker, or produce a better medicine. But with the AdvancedMarkets commitment they can develop products knowing that the poverty of the beneficiaries, or the behavior of donors, will not be a constraint on demand.
- AdvancedMarkets supports and reinforces the principle that firms should be compensated for the costs of developing a medicine because it allows them to charge a price above the cost of manufacturing, while at the same time ensuring affordable access to essential medicines to those who need them.
- AdvancedMarkets reduces the risk of growing activism and anger directed at pharmaceutical companies because of the perceived lack of investment in neglected diseases, and because of the need to charge prices which make essential medicines unaffordable to the very poor.

3.3.3 Advantages for developing countries

Most of all, AdvancedMarkets would have significant benefits for the people of developing countries.

- The AdvancedMarkets commitment may significantly accelerate the development of essential medicines, which would make a critical contribution to improving the health of people in poor countries. In the absence of an incentive of this sort, there is unlikely to be sufficient research and development into vaccines and medicines sufficiently to accelerate the search for medicines for the neglected diseases of the developing world.
- AdvancedMarkets guarantees that, if a new vaccine is developed, it will be rapidly available in developing countries at an affordable price (in contrast to previous experience of a long delay before new vaccines have been available at high volumes and low prices).

- AdvancedMarkets ensures that, once the developer of a vaccine has received a fair return on its investment, the vaccine will be available to all eligible countries at affordable prices. This ensures that vaccine programs are sustainable in the long run.
- There are no adverse macroeconomic or exchange rate effects for developing countries from receiving increased development assistance provided in the form of co-payments for imported pharmaceuticals.

3.3.4 Resolving the trade-off between access and innovation

There is a serious and growing tension between those who believe that essential medicines should be available at the lowest possible price, so that they are available to everyone who needs them; and those who believe that firms should be able to charge a higher price to enable them to continue to develop new medicines for the future. Many people have some sympathy with both views. AdvancedMarkets resolves these positions, by ensuring an adequate return for the developers of new drugs, while simultaneously ensuring rapid and affordable access for those who need them.

3.3.5 AdvancedMarkets would complement other strategies

The Working Group does not contend that AdvancedMarkets is a silver bullet that would solve all the problems of inventing new medicines for developing countries. Rather it would be an important additional tool to complement existing strategies to accelerate research and development. Because of the unusual nature of the intervention – with no significant budgetary cost unless and until it succeeds – AdvancedMarkets has no opportunity cost and could be introduced alongside existing, conventional programs.

3.4 AdvancedMarkets for late-stage and early-stage products

The idea of the AdvancedMarkets commitment is that, because the potential market is made larger and more certain, firms will make investment decisions that accelerate the development of products for developing countries and invest in manufacturing capacity to produce larger volumes. This analysis applies to **late-stage products** (that is, those which are in the final stages of regulatory approval and for which manufacturing capacity is being established) as well as to **early stage products** (that is, those for which scientific progress and extensive testing of candidate medicines is required).

3.4.1 The case of AdvancedMarkets for late-stage products

The argument for using AdvancedMarkets for late-stage products is that, even after a product has proven successful in clinical trials, the low and uncertain value of demand from developing countries continues to affect the firm's investment decisions, which will determine the speed, volume and price at which the vaccine will be made available. The firm's decisions that will be affected by market prospects include:

- whether and how quickly to conduct clinical trials in developing countries;[40]
- the speed with which regulatory approval is obtained for developing countries;
- whether enough production capacity is put in place for large scale production; and
- the price at which the product will be sold in developing countries.

Each of these decisions is critically affected by the prospects of future demand from developing countries and by the price the firm expects to obtain from those markets. Experience has shown that, in current market conditions, firms prefer to focus at first on producing new vaccines in low volumes and selling them into high-value, developed-country markets. Only when high-value market needs have been met, and as the competition from lower cost generic producers becomes more likely, do the producers move towards high-volume, low cost production that is needed for the developing world.

Using AdvancedMarkets for late-stage products would:

- accelerate the availability of new vaccines in large quantities and low prices for use in developing countries;
- ensure affordable access to those vaccines for people who need them; and
- add to the credibility of the commitment for early-stage products and so help to accelerate the development of new vaccines.

3.4.2 Design differences between early-stage and late-stage AdvancedMarkets

The rationale for AdvancedMarkets commitments is broadly the same whether the product is early-stage or late-stage, and the main features of the commitment would be the same in each

[40] Clinical trials in developing countries are needed to ensure that a vaccine is effective and safe in the environment, and against the strains of the disease prevalent in the region.

case. Chapter 8 sets out examples of how AdvancedMarkets would work for malaria (an early-stage product) and pneumococcus or rotavirus (late-stage products). These examples were developed in order to focus and discipline the thinking of the Working Group and should not be taken to imply that these should necessarily be the diseases for which AdvancedMarkets would be most appropriate.

The main difference between the design of an early-stage commitment and a late-stage commitment is that the contract for late-stage products would be likely to be with specific, named suppliers, whereas the contract for early-stage products would initially be an open framework agreement, in which firms compete for the right to benefit from the guaranteed price in the second contract.

3.5 Is it practical?

The Working Group found the theoretical case for AdvancedMarkets compelling. But the key question is whether it can be implemented in practice, and how some of the possible risks can best be managed.

The Working Group was convened as an interdisciplinary group, including lawyers, health professionals, policy-makers, venture capital investors, economists and representatives of industry. This enabled the group to work through the practical issues and assure itself that the scheme could be designed to be practical to implement. The following chapter looks at the questions of implementation in more detail.

Chapter 4: Practical issues

Chapter 3 outlined a possible framework for an AdvancedMarkets program, and set out the benefits that a commitment would have for sponsors, industry and developing countries. This chapter draws on discussions with industry, and sponsors, and with global health professionals, as well as the range of expertise within the Working Group, to consider some of the practical issues in the design of a possible commitment. It sets out some ways in which a mechanism might work in the real world, recognizing that there are many ways in which advanced commitments could be implemented.

4.1 Legal issues: the contract structure

The AdvancedMarkets commitment would derive much of its credibility – and therefore its ability to influence investment behavior – from the legal enforceability of the contracts. This is essential to provide sufficient assurances to developers to induce them to undertake the large investment necessary to develop a new product.

The structure of the contracts must be fixed enough to avoid the danger that the sponsor would renege, but flexible enough to accommodate contingencies that were not foreseen at the time the rules were established. Standard contract law provides a legal basis for this, and the component parts of the proposed legal structure are familiar in law and business.

Some elements of the contract design and incentive structure will vary according to the particular product for which the AdvancedMarkets mechanism is implemented. But there are common core elements that are likely to be necessary to make AdvancedMarkets work for both late-stage and early-stage products.

4.1.1. Sponsor(s), Developer(s) and Designated Supplier(s)

Three parties are fundamental to the design – and eventual success – of AdvancedMarkets. The first is the sponsor – the entity that accepts the contractual obligations associated with funding the market demand. This may be one or more non-governmental or government grant-making organizations, and must be a legal entity. The second is a developer – one or more pharmaceutical or biotech companies that are interested in pursuing the contract offered by the sponsor. The third, and final, party is a designated supplier – that is, the developer(s) who actually end up signing the agreement to supply the targeted product. In the case of near-term products, there may be a single developer which is also the designated supplier.

4.1.2 Legally binding bilateral contracts

A bilateral contract is one that is signed by two parties; it becomes binding on the parties as soon as they sign and it allows either party to pursue standard contract remedies, such as money damages and specific performance, if the other party fails to satisfy its contractual commitments. The bilateral structure locks in commitments and makes the funding commitment of the sponsor more credible. The contractual commitments of the sponsor are clear from the outset – to provide the promised reward, *e.g.* price or guaranteed purchase, upon satisfaction of the eligibility criteria. Requirements on the developers would be minimal, consisting only of light reporting obligations.

The commitment would involve two types of legally binding agreement:

- First, an open offer – the **Framework Agreement** – indicating the availability of a "prize" for any firms meeting pre-specified conditions. In this case, the prize would be the second contract.
- Second, a bilateral procurement agreement or **Guarantee Agreement**.

An AdvancedMarkets commitment could use both contracts, or skip the open offer in favor of directly negotiating bilateral procurement agreements. In the case of early-stage products, it would be important to have an open offer so that many firms could compete to develop a product. However, in the case of late-stage products where the market landscape (*e.g.* first-generation suppliers and the time lag to second-generation candidates) and product profile are already known with some certainty, it may make sense to proceed directly to the bilateral procurement stage.

4.1.3 The Framework Agreement

The Framework Agreement establishes the rules for the competition among potential vaccine developers. It is issued by the sponsors and must be signed by interested companies to become binding, though at this stage there would be only minimal obligations on the part of the signing companies. The Framework Agreement also sets forth eligibility requirements for the vaccine, creating an Independent Adjudication Committee (IAC) to adjudicate whether the requirements have been met by any candidate vaccine, and establishing the rules with respect to legal recourse. Finally, the Framework Agreement specifies the incentive mechanism or prize: namely, that a developer of a vaccine that meets the technical specifications and usability

requirements is entitled to enter into the Guarantee Agreement with the sponsor. A sample draft term sheet for the Framework Agreement is included at Annex B.

4.1.3 The Guarantee Agreement

The Guarantee Agreement is a bilateral contract between the sponsor and any winners from the open stage, or "designated suppliers". The sponsor must irrevocably and unconditionally guarantee that the designated supplier receives the pre-specified reward (*i.e.* price guarantee, *etc.*) for any qualified sales, subject to some also pre-specified cap on the sponsor's total commitment. The agreement is likely to cover a long-term procurement, perhaps ten years or more, though this is not a fixed period. Qualified sales would be restricted to those that meet criteria established in the original commitment (*e.g.* that the vaccine will be used in a Vaccine Fund eligible country).

Guarantee Agreements could be signed with one designated supplier or with multiple suppliers, depending on the rules set out in the framework agreement, which would in turn depend on the objectives of the sponsors. The Guarantee must also specify rules related to intellectual property rights, where relevant. A draft term sheet for the Guarantee Agreement is included at Annex C.

4.1.4 The Independent Adjudication Committee

The Independent Adjudication Committee (IAC) would be the impartial oversight body at the heart of the credibility of AdvancedMarkets. The IAC would:

- decide if a product has met the eligibility criteria. It would have authority to waive or modify technical specifications and usability requirements as appropriate. It would be a requirement that modifications can lower the bar to accept vaccines that do not meet the specification in full, but the IAC must not have discretion to raise the bar once the framework offer has been made;
- designate approved regulatory bodies (or more likely, designate another authority – such as the WHO – to approve); and
- be the main point of contact with developers throughout the competition.

Once a qualifying vaccine has been identified, the IAC would monitor sales, use and performance of approved vaccines, and designate new vaccines as approved under the terms of

the Framework. Finally, in extreme circumstances the IAC would have the power to terminate the sponsors' payment obligations if *force majeure* clauses[41] were triggered (see section 4.1.6).

Importantly, the IAC's operational budget – to be provided by the sponsors – would need to be independent so that the sponsors will be unable to influence the decisions of the committee that occur after the establishment of the rules of the game. Similarly, there would be straightforward rules allowing the IAC to recruit new members in the case of resignation.

The composition of the IAC is critical to the success of AdvancedMarkets. It should consist of a combination of ex-industry, global health experts, vaccine scientists, and legal specialists convened around a specific product.

In the Working Group's consultations with industry, firms emphasized the need for a credible adjudication body, and expressed concern about the potential for abuse. The rules must be clearly determined in advance, including dispute resolution. There was strong opinion in favor of having current or recent industry experience represented on the committee.

4.1.5 Dispute resolution

It is impossible to foresee all events that may occur during the life of the AdvancedMarkets Framework and Guarantee, or even the duration of the Guarantee. While a number of scenarios can be imagined in advance and addressed in the contracts, the most useful approach to the many unknown scenarios is to establish a clear and credible process for making decisions as events unfold.

While most decisions will be made by the IAC, a decision to invoke the *force majeure* clause should be subject to legal recourse through the courts if necessary.

4.1.6 Exit provisions

It may be sensible to include **sunset provisions** into the contract to allow for an exit for sponsors after a certain length of time. For example, if 30 years pass and no substantial progress has been made on the product of interest, a vaccine commitment may not be the most useful approach, and the policy would be worth re-evaluating. So, for example, a sunset clause might be included

[41] Force majeure is a standard contracting clause that declares the contract null and void – and neither party liable for damages – if unforeseeable events fundamentally change the landscape in which the contract was written.

to specify that, at any time after 20 years had passed, sponsors could give notice that they would let the commitment lapse after 10 years, if no vaccine had been developed by then.

Another type of exit provision – a ***force majeure*** clause – could allow the obligations to end if the disease environment changed sufficiently to obviate or radically reduce the need for the vaccine. Such changes could occur, for example, if other technologies were developed to control the disease, such as better insecticides against the mosquitoes that transmit malaria. To deal with such contingencies, a vaccine commitment might specify that the sponsor's obligation would end if the independent adjudication committee determined that the burden of disease had fallen by more than 50 or 75 percent.

To avoid the danger that a *force majeure* clause might be used by a sponsor to renege on the commitment, it would be important to

- vest the authority to invoke this clause with the IAC, which would be chosen for its credibility, rather than the sponsor, which might have a financial interest in the decision;
- require a supermajority of the IAC – perhaps a three-quarters vote – to invoke such a clause; and
- make any decision to invoke the clause subject to legal challenge.

4.2 Eligibility requirements

Eligibility requirements would define the desired product and other elements required of the developer of the desired product to qualify as a designated supplier. Defining appropriate eligibility requirements is critical to the success of the commitment.

The eligibility requirements would be set by the sponsors in advance, after discussion with key stakeholders. The requirements might include:

- technical requirements on the product: indication, target population, minimum efficacy requirements, duration of protection, interference;
- usability requirements on the product: dosage, route of immunization, presentation, storage, safety requirements; and
- specifications of regulatory approval and quality control.

Because these would become the targets of research and product development once established, the framework agreement must not allow sponsors to make the requirements more demanding after it is established. Since products may be useful without perfectly matching all eligibility criteria, however, the adjudication committee might be given authority to relax the requirements to accept products that nearly meet the pre-established requirement.

In addition, sponsors may establish eligibility requirements on "qualified sales" of a product – for example, that products be sold to a UN agency, developing country or other approved buyer, or that products must be used in a Vaccine Fund or other eligible country. These too must be clearly established from the outset, and must not be subsequently changed to become more onerous.

In consultations with industry, all firms were in favor of setting the bar on product specifications high enough that the sponsor could have reasonable assurance that the product would serve public health needs and be accepted by the relevant developing country governments. There was also a consensus that there should be a procedure to make the specifications less onerous in case a useful product were developed that did not completely meet all specifications. Industry representatives indicated that they should have the opportunity to review and provide input on product specifications before those specifications were set.

Some firms wanted the opportunity to engage in a dialogue with the adjudication committee during the process to determine whether the committee would be likely to grant waivers from the stated eligibility guidelines and to learn more about how those guidelines would be interpreted. (This is similar to procedures under which firms have the opportunity to consult with the US Food and Drug Administration to learn about how to prepare applications.)

A small number of public health experts were concerned that it would be difficult to establish in advance technical requirements that a vaccine would need to meet. Clearly, it is difficult to say in advance exactly what the structure of a successful vaccine will be. However, there was a consensus that, provided the requirements were framed as outputs, rather than a specification of inputs, it would be possible – though complicated – to agree to product requirements in advance. For example, while it would not be desirable to specify in advance whether a malaria vaccine should be a 'blood stage' vaccine, it would make sense for the specification to include some minimum duration of protection against severe malaria.

4.3 Co-payment and the absence of quantity guarantee

4.3.1 The case against a quantity guarantee and for co-payment

It is possible that a product might meet all the pre-announced eligibility requirements, and still be unsuitable for use in poor countries. For example, if a vaccine generated side-effects that were medically harmless but culturally unacceptable, there might be an unwillingness to use the vaccine. Attempts to impose its use might even be counterproductive, reducing the acceptability of vaccination in general.

It is impossible to anticipate all the possible contingencies in which the purchase of a seemingly effective vaccine would not be warranted, and consequently it is not possible to attempt to write them into the technical specification.

The Working Group therefore concluded that the commitment should be to pay for vaccine doses only if a recipient country chose to use the vaccine and took the steps necessary to ensure that the product could be delivered to those who need it. It would appropriate to include a modest co-payment requirement, from either the country or a donor acting on its behalf, both as a market test of interest in the vaccine and to reduce the risk of wastage. This means that the commitment would not guarantee to pay a certain quantity of the vaccine.

The absence of a quantity guarantee also helps avoid another possible pitfall of an advance contract. It avoids the problem of deciding what to do in the event that several competing products are successfully introduced: if a superior product becomes available and also qualifies for the price guarantee, the recipient countries would be able to choose which products they wanted to use.

4.3.2 Keeping the co-payment low

A disadvantage of the co-payment is that it adds another decision maker (namely, the developing country) to the process. To the extent that this adds to uncertainty about whether a product will eventually be purchased, it also increases the firm's assessment of risk for its investment. This suggests co-payments should be modest. Insisting on a large co-payment would limit access to the product, and by reducing the prospects of adoption, it would also reduce incentives for developers. Too large a co-payment could also lead recipient countries to opt for generic versions, thereby undermining research and development incentives.

4.3.3 The allocation of demand risk

The absence of a quantity guarantee, and a requirement for co-payments from developing countries, leave a degree of demand risk in the hands of the developers. It is reasonable to ask whether, given that the objective is to make investment in medicines for neglected diseases more attractive and less risky, the program would be more successful if sponsors took over all the demand risk.

In consultations with industry, firms expressed broad comfort with a program that included a price guarantee but no guarantee of quantity for early stage products. This allocation of risk most closely resembles the market for medicines in developed countries, in which ability to pay is relatively favorable, but quantities are not guaranteed and firms must bear the risk that customers will not want their product or that a better product will appear and they will lose market share.

The proposed pricing structure – in which a high price is paid for the first treatments bought with a low price thereafter – actually transfers a substantial portion of the demand risk from the firms to the sponsors, since the net present value of the revenues to the company is much more stable that it would be under a single price charged over a longer time period. (The spreadsheet model, available on the Center for Global Development website at http://www.cgdev.org/globalhealth/ demonstrates this.)

It is most efficient for risks to be borne by the partner who can manage them best. It is desirable for the industry to bear some of the demand risk, so that they have an incentive to push towards the most effective and useable product. Under the AdvancedMarkets proposal favored by the Working Group, the sponsors would bear the risks associated with unpredictable donor funding and public sector procurement policies, while leaving the industry to manage the risks associated with the usefulness of the product.

4.4 The Guaranteed Price

4.4.1 Considerations in setting the price

Chapter 5 looks in more detail at the calculation of the appropriate guaranteed price. The goal is to set a price which is high enough to accelerate research and development in a vaccine for the disease, but at a level at which the purchase of the vaccine, if and when one is developed, is a cost-effective use of aid resources.

To get the full advantage of the commitment, sponsors would need to commit to an overall price well above the pennies-per-dose now paid in developing countries for existing vaccines. These low prices are beneficial in that they ensure access to existing vaccines, but they are neither sufficient to generate investment in new vaccines, nor to ensure that new vaccines are rapidly made available in developing countries. It will be an important change of mindset for sponsors to accept that paying significantly more – say $15-$25 for the first 200 million malaria vaccine treatments instead of less than $1 for today's vaccines – is a cost-effective use of scarce resources. The calculations in Chapter 5 show that it is not only cost effective, it is a bargain: at a cost per DALY[42] saved of $15-25 (less than $500 per life saved) it would be one of the most cost effective interventions in health and in development spending generally.

A price guarantee at this level would provide firms with a market of about $2-3 billion (in net present value terms). This is roughly comparable to the upper quartile of market sizes for which new medicines were developed and introduced in the early 1990s – so it is well within the range of market size that firms are willing to invest in.

In short, there is no correct guaranteed price: a higher price would be likely to increase investment and so accelerate vaccine development; but there is no way to know how much more quickly a vaccine would be produced. What the analysis does show, however, is that within a broad range of possible guaranteed prices, expenditure on vaccines would be highly cost effective for donors, while providing the biotech and pharmaceutical industry with a realistic market return sufficient to stimulate considerably more private investment.

4.5 Two-stage pricing

4.5.1 Why have two-stage pricing?

The Working Group favors a two-stage pricing system. In the first phase, a relatively high price (the "guaranteed price") would be guaranteed up to a fixed maximum of treatments purchased. In return for the right to sell at that higher price for the initial treatments sold, the supplier would be contractually committed to supplying further treatments at a lower price close to the cost of production (the "base price").

[42] Disability Adjusted Life Year – see box 5.1 in Chapter 5.

Two stage pricing is attractive to developing countries and sponsors because it would ensure long term sustainability of the vaccine program. This price structure would also create a strong incentive for firms to accelerate development, as there would be a more substantial reward for the first developer (because they could capture the bulk of the high price market), while preserving an incentive for the development of improved vaccines later.

A two-stage pricing structure is also attractive to the vaccine developers, because they would receive a higher price for a shorter time than they would under a single price contract. This front-loading of payments would enable them to recover their investment more quickly and with greater certainty. In its consultations with industry, the Working Group found that the two-stage pricing proposal was both understood and welcomed.

4.5.2 How would two-stage pricing be implemented in practice?

The guaranteed (higher) price would be set in advance in the Framework Agreement, at the outset of the commitment. The Framework Agreement would specify how it was to be adjusted for inflation. The price would vary according to the disease because it would need to take account of the likely complexity of identifying and producing a vaccine, the cost of the disease burden, and the willingness of sponsors and recipient governments to pay.

The base (lower) price could either be set in advance as a dollar amount per treatment; or determined by an agreed formula related to the cost of production. (There are advantages and disadvantages to either approach.)

In return for receiving the guaranteed price for the initial doses, the designated suppliers would be contractually required to supply subsequent doses to eligible countries at the base price, provided reasonable notice was given. If a company could not or would not do so, they might face financial penalties under the contract, or have the technology compulsorily licensed.

4.6 Second entrants and later products

An advance contract does not necessarily imply a winner-takes-all agreement. The Working Group proposes that second and subsequent vaccine suppliers be allowed to share the market as designated suppliers, provided their products are deemed (by the Independent Adjudication Committee) to be material improvements on the first designated supplier.

This formulation is intended to rule out “me too” vaccines (that is, vaccines created by copying the first vaccine), while allowing vaccines which are a genuine improvement to be bought and used by developing countries.

The guaranteed price would apply to the total number of treatments sold to all firms – in other words, if there were more than one designated supplier, it would be likely that no single firm would sell the designated number of treatments at the guaranteed price. Once the designated number of treatments had been bought, the suppliers would then be required to provide vaccines at a lower price, but in this case, each supplier could charge a mark-up over the agreed base price, until their total revenues reached a pre-determined minimum amount.

During consultations, industry indicated that this is an important issue to get right. Many firms felt that markets for global health products were so small that having to compete with “me too” products would represent a disincentive to investment. However, they also felt that the risk of competition from a technically superior product was part of the normal course of business. The firms agreed that if superior products were developed, customers should be free to choose between those products and the initial products. Industry partners emphasized that transparent and predictable procedures would have to be worked out for determining whether later products were in fact superior, and agreed with the Working Group that this would be an important role for the Independent Adjudication Committee. The proposal to allow suppliers of a superior product to become designated suppliers meets all the concerns expressed by industry on this point, while still ensuring that developing countries are able to take advantage of the development of improved vaccines.

4.7 Improving the terms over time

Some industry representatives suggested that sponsors could establish an initial contract, but might reserve the right to improve the offer depending on market response. One suggestion was that sponsors could be encouraged to add to the prize as a successful candidate emerges. Firms with a promising candidate would then be motivated to invest in increasingly expensive trials in order to reach the growing market. Others suggested that prices or other contract terms be made more attractive to industry over time if the initial terms do not generate the expected response. This approach has many of the attributes of an auction, which could identify low-cost producers. Provided the price did not rise too quickly, it would be unlikely that it would lead to strategic delay. However, the Working Group felt that it was not necessary to build this additional complexity into the AdvancedMarkets proposals at the outset.

Chapter 5: Cost effectiveness and price

5.1 Determining the guaranteed price

In setting the price, the sponsors should aim to:

- set the guaranteed price high enough to accelerate research and development in the selected vaccine; and
- set the price below the social value of the vaccine, so that the sponsors do not commit themselves to paying more for the vaccine than it is worth to society; specifically, the price should be low enough that spending on the vaccine is cost-effective compared with alternative development interventions.

It turns out that there is a large window between these lower and upper bounds within which a guaranteed price can be set. In other words, a wide range of prices would be sufficient to give firms a good return on their investment and still represent an excellent bargain for sponsors seeking to maximize the effectiveness of their spending.

5.1.1 What price is needed to accelerate vaccine development?

There is no way of knowing in advance how big the return needs to be in order to induce an increased level of research and development. The larger the potential market, the more firms will enter the field, the more research leads each firm will pursue and the faster a product is likely to be developed. In light of the enormous burden of disease imposed by diseases such as malaria, it is important to provide sufficient incentives for multiple researchers to enter the field and to induce major pharmaceutical firms to pursue many avenues of research simultaneously so that vaccines can be developed quickly. The more that sponsors are willing to pay, the greater the likely acceleration of the vaccine. But it is uncertain how much more quickly a vaccine would be developed as a result of an increase in the guaranteed price.

It is possible to calibrate the appropriate value of an AdvancedMarkets commitment by looking at the size of private markets that currently motivate biotech and pharmaceutical companies to invest.

A recent comprehensive analysis of sales revenue for pharmaceutical products[43] looks at 118 new medicines introduced into the United States between 1990 and 1994. Based on this analysis, it is possible to estimate[44] that an advance contract for a vaccine would need to provide $2.5 billion[45] to match the average commercial product. To the extent that developing a vaccine is more technologically challenging than developing other medicines, the appropriate payment would be greater. An appropriate benchmark might be the average of the sales of products between the 70th and 80th percentiles of the revenue distribution, which is calculated to be $3.0 billion dollars (in 2004 dollars)[46].

Vaccine suppliers would earn some revenues other than from sales under the purchase commitment. As an example, in the case of a malaria vaccine there would be sales to travelers and the military, to middle-income countries such as Brazil, and to the private sector in poor countries. For malaria, the net present value of purchases in these markets would be about $700 million, which means that an advance contract would need to generate approximately $2.3 billion in sales to meet a $3.0 billion benchmark.[47]

In the case of a malaria vaccine, under fairly pessimistic assumptions on uptake rates, this would correspond to a commitment to pay $15 (in today's prices) for each of the first 200 million people immunized under the program. (Thus for a three-dose vaccine, this would be $5 per dose, uplifted for inflation.)

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[43] Grabowski, H.G., Vernon, J., & DiMasi, J.A., (2002)

[44] Berndt, Bruce, Kremer & Weizsacker (2003)

[45] Net present value of sales, in 2004 dollars

[46] Berndt, Bruce, Kremer & Weizsacker (2003) These figures make a ten percent adjustment for lower marketing costs, as the revenues reported in Grabowski et al. (2002) were partially spent on marketing, as the marketing costs would be lower. Rosenthal *et al.* (2002) estimate that, relative to sales, expenditure on promotion by U.S. pharmaceutical companies has remained fairly constant at about 15 percent of revenue, and has fallen slightly since 1998.

[47] An estimate from the popular press (Reuters, in 2003) and correspondence with Pfizer suggest that the annual market for malaria prophylaxis drugs from sales to travelers and tourists from industrialized countries and the military could be as much as $200 million, but others cite much lower figures. At an 8 percent real cost of capital, if a vaccine captured a $100 million market in peak annual sales and the profile of sales over time followed that of a typical pharmaceutical (Grabowski *et al.*, 2002), the net present value of those sales would be about $650 million. Adding in $100 million of additional revenues from private sales in developing countries yields $750 million in net present value of revenues outside of the commitment program.

Some firms suggested the creation of a flexible pricing mechanism (*e.g.*, cost plus some mark-up) instead of trying to set a price in advance. The rationale for this is that it is difficult to predict which technologies will succeed and hence hard to anticipate the cost of production. Firms could be sheltered from some of this risk through cost-plus pricing, albeit with a corresponding increase in the risk to sponsors. The Working Group felt that this approach would reduce incentives to develop products that could be produced cheaply or to develop inexpensive manufacturing processes; and might add uncertainty to the commitment. Moreover, if a product were too expensive it would not be a cost-effective use of a sponsor's funds to purchase it. The Working Group therefore concluded that it would be preferable for the purchase price to be determined for each product in advance, and set in the contract.

Box 5.1 What is a DALY?

A Disability-Adjusted Life Years, or DALY, is a unit used for measuring both the global burden of disease and the effectiveness of health intervention. DALYs are intended to combine (a) losses from premature death, which is defined as the differences between actual age at death and life expectancy at that age in a low-mortality population, and (b) loss of healthy life resulting from disability. As the benefits of all health interventions can be measured this way, this allows comparisons to be made between different interventions, and overcomes some of the problems associated with using analysis that is only relevant for specific conditions, or which relies on placing a monetary value on saving lives.

DALYs were first introduced as a unit of measurement in the 1993 World Development Report (The World Bank, 1993) and in 1996 a joint effort by WHO, World Bank and the Harvard School of Public Health produced The Global Burden of Disease (Murray & Lopez, 1996) in which DALY methodology and findings were presented in more detail.

5.1.2 What price is worth paying for vaccines?

Developing countries – and donors on their behalf – currently pay less than fifty cents a dose for most vaccines. This has the advantage of reducing the cost to highly stretched health budgets. But as set out in Chapter 1, it means that the introduction of new vaccines to poor countries is significantly delayed, and that there is insufficient incentive to develop new vaccines for diseases in developing countries.

Implementing an AdvancedMarkets commitment would require a change of mindset on the part of sponsors. While long-term contracting, even at pennies-per-dose, would provide benefits in the supply of already-existing products, some of the most significant benefits of this commitment would come from enhancing the size and predictability of the market, by committing to pay a price for new medicines which meets the cost of innovation.

Importantly for potential sponsors, a price guarantee that is considerably higher than pennies-per-dose would still be highly cost-effective relative to other health, and other development, policies.

The Working Group looked at the example of malaria in detail (cost-effectiveness calculations for tuberculosis and HIV/AIDS yield similar results). Consider a commitment to purchase a malaria vaccine at a price of $15 (in today's prices) per person immunized for the first 200 million people immunized, in exchange for a commitment to a base price of $1 per person thereafter. (These are the same prices as exemplified in the previous section, which are estimates of what is needed to provide an appropriate market size for prospective developers.)

The cost-effectiveness of such a commitment would depend on a number of assumptions. To get an idea of the magnitudes assume that:

- the contract covered all countries with a GNP of less than $1,000 per year with sufficient disease prevalence to make vaccination worthwhile;

- countries adopted the vaccine over seven years and eventually attained a steady-state immunization level 5 percentage points above that of the EPI program;

- the vaccine required three doses but could be delivered with the EPI package at an incremental delivery cost of $0.75; and

- the vaccine was 60 percent effective, protected against infection for 5 years and did not lead to a rebound effect by weakening limited natural immunity.

Given these assumptions, and data on population, fertility, and disease prevalence, the cost — including incremental delivery costs — per DALY saved would be about $15 (discounted in 2004 dollars), making vaccine purchases under the program one of the world's most cost effective health interventions. This program would cost around $450 per life saved.

Table 5.1.1 Some estimates of cost per DALY of development interventions

Intervention	**Cost per DALY ($)**
Condom distribution[48]	12-99
IMCI (Integrated management of childhood illness)[49]	30-100
TB prevention[47]	169-288
Anti retroviral therapy for HIV[50]	1 100-1 800
Family planning[51]	20-30
Pre-natal and delivery care[50]	30-50
Water supply (village pump)[52]	94
Malaria bednets[53]	57
Memo: AdvancedMarkets malaria vaccine @ $15 per treatment	*15*

The value for money from such a program is robust to changes in assumptions about efficacy, uptake rates, or the price offered. Furthermore, it is almost certainly too pessimistic. The calculation does not include epidemiological benefits – vaccinating a significant fraction of the population may slow the spread of a disease, and thus benefits may spill over to the unvaccinated. It does not include savings to developing country health systems from lower rates of illness and morbidity. It does not include health benefits to people in middle- and high-income countries, or benefits to adults in low-income countries who purchase a vaccine privately. It assumes that the vaccine would be given randomly throughout a country and thus does not include the efficiency benefits of targeting vaccine delivery within countries to areas that have the most severe disease problems. Finally, it does not include any benefits of increasing vaccination rates for other diseases that might arise if parents know they can vaccinate their children against malaria by bringing them to a clinic.

These estimates demonstrate that, once a vaccine is developed, purchasing it at a significant price, well above current prices paid for vaccines in developing countries, would still be one of the most cost-effective health interventions, and it would be more cost-effective than a wide

[48] Creese, Floyd, Alban & Guinness (2002).

[49] Murray & Lopez (1996). Figures not adjusted for inflation.

[50] Creese, Floyd, Alban & Guinness (2002). The cost of antiretroviral therapy has fallen since this study.

[51] World Bank World Development Report (1993). Figures not adjusted for inflation.

[52] Cairncross & Valdmanis (2004)

[53] Hanson *et al* (2003)

range of other development expenditures.

5.2 How much is the AdvancedMarkets commitment worth?

The calculation above shows that payments for vaccines under the AdvancedMarkets program would be highly cost-effective, even at higher costs-per-treatment than is being paid for existing vaccines.

To assess the cost effectiveness of making an AdvancedMarkets commitment in accelerating the development and distribution of a vaccine, it is necessary to make assumptions about what would have happened in the absence of a commitment. This requires assumptions both about the extra cost of paying more for vaccines, the extent to which this would accelerate the development of a vaccine, and the speed with which it would be adopted and made available.

In the absence of a price commitment, both development and adoption of the vaccine could be significantly delayed. Experience suggests that adoption of new vaccines in developing countries could easily be delayed by 10 to 15 years in the absence of a long term purchase agreement.[54] The health benefits of accelerating development and adoption of a malaria vaccine would be large because the disease kills about a million people each year (and possibly more). If a vaccine commitment accelerated vaccine development by 10 years and accelerated access in poor countries by 10 years, it would still cost only about $22 per additional DALY saved relative to the alternative of waiting for a vaccine to be developed without an advance contract. Even in the extreme case in which a price commitment sped up vaccine development by only one year and adoption in poor countries by only two years, the program would cost about $80-90 per additional DALY saved—still less than the $100 per DALY threshold often used to identify the most cost-effective interventions.

[54] We estimate delays in access based on the historical record, but one could argue that donors are now more willing to spend on vaccines. However, if one believes that even in the absence of a commitment donors would immediately buy a vaccine and distribute it at a price comparable to the initial price offered under the vaccine commitment, then the cost of purchasing and distributing the vaccine would be the same with or without a vaccine commitment, and the benefits of accelerated development associated with announcing a commitment in advance would be without cost. If the money is going to be spent on the vaccine anyway, it is clearly more cost effective to reap the benefits of faster development by announcing this policy in advance and entering into a vaccine commitment. Conversely, if one believes that companies would have to give away a vaccine in poor countries at cost, it is difficult to argue that a vaccine commitment would not be critical in providing a financial incentive to advance vaccine development.

5.3 The case for a bigger commitment

Following this line of reasoning, if an increase in the size of the commitment would accelerate development of a vaccine, it may be worth making a commitment to a higher price or paying for a larger number of doses. Paying $25 per person for the first 225 million people immunized rather than $15 per person for the first 200 million people would allow the program to match the average net present value of products between the 80th and 90th percentiles of existing commercial products. This larger commitment would create a very attractive market for developers, and would still cost only about $21 per DALY saved overall. (The additional cost of *increasing* the commitment to this level is less than $100 per *additional* DALY saved.)

Under a large range of assumptions and contract structures a vaccine commitment could be priced at a level which would be sufficient to stimulate substantial research, yet still be extremely cost-effective. A commitment of $15-25 for each of the first 200-250 million people immunized would be a bargain. The larger the commitment, the more firms will enter the search for a vaccine, and the faster a vaccine is likely to be developed.

5.4 Alternative calculations

Michael Kremer and Rachel Glennerster have developed a spreadsheet model which enables these calculations to be performed using a variety of assumptions about delivery costs, take-up, disease burden, eligibility, and so on. The spreadsheet analyzes the costs and benefits of a commitment for a vaccine for Malaria, HIV and Tuberculosis. It can also calculate the net present value of the benefits for a vaccine developer. The spreadsheet can be downloaded from the Center for Global Development website at http://www.cgdev.org/globalhealth/

Although the Working Group used the example of malaria to discipline its thinking and provide a quantified example, the spreadsheet shows that similar cost-effectiveness would be obtained from a commitment to pay for vaccines for tuberculosis or HIV.

Chapter 6: Industry perspectives

The AdvancedMarkets commitment depends for its success on generating the intended response among potential developers and suppliers. The program is intended to create incentives to accelerate development of new vaccines, but the details of the design may make a significant difference to the incentives that the contract creates. Critical determinants of its success include the size of the reward; the contractual requirements placed on the firm (for example, the eligibility requirements); and the public relations impact of participation.

The goal is not to encourage *all* firms to work on these products; it is to accelerate the development of a vaccine by providing sufficient incentive for *some* firms to begin research and development on these problems, and for others to devote extra resources and priority to their existing work.

Initial research is often done by biotech companies; typically, their work is then either licensed to, or bought by, larger pharmaceutical companies for the later stages of development, marketing and manufacturing. An important ingredient in the proposal is that it should generate a response from biotechs and other early-stage researchers.

6.1 Summary of consultations with industry

The only way to know for sure how firms would react is to implement a commitment and observe what happens. In the meantime, it is possible to obtain information through structured consultations with informed individuals, particularly those who are currently facing difficult choices about where to invest in research and development to yield the best outcome for shareholders. The Working Group conducted consultations with representatives of three industry groups – biotechnology firms of various sizes and orientations, multinational vaccine manufacturers, and emerging market suppliers. These consultations sought feedback about the overall concept and tried to identify specific ways in which the advance contract concept could be structured to most likely generate a change in investment behavior. The results of these discussions, which are summarized below, were invaluable for the development of the Working Group's recommendations.

However, the Working Group fully recognizes that for a variety of reasons, what people say they are going to do – and what they believe they would do – may differ from what they do in practice; and so the information from the consultations has limitations. Nonetheless, the

consultations found an overall positive reaction from industry representatives to the AdvancedMarkets proposal.

Box 6.1. Industry consultations

Biotechs: Ardana, Avant, Human Genome Sciences, Mojave Therapeutics, Maxygen, Mojave Therapeutics, Nectar Therapeutics, Targeted Genetics, Vertex

Multinational Vaccine Manufacturers: Aventis-Pasteur, Chiron, GSK Biologicals, Merck Vaccine Division, Wyeth

Emerging Suppliers: Serum Institute of India

In addition, the Working Group spoke with several former senior industry executives, including Michel Greco (formerly Aventis-Pasteur), Tim Cooke (formerly Merck), and Jerry Sadoff (formerly Merck).

6.1.1 Industry response varies

Firms had various reactions to the idea of an advance commitment, depending on their own risk tolerance, product pipeline (therefore opportunity costs) and their business model. There was a greater degree of consistency within industry categories (*i.e.*, biotechs, multinationals and emerging suppliers) but even within these groupings each firm indicated a unique character and strategic agenda.

Many firms expressed a view that an AdvancedMarkets commitment, if structured in the right way, would be exactly what they needed to make the case for keeping global health products in the development pathway; others felt there was little commercial motivation that could stimulate a dramatic change in their research pipelines.

6.1.2 Key industry requirements

A number of consistent themes emerged from the consultations.

- A commitment is likely to have more impact on some firms than others. For products at an early stage, for example, an AdvancedMarkets commitment may initially motivate biotech companies, and 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.

- For many firms, the establishment of a significant financial reward to the successful developer would play an important role in the within-firm analysis and negotiations about which products to move ahead with and at what pace. These firms particularly cited the moments in the development pathway when relatively costly decisions are taken to test products in humans.

- Some respondents indicated that an AdvancedMarkets commitment would address industry concerns about the appropriation of intellectual property and the downward pressure on prices that occurs when an essential medicine is developed but is seen as unaffordable to the developing world.

- Commercial decisions to develop a particular candidate are based on market prospects but also – critically – science. Access to a promising scientific pathway will be the primary determinant of some firms' investment decisions in early research. There was a wide range of opinions about the challenges of developing a malaria vaccine, for example, and some firms reported that they are unwilling to invest given the current state of science. The public sector will need to keep investing in basic research and lead development to advance the science.

- Firms do not evaluate incentives independently but look at the comprehensive picture of risks and rewards they will face through the development pipeline.

- AdvancedMarkets, or indeed any similar mechanism focused on creating a market, would need to be implemented in coordination with other interventions – push funding, demand creation, and capacity building for distribution and delivery.

- Weaknesses in the current system of procurement and delivery of vaccines for the developing world are a major deterrent to investment. Most firms supplying developing country markets through public procurement are frustrated with inefficiencies in the current system – the lack of long-term credible contracts, unreliable demand forecasts, under-use of existing vaccines – and this reality colors their view of future promises from the public sector. The public sector can improve its credibility by increasing use of existing products and by improving demand forecasts.

- The credibility of the commitment is closely related to the credibility of the sponsor. Citing real-world examples, including recent experiences with procurement of the flu vaccine in which firms felt that the US Government had reneged on a commitment, firms were not convinced of the public sector's ability to live up to its funding agreements, and they particularly noted that a private pharmaceutical company would be unlikely to take a UN agency to court in the case of breach of contract. Firms indicated that the inclusion of a private foundation as a sponsor would enormously add to the credibility of the proposal. It was clear from the consultations that it would be essential for an AdvancedMarkets commitment to be legally binding on the sponsors.

- Given the novel nature of the AdvancedMarkets commitment for the public sector, industry will be most persuaded by successful execution. Firms expressed uniform enthusiasm for implementing long-term contracts for late-stage (and existing) products. As well as being directly beneficial by increasing affordable access to those vaccines, this would build up the credibility of similar commitments for early-stage products.

The Working Group has looked carefully at each of these industry considerations; and sought to ensure that the AdvancedMarkets proposal fully takes these concerns into account.

Firms also gave specific feedback on the proposed structure of advance contracts, particularly the Framework and Guarantee, described above. These points have been taken into account in the AdvancedMarkets proposal set out in Chapters 3 and 4 and are reflected in the discussion in those chapters.

Chapter 7: Sponsor perspectives

AdvancedMarkets would require the sponsors to make a contract, enforceable by law, to make multi-year payments at some unknown time in the future which are of uncertain size and duration (though with a known upper limit).

This raises the question as to whether possible sponsors are able, as matter of practical fact, to make a commitment of this sort. In particular, it is important to understand whether there are any institutional or legal obstacles to making commitments and how such commitments would be treated in the budget process.

One of the attractive features of AdvancedMarkets for potential sponsors is that there is no cash outlay unless and until a vaccine is developed and used (apart from some small institutional costs for the Independent Adjudication Committee.) This means that there is no opportunity cost to making the commitment, so that in the meantime sponsors can use their resources for existing priorities and programs. That is why, for example, it is not recommended that funds for the purchase of vaccines should be put in trust or in escrow. To ensure that making the commitment has no opportunity cost, consideration has to be given to the budgetary treatment of the commitment.

The analysis that follows finds that there are no obstacles for either public, multilateral or private sector organizations to make this commitment, if they have the political will to do so. The situation in the US is the most complex.

7.1 Possible Government sponsors

7.1.1 The United States

The US government enters into long-term contracts as a matter of course for everything from fighter jets to catering. It has budgeting mechanisms to authorize and deliver multi-year funding streams in the future. These obligations are legally binding and are credible in markets even in the face of a degree of uncertainty about the appropriations process.

Making a legally binding commitment

An example of a legally binding government commitment is the sale of government bonds, which are contracts that oblige the government to pay money in the future. The US government

faces no legal difficulty making such commitments, and the contract is legally binding and credible.

To enter a contractual commitment to buy vaccines in the future, the Executive would need to have specific legislative authority. Once that authority exists, the mechanics of signing a legally binding commitment are uncomplicated.

However, the measure granting the legislative authority to sign the contract must initially be enacted by Congress and would be scored in the budget. This authority would have to take the form either of an appropriation, or of funding outside the annual appropriations process. (Examples of programs funded outside annual appropriations are Medicare and Medicaid.) The distinction is that the appropriations process covers 40 percent of budgetary costs that are determined annually; the Appropriations Committee writes this legislation. By contrast, the remaining 60 percent of costs are funded by legislation written by other committees, and that legislation provides permanent funding (or funding for many years) and so does not require annual approval by Congress.

How the commitment and spending would score in the budget

A complicating factor is the way that such measures are scored in the US budget process. The commitment would not add to the measured budget deficit at the time it was made. If and when a vaccine were available, the payments made by the US authorities to buy vaccines would form part of the deficit, unless they were offset by lower spending elsewhere, but that would be several years away. However, the annual US budget process sets Congressional targets[55] for both budget authority (funding) and outlays (expenditures). Any legal authority to sign a commitment would be likely to score against both targets, in the following ways:

- the full amount of the commitment, not discounted for time, would be scored against **budget authority** in the year the legislative approval was given (if it were deemed likely that the spending was likely to occur at any point in the future); and

[55] The Congressional targets do not apply to the Executive, which instead is constrained by the terms of the specific budgetary legislation enacted by Congress.

- the expected future expenditure, on some assumption about when a vaccine might actually be available, would score as an **outlay** against the years in which the expenditure was expected to occur (which might be ten or more years in the future).

Budget authority is typically the binding constraint in the annual **appropriations process**. Congress generally agrees in the spring to a budget plan that sets an overall budget authority target for that year's appropriations legislation. Congressional rules can be used to thwart appropriations legislation that provides more budget authority than targeted, so the targets can acts as ceilings on the Appropriations Committee. The overall budget authority figure is highly visible and is normally considered important by both the Congressional leadership and the White House. Because the full cash cost of a commitment would be scored against the appropriations ceiling in the year that legislative approval was given, this would reduce budget authority available for other expenditures. This would mean that Congress would face a significant opportunity cost of approving the commitment if it were included in the appropriations process.

By contrast to the politics of appropriated spending, the politics of **programs funded outside the appropriations process** are largely driven by the targets for annual outlays (rather than budget authority). The outlay estimates would be scored when the approval was given, but only as modest annual amounts in the outer years of the budget-planning horizon. Depending on the length of the budget-planning horizon in use, the expected outlays might be sufficiently far in the future that they would not be included at all in the projections. The outlay figures for the outer years of the budget are in any case largely illustrative, and the cost of a vaccine commitment would be small relative to the other determinants of the deficit. So if the legislative approval were given in the form of funding outside the appropriation process, there would be a negligible opportunity cost to the budget.

So the budget authority for the AdvancedMarkets commitment would be scored up-front whether it was provided in an appropriations bill or provided by legislation outside the annual appropriations process. It is likely to be simpler to include the AdvancedMarkets proposal in legislation outside the appropriations process, for two reasons.

First, the Congressional budget plan approved in the spring might explicitly accommodate the budget authority and outlays needed for the program. Since this budget authority would not compete against the very visible budget authority target for the appropriations process – as the budget authority would instead be provided by legislation reported from a *different* committee – there would be no focus on the needed up-front budget authority. There would be little or no

opportunity cost for Congress to include the up-front budget authority in its overall plan. It would remain true that the forecast outlays in later years would compete against the desire to show lower deficits, but as noted above, these outlays are likely to be small, or even nonexistent, within the time-frame of the congressional budget plan.

Second, even if the Congress did not make room for the AdvancedMarkets program in its spring budget plan, a committee other than Appropriations could seek to have Congress approve the legislation later in the year. If so, the political focus would be only on the small amount of additional outlays, not the large amount of additional budget authority; this fact might make the Congressional leadership more likely to support waiving the budget rules in this instance.

So for the US to become a sponsor of the Advanced Markets commitment:

- it would be necessary to obtain legislative approval to enter into a legally binding commitment;
- to avoid having to set aside budgetary allocations that could be used for another purpose until a vaccine is available, that legislative approval would ideally be made outside the appropriations process, *i.e.* a committee other than the Appropriations Committee would need provide the funding. This would score against the outlays ceilings for the later budget years.
- Enactment of funding for the program would be more likely to occur if Congress incorporates its costs into its annual budget plans, agreed to each spring.

7.1.2 The United Kingdom

The UK Government, through the Department for International Development (DFID), could commit to AdvancedMarkets within its existing budget mechanisms.

UK public spending is structured around a rolling three-year budget cycle, with allocations made to spending departments such as DFID through the establishment of Departmental Expenditure Limits (DEL). All Departments are required to agree to a "business plan" with Her Majesty's Treasury, spelling out how resources under the DEL will be directed to meet key objectives. Divisional allocations within each department are determined during annual Resource Allocation Rounds, which in DFID result in the annual Aid Framework.

Making a legally binding commitment

DFID's default approach to delivering aid is to provide grant support, in arrears if possible, unless there are compelling policy reasons for doing otherwise. In recent years, DFID has shifted away from supporting individual projects to delivering direct budget assistance to support the implementation of poverty reduction plans.

While there is no precedent within DFID for making legally binding commitments to procure products that do not yet exist, it has implemented a number of innovative financing approaches that have similar characteristics. Examples include trust funds, endowments, and provisions for guarantees, as well as statements of intent to provide long term funding support for country programs. DFID has issues guarantees to a company operating on a capital aid project to meet the costs of certain disputed claims (£30 million) to the Bank of Montserrat in respect of a project to make mortgage loans for the construction of new private sector housing (£0.4 million). Other contingent liabilities on the books include the UK's share of callable capital at the International Bank for Reconstruction and Development (5.5 billion euro) and share of callable capital to international financial institutions, and Government guarantees to those institutions in respect of UK loans made to dependent territories (£2.4 billion).

Perhaps most importantly, DFID has demonstrated a clear recognition of the need to develop innovative financing mechanisms and the advantages of predictability. The International Development Act of 2002 empowered the Secretary of State to use "non-grant financial instruments including guarantees" in pursuit of the Department's objectives. No further legislative authority is required for DFID to enter into a commitment of the kind envisaged under AdvancedMarkets.

How the commitment and spending would score in the budget

The scoring of expenditure in the UK budget is intended to closely follow private sector accounting rules.

Under UK accounting rules (as set out in FRS 12[56]), the AdvancedMarkets commitment would be deemed to be an *executory contract* (that is, a contract in which both parties have not yet fully performed their obligations). Under FRS12, obligations under contracts to make or take future

[56] Financial Reporting Standard 12 *Provisions, Contingent Liabilities and Contingent Assets* September 1998.

supplies of goods and services do not normally need to be included on the balance sheet, and so do not give rise to contingent liabilities or require the body to take a provision. The exception is an 'onerous contract', in which the unavoidable costs of meeting the obligations under it exceed the economic benefits expected to be received from it. As we have seen in Chapter 5, the economic benefits of the AdvancedMarkets commitment exceed the cost, so the commitment is not onerous and would not require DFID to include a contingent liability or provision in the balance sheet.

Because an AdvancedMarkets commitment would not have to be included on the Department's balance sheet, there would be no impact on the Departmental Expenditure Limit at the time the commitment was made. There would therefore be no need to make budgetary provision at the time the commitment was made, and there would be no opportunity cost for DFID.

If and when a vaccine was available and spending actually occurred, DFID would be required to meet the costs from within its Departmental Expenditure Limit. For a given expenditure limit, this would require lower spending elsewhere. As shown in Chapter 5, spending on vaccine purchase would represent very good value for money – more cost effective than many other programs. However, at this stage the expenditure would require some reallocation of spending from other priorities.

The UK Government has chosen to base its overall fiscal framework, including targets for spending and the deficit, on national accounts measures. The expenditure would not be recorded in the UK national accounts until the government was actually buying vaccines.

So for the UK to become a sponsor of the AdvancedMarkets commitment:

- no further specific legislative approval would be needed for the Government to enter into a legally binding commitment;

- if the commitment were deemed an executory contract, there would be no impact on DFID's balance sheet at the time the commitment was made; nor would the commitment count towards the Departmental Expenditure Limit until and unless payments for vaccines were actually made;

- if and when a vaccine is available, and spending occurs, the outlays would count towards the Departmental Expenditure Limit, and

- for a given Departmental Expenditure Limit, the actual spending on vaccines would require offsetting savings elsewhere in DFID's program. But no offsetting reductions would be needed to enable DFID to make a commitment before the vaccine is available.

7.2 The World Bank

The International Development Association (IDA) of the World Bank,[57] which provides subsidized loans and grants, could also be a sponsor of an AdvancedMarkets commitment. However, the normal operation of World Bank lending would need to be slightly modified.

7.2.1 Forward commitment

Sponsors would need to make a legally binding commitment, perhaps ten or more years in advance of the likely spending. But the priorities for IDA loans and grants are usually only set over a five-year time horizon and the Bank has, in the past, been reluctant to earmark specific sums for specific programs.

There does not appear to be any legal impediment to the Bank legally binding itself to provide IDA loans to any member state that wants to purchase the vaccine under the AdvancedMarkets program. This would, however, be a departure from current practice.

7.2.2 Loans or grants?

IDA loans[58], which are below-market rates, carry an implicit subsidy of roughly 60 percent. Since the bulk of the expense of purchasing the vaccine represents the cost of research and development, which is a global public good, it is appropriate for these costs to be met from grants rather than the 40 percent co-payment by developing countries implicit in IDA terms. This could be achieved through IDA if the Bank were to increase the subsidy on the loans (*i.e.* reduce recipient countries' co-payment) by offsetting part of the vaccine purchase price through grants.

Alternatively, other donors – either private foundations or governments – could make a commitment to "buy down" IDA loans used to purchase vaccine. In other words, they could give the member money to repay the loan – as was done in the case of Nigeria's polio eradication campaign. One particularly attractive element of this buy-down approach is that governments or

[57] Glennerster and Kremer (2000)

[58] IDA terms are a 10-year grace period, a 0 percent interest rate, and maturities of 35 or 40 years.

private foundations could deposit promissory notes with a World Bank trust fund now, but would not need to make payments until appropriate vaccines were developed and IDA loans were extended for purchases. In cases where national budgeting rules were amenable, the commitment would not count toward government outlays until the funds were drawn.

7.2.3 Additionality

For the World Bank commitment to be effective, the Bank would need to commit itself in advance that IDA loans and grants made to purchase vaccines under the AdvancedMarkets commitment would not score as part of the allocation for IDA for the country in which they were being used. Otherwise, since countries are restricted in the value of IDA credits they can use in a single year, it is possible that developing countries would be reluctant to purchase vaccines, since this would use up a portion of their IDA allocation which they might need for other purposes.

7.3 Foundations

Private foundations such as the Bill & Melinda Gates Foundation would have no problems making a commitment to an AdvancedMarkets program.

Foundations would be particularly desirable sponsors for AdvancedMarkets because:

- they have greater continuity of leadership and strategic focus, so they are perceived as less likely to change direction;
- foundations are less vulnerable to lobbying from special interest groups; and
- foundations have a substantial asset base and no ability to legislate away their obligations, so their commitment is regarded as highly reliable.

United States law requires private foundations to spend at least five percent of their assets annually. This suggests that a US-based foundation interested in promoting vaccine development might naturally combine “push” and “pull” incentives, by using current grants to fund research and development, and to expand the use of existing vaccines, while putting its principal to effective use by making a legal commitment that if a vaccine were actually developed, it would in the future help finance purchases. This would be an innovative way to make the foundation’s assets work even harder in the interests of the poor.

7.4 GAVI and Vaccine Fund

7.4.1 The mandate of GAVI

The Global Alliance for Vaccines and Immunization is an alliance between the private and public sector, with the mission of saving children's lives and protecting people's health through the widespread use of vaccines. GAVI brings together governments in developing and industrialized countries, established and emerging vaccine manufacturers, nongovernmental organizations (NGOs), research institutes, UNICEF, the World Health Organization, the Bill & Melinda Gates Foundation and the World Bank.

The alliance seeks to focus on areas in which no one partner can work effectively alone and to add value to what partners are already doing. GAVI's added value has been defined in four areas:

- coordination and consensus-building;
- funding support to countries, through the Vaccine Fund; resources are provided to countries to purchase vaccines and other supplies and to support the operational costs of immunization.;
- innovation – examples include the country proposal and review process, performance-based grants for immunization services support, financial sustainability planning, the Data Quality Audit (DQA), the Vaccine Provision Project (VPP) and the Accelerated Development and Introduction Plans (ADIPs); and
- advocacy and communications – particularly to inform decision-making among policy makers and donors on the value of vaccination for reducing poverty and infant mortality in the developing world.

GAVI has a unique and vital role in increasing resources allocated to the purchase and use of vaccines and in improving the way in which those resources are used.

7.4.2 The possible role of GAVI and the Vaccine Fund in AdvancedMarkets

There is a strong fit between these four priorities and the AdvancedMarkets mechanism. Given their mandates, GAVI and the Vaccine Fund are natural partners in an AdvancedMarkets mechanism. In particular, GAVI is a natural candidate for the forum within which donors could reach a consensus about the AdvancedMarkets approach, and agree the details of the

commitment. Commitments might be made by donors directly, or through guarantees to the Vaccine Fund.

The Vaccine Fund could become a sponsor of an AdvancedMarkets program, provided it was suitably capitalized or underwritten by its donors to do so. Capitalizing the Vaccine Fund for this purpose is not attractive, as it would tie up money that could be used productively in the meantime. Therefore, for the Vaccine Fund to make a commitment it would need suitable (legally binding) guarantees from donors – for example through the International Finance Facility (see next section).

7.5 The International Financing Facility

7.5.1 About the IFF

The UK Treasury has proposed the establishment of an International Financing Facility (IFF) to accelerate progress towards the Millennium Development Goals by issuing bonds on international markets. If adopted, the IFF would:

- create a financing mechanism which would provide up to an additional $50 billion a year in development assistance up to 2015;
- lever additional money from the international capital markets by issuing bonds based on legally-binding long-term donor commitments;
- repay bondholders using future donor payment streams; and
- disburse resources through existing multilateral and bilateral mechanisms.

The IFF proposal has generated interest and support from emerging markets, developing countries, international institutions, faith communities, NGOs and businesses.

7.5.2 The IFF Immunization Initiative

There are discussions between DFID, the UK Treasury and GAVI to consider options for piloting the IFF approach through the Vaccine Fund. A Working Group including the Bill and Melinda Gates Foundation, GAVI and Vaccine Fund is looking at the technical case for this approach.

The IFF Immunization Initiative is intended to create a framework in which:

- donor funding for vaccines over the next 15 years is pre-committed;
- on the strength of these commitments, the IFFII is able to plan spending over a ten year horizon; and
- funding for vaccines is therefore better planned, sequenced and prioritized, more predictable, and delivered sooner.

There are several arguments for frontloading spending on vaccines in the way that is implied by using the IFF:

- quicker impact on immunization and therefore reduction in infant mortality and so accelerating economic growth
- incentives for vaccine producers to invest in production facilities and to develop new vaccines through greater market certainty, or a short term price top-up to allow producers to cover development costs earlier
- acceleration of new products through research and development and trials of new vaccines.
- development of health systems with long-term benefits of capacity for the future.

These characteristics would enable the IFFII to secure much greater value with the same commitment of donor funds, compared to the existing situation in which funds are allocated from one year to the next.

7.5.3 Using the IFF to implement an AdvancedMarkets program

Like the AdvancedMarkets proposal, the IFF Immunization Initiative is based on the idea that by making binding commitments today, and so eliminating uncertainty about their future behavior, donors can increase the productivity of their spending. The market for vaccines would be more efficient, providing vaccines to more people at a lower cost, if there were greater certainty of demand, which is presently hampered by unpredictable funding. A more reliable market would enable firms to invest more at every stage of the process, from scientific research, through clinical trials, to investment in production capacity. This would result in new vaccines becoming available more quickly, and larger volumes being available more cheaply.

The IFF Immunization Initiative can implement the AdvancedMarkets commitment in its proposed contracts for new vaccines. In particular, because it will have funding over ten years, it could:

- enter a legally binding commitment, in advance, to purchase vaccines when they become available; and
- negotiate a price for this commitment that balances the need to ensure access to as many people as possible, with the need to provide sufficient return to vaccine suppliers, over the lifetime of the contract.

The Working Group believes that the proposed contract structure set out in this report creates desirable incentives and rewards, and balances the interests of all stakeholders. In particular, it delivers the best possible long-term results for the poor in developing countries. It follows that this would provide a basis for the procurement of new vaccines by the IFF Immunization Initiative.

However, it would not be appropriate for the IFF Immunization Initiative to make a long term, legally binding commitment to vaccines which are not likely to be available over the next ten years, as this would be outside the lifespan of the IFF Initiative. There would therefore be a strong case for a group of donors to make a separate, legally-binding AdvancedMarkets commitment for vaccines for malaria, tuberculosis and HIV, in addition to the proposed commitment to purchasing vaccines through the IFF.

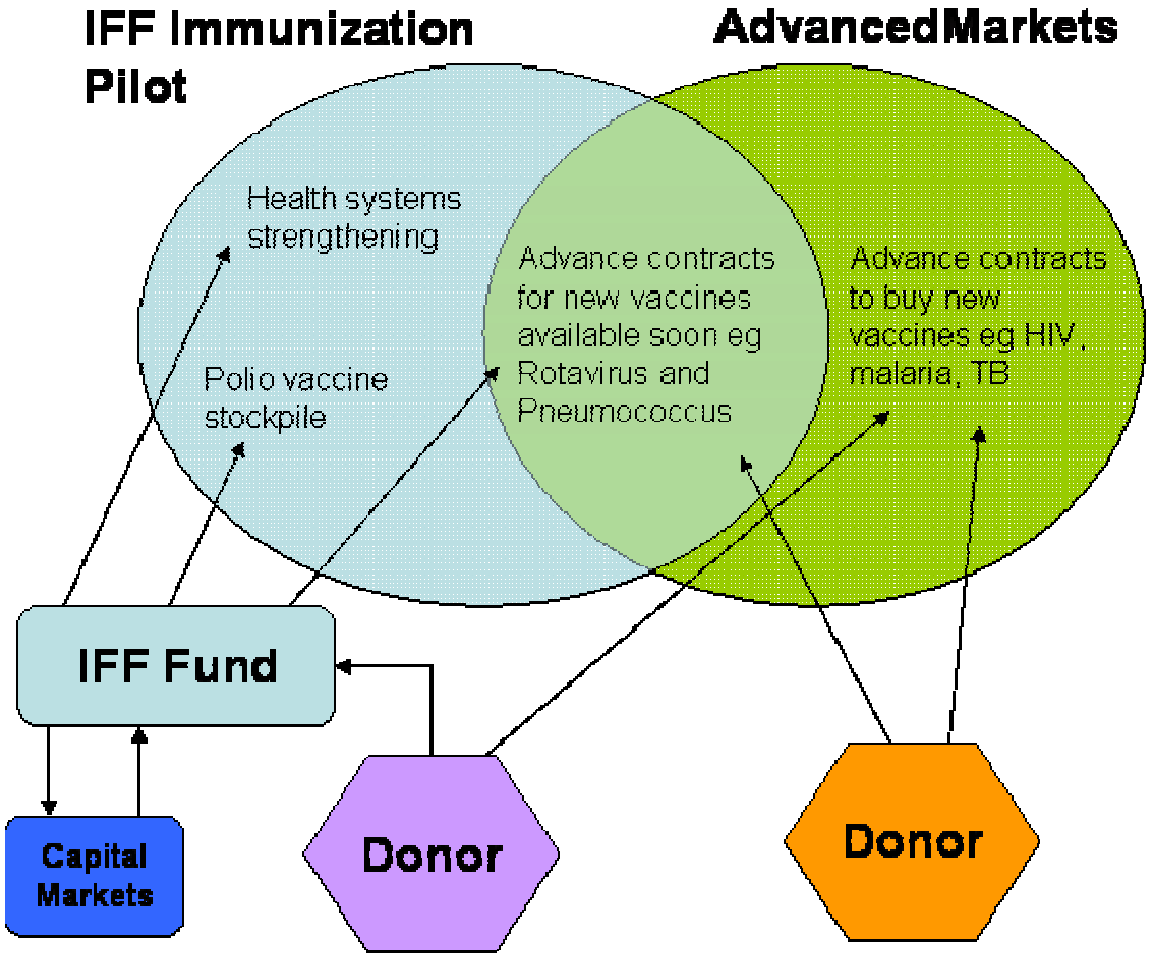
7.5.4 AdvancedMarkets as a complementary financing mechanism for the IFF

The IFF financial mechanism requires donors to commit to payments to a financial vehicle, which, on the strength of those commitments, can borrow in financial markets to rephase and commit that spending. However, because of constraints on budget processes, financial accounting or limitations on legal powers, some donors may not be able to make a commitment of this kind.

The AdvancedMarkets commitment is a different kind of commitment, taking the form of a long-term procurement contract. Most Governments have ways to make long term commitments of this kind, and there are well-established budgetary procedures for them. It is therefore possible that some donors would be able to make an AdvancedMarkets commitment who could not contribute directly through the IFFII financial mechanism.

However, if a donor can make a legally binding commitment to contribute to and AdvancedMarkets contract for new vaccines, this commitment could be taken into account in the overall planning of the IFF Immunization Initiative. This provides a new way for donors to contribute to the IFF Immunization Initiative, even if they are not yet able to contribute through the financial mechanism.

Figure 7.1: Possible relationship between IFF Pilot and Advanced Markets



Chapter 8: Regulatory and procurement considerations

8.1 Existing regulatory and procurement systems

Current procurement and regulatory systems for developing world vaccines depend heavily, though not exclusively, on the WHO[59] and UNICEF[60]. UNICEF – through its Supply Division – is the main agent for procuring and delivering vaccines to low-income countries.

UNICEF only purchases vaccines that are "prequalified" by the WHO, the official body advising UN agencies on the suitability of specific vaccine products for purchase. Not only do UN agencies purchase only those products on the WHO prequalified list, but many countries in the developing world also use it as a basis for their own product licensing and selection.

Countries currently buy vaccines for national immunization programs from one or a combination of three sources: domestic production; procurement directly from a manufacturer or manufacturer's agent; and sourcing through a bulk procurement agency such as UNICEF (or the Pan-American Health Organization for Latin America and the Caribbean). In 2002, UNICEF purchased $220 million worth of vaccines for use in 100 countries, representing two billion doses of vaccines.[61] While some large countries – such as India, China and Indonesia – produce or buy their own vaccines, UNICEF is the primary agent of vaccine procurement for developing countries (except Latin America and the Caribbean); certainly for Vaccine Fund eligible countries it is the dominant global procurement system today.

The UNICEF procurement process has six steps, including prequalification: the decision to purchase a vaccine, development of specifications, identification of products meeting specifications (through WHO prequalification), publication of the tender, the adjudication and award process and receipt and release of the vaccine products.

8.2 The need for long term contracting

During the Working Group's discussions with industry, it became clear that industry attaches a great deal of importance to the further development and widespread use of long-term contracts for vaccines for developing countries.

[59] World Health Organisation

[60] United Nations International Children's Fund

[61] UNICEF Supply Division Annual Report 2002

At present, UNICEF's usual procurement award for most commodities is a "long-term arrangement" (LTA). Under an LTA, UNICEF and manufacturers agree to the commercial terms for products, such as prices, delivery schedules and packing requirements, so that when an order is placed, it can be delivered rapidly. In the past, LTAs have typically had a duration of 1-2 years, but they can last as long as five years. UNICEF also provides the vaccine industry with forecasts for vaccine requirements (in 3-4 year increments), but these are indicative only (that is, they do not form an enforceable contract).

Industry consultations forcibly made the point that the lack of a long-term contract makes it difficult for potential suppliers to invest in long-term productive capacity, which would increase supply and reduce the price. The result is higher prices for developing countries, lower usage and, occasionally, supply constraints.

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

This situation also highlights the urgent need for reliable demand forecasts. Initiatives like the Accelerated Development and Introduction Plans (ADIPs) for Pneumococcus and Rotavirus vaccine are attempting to correct the public sector's poor record and recognize the pivotal importance of having an accurate forecast of demand in advance. Improving accuracy in this area would be an important contribution to reducing risk for all parties.

8.3 Regulatory and procurement implications of AdvancedMarkets

AdvancedMarkets can be designed in a way which is consistent with the existing system of regulation and procurement, subject to some important changes. For example, a price guarantee contract could provide top-up payments to supplement those made by UNICEF or other qualified buyers supplying the public sector in eligible countries (see Box 8.1 for a hypothetical example.)

8.2.1 Prequalification

Contracts could be made subject to successful prequalification (or qualification by some set of pre-specified authorities). Because the prequalification process can begin before a product is licensed, the existing process is broadly consistent with an AdvancedMarkets contract: manufacturers responding to the Framework Agreement are those intending to enter the prequalification process, so once they have a product they can begin working with WHO and national regulatory agencies to prequalify. This prequalification decision could be made official once licensing is successful.

An additional challenge for prequalification of new products (as opposed to the mature products usually prequalified by the WHO) is the demonstration of appropriate safety and efficacy in the target population. For a vaccine intended for global use, this may require multiple trials in representative target countries.

8.2.2 Procurement

The detailed arrangements for procurement would need to be determined in the contract.

The AdvancedMarkets approach would be novel for UNICEF in several ways. First, it would require UNICEF Supply Division to use product specifications set not by the WHO, but by an independent sponsoring group or adjudication committee (though they might be endorsed by the WHO). Second, it would require UNICEF to buy vaccines without a conventional competitive tender process. (In principle, the Framework Agreement is the tender and the Guarantee is the award.) This might require some change in, or exception to, UNICEF's procurement rules. Third, it would require UNICEF to sign a multi-year legally-binding purchase commitment. Though this is rare, the existence of the legally-binding sponsors' guarantee should give UNICEF the comfort it needs to enter such a contract.

In the event that UNICEF is not able to adapt its procurement arrangements to the AdvancedMarkets contract structure, it may be necessary for alternative agencies to undertake the centralized procurement.

Box 8.1: Procurement under a price guarantee

Suppose that a sponsor or consortium of sponsors guaranteed a price of $15 per person immunized for a malaria vaccine, conditional on a base price of $1.50. Suppose then that a supplier, developed a malaria vaccine. The vaccine would presumably go through the WHO prequalification process and the supplier would then negotiate a price with UNICEF. As long as the supplier got the vaccine through their prequalification process, and UNICEF and countries were willing to pay $1.50 per person immunized, (for example $0.50 per dose per three-dose vaccine), the supplier would receive an additional $13.50 payment per person under the price guarantee. If there were multiple suppliers, then depending on the way the guarantee was written, they all might be eligible for the price guarantee, or only some of them would be eligible. In the latter case, those firms eligible for the price guarantee would have a strong advantage in bidding for UNICEF procurement contracts. (For example, the price guarantee might favor the initial suppliers over “me too” suppliers that made only minor technological changes on the original product that did not result in a better product.) Another eventuality worth considering would be a case in which for some reason a country wanted a vaccine but could not obtain it through the UNICEF process. Depending on the list of qualified buyers in the framework agreement, the country might be able to purchase directly from the supplier, with the price guarantee still applicable.

Chapter 9: AdvancedMarkets examples for two products

9.1 AdvancedMarkets for an early stage product: Malaria

Vaccine development for the world's most important diseases for which no vaccine is yet available – including AIDS, TB and malaria – need advance contracting to increase investment in research, to support development and testing of products that will meet the needs of the developing world, to ensure access as soon as a sustainable product is developed.

The Working Group looked at malaria as an example of a specific case where advance contracting is needed to complement ongoing push funding efforts to accelerate development of an essential vaccine. Similar analysis demonstrates benefits of this approach for HIV/AIDS and for tuberculosis.

9.1.1 The need for advance contracting for malaria

The World Health Organization estimates that at least 2.3 billion people are at risk from malaria and at least 1 million, possibly as many as 2 million, people die of the disease each year.[62] More than half of all malaria deaths are among children in Sub-Saharan Africa. The disease is estimated to have a significant negative impact on growth in Africa.[63]

Malaria transmission occurs through the bite of an infected anopheles mosquito. Parasites multiply in the liver and red blood cells of affected people. Symptoms include fever, headache, muscular aches and weakness, vomiting, and diarrhea; the disease may result in long-term debilitation or may be fatal if untreated or treated with insufficiently effective drugs.

Malaria was almost completely eradicated from North American and Europe using insecticides and environmental management. But it does not follow that the same can be achieved elsewhere, for a combination of climatic and biological reasons. Africa's temperatures, mosquito species, and humidity give the continent the highest malaria burden. Africa's malaria mosquitoes almost exclusively bite humans, which enhances the chain of human-to-human transmission. The combination of high temperatures, sufficient rainfall for mosquito breeding and human-biting anopheles mosquitoes, make it more much more difficult to control the disease than elsewhere.

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[62] See the website of the Malaria Vaccine Initiative: www.malariavaccine.org

[63] McCarthy, Wolf & Wu, "The Growth Costs of Malaria", December 1999 (at www.malaria.org/Wolf_Wu_McCarthy.pdf)

In addition, there is increasingly widespread resistance to malaria drugs and insecticides in Africa, Latin America and Asia. Given the challenge of controlling the mosquito vector, a successful malaria vaccine suitable for young children and women of childbearing age would be an almost ideal solution.

In addition to public funding through organizations such as the NIH, two public initiatives provide push support for malaria vaccines:

- The Malaria Vaccine Initiative was founded at the Program for Appropriate Technology in Health in 1999 with funding from the Bill & Melinda Gates Foundation. Of the 20 vaccine candidates MVI is supporting, eight have entered clinical development (phase-I or phase-II clinical trials); and

- The European Malaria Vaccine Initiative founded in 1998 by the European Union provides a mechanism to facilitate the development of candidate molecules through post validation phase of nationally and internationally funded malaria vaccine R&D, and to see candidate molecules through to limited clinical trials in close collaboration with the African Malaria Network Trust, to assure appropriate vaccines are developed as quickly as possible.

Malaria vaccine research has made painstaking gains over many years. With its multi-stage lifecycle, malaria presents a unique and complex vaccine challenge. There are currently no vaccines on the market, but there are three types of vaccines in development targeting different points in the malaria life cycle: pre-erythrocytic, blood stage and transmission stage.

In October 2004, researchers reported preliminary results from the largest vaccine efficacy trial ever conducted in Africa.[64] This phase-II trial in Mozambique of a vaccine[65] was supported by the Malaria Vaccine Initiative (which is funded by the Bill and Melinda Gates Foundation) and GSK Biologicals. The trial found vaccine efficacy against clinical malaria attacks of 30 percent; efficacy against primary infection with *Plasmodium falciparum* of 45 percent; and efficacy against severe disease of 58 percent. Further progress on this candidate vaccine, however, will

[64] Philippe Van de Perre, Jean-Pierre Dedet, "Vaccine efficacy: winning a battle (not war) against malaria", *The Lancet*, 16 October, 2004.

[65] The vaccine was originally developed in 1983 by the US Army's Walter Reed Army Institute of Research

depend on there being sufficient prospects of donors being willing to meet the cost of the vaccine.

While collaboration between philanthropic foundations and the private sector has had a significant impact on malaria vaccine development, a complementary mechanism to enhance the market is also needed for at least two reasons. First, more research is needed into a wider range of candidate vaccines, to identify the best opportunities and accelerate progress on those ideas. At present, funds are not sufficient to pursue enough of the possible avenues of research. Second, after phase-II trials, the cost of developing and testing a candidate vaccine in humans escalate, and progress towards commercialization will require that there is the prospect of a sufficient market to make it economically viable.

9.1.2 Proposed contract structure for malaria

The proposed structure for an AdvancedMarkets contract for malaria is set out in drafts at Annex B (the Framework Agreement) and Annex C (the Guarantee Agreement). These drafts are annotated with rationale and explanations.

The proposed structure closely matches the outline set out in Chapters 3 and 4 of this report.

- The sponsors would make a legally binding promise to pay 90% of the cost of up to 200 million treatments purchased, at a guaranteed price of $15 a dose (adjusted for inflation).
- In return, firms would agree to provide further treatments (after the 200 million) at the base price, reflecting the cost of production.
- This offer would be made in the form of a Framework Agreement; Firms would become eligible for this commitment by signing the Agreement.
- An Independent Adjudication Committee (IAC) would be established to determine whether the technical specification of the vaccine had been met.
- If a firm developed a subsequent, superior product (as agreed by the IAC), that product would also be eligible for the price guarantee (the price guarantee would apply to the first 200 million treatments bought, shared among the eligible products according to demand).
- As set out in Chapter 5, a commitment of this size would create a market comparable to a developed country pharmaceutical, while providing a very cost-effective investment for donors.

9.2 AdvancedMarkets for Rotavirus and Pneumococcus

A number of late-stage products – that is, those in late-stage clinical trials, close to licensing, or licensed but not yet mass-produced – are critically important to much of the developing world, but on current trends are not likely to be supplied in a profile or in quantities that will achieve a significant impact on global health. Examples are rotavirus and pneumococcal vaccines.

9.2.1 The need for advance contracts for rotavirus

Rotavirus is the most common cause of severe, dehydrating diarrhea among children worldwide.[66] Each year it causes over 100 million cases of disease, 25 million clinic visits, and between 350, 000 – 590, 000 deaths in children aged five or younger. Nearly every child in the world is exposed to rotavirus before reaching age five, but nearly all the children who die of rotavirus are in the very poorest countries.

At present, the only treatment for rotavirus involves preventing dehydration by providing fluids and salts until the disease runs its course; neither antibiotics nor other drugs can cure rotavirus. At least one rotavirus vaccine will become available on the global market in the next few years. The challenge will be to make a rotavirus vaccine available to those who need it most as rapidly as possible.

Two first generation products have been licensed, or are close to being licensed – a human-derived, monovalent, live, attenuated two- to three-dose oral vaccine developed by Avant Immunotherapeutics and licensed to Glaxo-Smith Kline; and a bovine-human reassortant, pentavalent, live-attenuated 3 oral dose vaccine developed by Merck. The GSK product is in Phase III trials in Latin America and Phase II trials in South Africa, Singapore and Bangladesh; the Merck product is in Phase III trials in Central and South America. In addition, Biovirx Inc. has recently indicated it will pursue licensing for a rotavirus vaccine that had previously been sold in the US market, but was withdrawn for fears of adverse effects.[67]

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[66] See the Rotavirus Vaccine Program website: www.roativirusvaccine.org

[67] Rotashield, the world's first rotavirus vaccine, was licensed for use in the US in 1998. Prior to licensing, clinical trials in the United States, Finland and Venezuela had found it to be 80-100 percent effective at preventing severe rotavirus diarrhea, and researchers had detected no statistically significant serious adverse effects. But Wyeth, the manufacturer of Rotashield, withdrew the vaccine from the market in 1999, after it was discovered that it might have contributed to an increased risk of intussusception, or bowel obstruction, in one of every 12, 000 vaccinated infants. See http://www.cnn.com/2004/HEALTH/05/04/rotavirus.vaccine.reut/index.html.

Second generation products – at the Lanzhou Institute in China, Bharat Pharmaceuticals in India, Bio-Farma in Indonesia, and the NIH – are in progress but several years behind.

The Rotavirus Vaccine Program – another GAVI-supported ADIP – was established to lay the foundation for rapid introduction and sustainable supply of first generation rotavirus vaccines. One of the most important elements of this project is to secure supply of affordable vaccines in predictable quantities.

An AdvancedMarkets contract would:

- ensure that first-generation products are tested in the populations that need them most;
- provide an incentive for suppliers to produce the vaccine in quantities that will meet the needs of the developing world over time;
- influence decisions about the presentation and characteristics of the product so that it better meets the needs of the developing world;
- influence the long term pricing of this product; and
- reduce the risk of wasteful investment in "me too" products.

There is a clear need for advance contracting to secure the right profile, price and supply of several vaccines near to licensing – this, combined with more concerted demand-side interventions, will be instrumental to shortening the gap of 10-15 years seen in the introduction of recent vaccines, such as Hepatitis B and Hib vaccine. The ADIPs for Pneumococcus and Rotavirus are important steps in this direction and, while they do not yet have the mandate to negotiate such contracts, they see long-term advance contracting as potentially critical to achieving their mission.

9.2.2 Pneumococcus vaccine[68]

More children die each year from Pneumonia than from any other disease – even more than malaria or AIDS – and nearly all of these deaths occur in the world's poorest countries. Unlike malaria and AIDS, vaccines are currently available to prevent these deaths. But without a coordinated effort and forward planning, it will probably take 20 years or more for these vaccines to reach even half of the children in the world's poorest countries – in part because of the high cost of these vaccines, but also because of the lack of a reliable and predictable demand.

[68] See the ADIP website: www.pneumoadip.org

A vaccine against the second-leading cause of bacterial Pneumonia deaths – a bacterium called Hib (*Haemophilus influenzae* type B) – has been available since the late 1980s. It has been widely used in all wealthy countries and, as a result, Hib disease has nearly disappeared altogether. However, in 2002 – fifteen years after the vaccine was first used in wealthy countries – fewer than 15 percent of the world's poorest children were receiving the vaccine.

The leading cause of bacterial Pneumonia deaths – a bacterium called *Streptococcus pneumoniae* (*pneumococcus*) – is now preventable by immunization with a vaccine very similar to the *Hi*B vaccine. In 2000, the United States licensed a Pneumococcal conjugate vaccine for prevention of severe Pneumococcal infections in infants and young children. Like the Hib conjugate vaccines, this vaccine has proven to be safe and very effective in randomized clinical trials. In studies in the United States and Finland, the vaccine was shown significantly to reduce the incidence of severe Pneumococcal infections such as Meningitis, Pneumonia, and septicemia, and to prevent ear infections. Since 2000, it has been routinely used in the United States and other wealthy countries, but not in the developed world.

A new initiative – GAVI's Pneumococcal ADIP – aims to increase access to new, life-saving pneumococcal vaccines and ultimately prevent millions of deaths by getting vaccines where they are needed the most, faster than ever before. The ADIP has articulated a three-part mission: to establish, communicate and deliver the value of existing (and next generation) pneumococcal vaccines. The ADIP is currently funding disease surveillance networks, clinical trials in target populations, and cost effectiveness studies. An important part of its mission will depend on delivering products to GAVI's target countries at a price and volume that they can afford.

9.2.3 Proposed contract structure for a late-stage product

The Working Group considered an advance contract for late stage products, which could be applied to vaccines for rotavirus and pneumococcus.

Unlike the early-stage contract, the late-stage contract in these cases would be with one or more specific suppliers. The Framework Agreement stage would be unnecessary. The contract with the supplier would be very similar to the Guarantee Agreement of an early-stage product.

- The sponsors would commit to pay a relatively high price for each person immunized, up to a certain number (say the first 100 million people immunized).

- In return for receiving the higher price at first, the supplier would provide vaccine at a much lower price after the initial sales. The lower, long-run price would be set at a reasonable mark-up over the estimated production cost. The supplier would agree to meet public sector demand in low-income countries at this price, given some reasonable notification period.
- If the supplier did not fulfill demand, given adequate notice, the contract would provide for damages, or require a restricted license be given to the sponsor (to be used to supply only Vaccine Fund eligible countries).
- The contract might commit the sponsor to guarantee some minimum order but after the initial volume had been reached, the vaccine would have to compete against other products, so there would still be an incentive for other firms to enter if they could produce superior products or manufacture more cheaply.
- The contract could be signed prior to regulatory approval, but would be conditional on regulatory approval and expected performance of the vaccine.

There are a number of advantages to this approach, for developing countries, suppliers and sponsors.

- The supplier obtains a predictable revenue stream.
- The supplier has incentives to install capacity quickly, since the net present value of its revenue will be greater the faster the first hundred million people are immunized.
- There is no commitment to buy the product if a superior product is developed later.
- Both suppliers and consumers are better off than with a system of short-run contracts with a single supplier. Uncertainty will be reduced for both parties. If prices are chosen appropriately, overall revenue and profits will increase, making the supplier better off, but the number of immunizations will also increase significantly, lowering the average price per person immunized and improving health cost-effectiveness.
- The contract ensures sustainability for countries and donors in the long-run. Because countries know that they will have access to the vaccine at affordable prices over the long-run, they can be more confident in adding it to their immunization schedules without fear that they will not be able to afford the vaccine later and will have to reverse their strategy.
- The contract sets a good precedent for AdvancedMarkets programs aimed at stimulating investment in early-stage products, and builds confidence in that commitment.

Chapter 10. Next steps

[Note: this is a consultation draft of the Working Group report. The Working Group hopes that progress will be made on a number of the actions listed below before the report is finalized. The detail of the next steps will depend on the extent of commitment that is secured from industry and possible donors during the consultation.]

The Working Group believes that AdvancedMarkets would make a significant impact in the development and supply of neglected developing country diseases. The analysis in this report shows that such contracts can be developed and implemented successfully. The Working Group makes the following recommendations for the implementation of AdvancedMarkets.

10.1.1 Through existing funding streams, such as the Vaccine Fund, the global health community should support AdvancedMarkets arrangements for late-stage products.

Long-term contracts can assure a sustained and adequate supply at affordable prices, while preserving incentives for innovation. In addition, AdvancedMarkets contracts for late-stage products will help to build confidence in similar arrangements for early-stage products.

Next steps

GAVI and the Vaccine Fund should convene procurement and financing partners for late-stage vaccines to:

- understand how to use AdvancedMarkets commitments in existing financing structures, in particular who has the mandate to sponsor, how budgets would be allocated, and how much could be available;

- conduct a market analysis of one or more late-stage products as the basis for a decision about priorities;

- for priority vaccines, design specific contracts through negotiations between sponsors and suppliers; and

- work with the WHO and UNICEF Supply Division to agree the details of how the contracts would be executed.

Consideration should be given to implementing AdvancedMarkets commitments for late-stage products as part of the proposed International Finance Facility Immunization pilot.

10.1.2 Donors should commit significant funds for an AdvancedMarkets program for one or more early stage products; applicability to other product categories should also be examined.

There is important research underway on vaccines for malaria, TB and AIDS; but the extent of innovation is limited to the number of candidates that can be supported by "push" funds. A guaranteed market enhancement like advance contracting could unlock innovation today, speed the development of a vaccine tomorrow, and assure rapid access – and lives saved – for many years to come. It is one of the most cost effective development interventions available to us.

Next steps

GAVI should consider where AdvancedMarkets is most needed for early-stage products. For target products, GAVI should then convene potential sponsors to:

- work with product development groups to understand the market-specific risks and uncertainties, then work with a legal team to draft AdvancedMarkets contracts;
- create the necessary adjudication, procurement and other institutions to facilitate implementation of contracts; and
- create a coalition of sponsors to make the commitment.

10.1.3 Funding and development groups for other product categories – drugs, diagnostics, devices – should consider the application of advance contracts principles to their market enhancement needs.

The Working Group focused on vaccines, and two in particular, but similar principles may apply to other product categories (drugs, diagnostic tests, devices) where the developing world does not represent a sufficiently large market to stimulate investment, development or supply. However, it is likely that the principles would need to be applied differently according to the type of product. Further analysis is needed.

Next step

- Potential sponsors and development partnerships should commission analysis on the applicability of advance contracting mechanisms in the markets in which they operate. The analysis should be conducted by a multidisciplinary group of individuals with expertise in law, economics, business and public health.

10.1.4 The world health community should recognize the long-term benefits of being willing to pay more for medicines, in order to stimulate investment for future medicines. The incentives to obtain the lowest possible price for vaccines should be set against the social value of ensuring that new vaccines are developed and made available.

Consideration should be given to modifying procurement specifications, awarding tenders, and signing multi-year agreements to facilitate both long-term and advance contracts.

Next step

- WHO and UNICEF should look at the specific regulatory and procurement needs of an advance commitment program, and whether they could facilitate this approach.

Conclusion

The major health problems of the developing world need new thinking to spur scientific progress. Past technological breakthroughs have done much to relieve suffering and prevent death; but we cannot rely on spin-offs from the developed world for future advances.

We depend on the commercial pharmaceutical and biotech sectors for much of what needs to be done. That is where we find not only the drivers of innovation, but also the capacity to move products through the regulatory process to commercialization and distribution. The process of scientific discovery is important; but it is not enough to bring new medicines to the people who need them.

Both theory and empirical evidence tell us that the commercial pharmaceutical sector cannot focus on the problems of the developing world, because of their obligations to shareholders, and the many competing demands for their investment.

There is a growing anxiety about access to essential medicines. Many of the solutions that are proposed to tackle the problem in the short run have negative long-term consequences for the development of the next generation of vital products.

Our proposal meets both the short-term and long-term challenges, providing both access and incentive to innovate. It is workable in practice. It demands serious attention from those who are concerned to ensure that the benefits of progress are shared across the globe.

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Appendix A: Recent Experiences with Vaccine Introduction

A.1 The Hepatitis B (HepB) Experience

Merck introduced a plasma-derived Hepatitis B vaccine in industrialized countries in 1981, at a price of about $30 per dose or nearly $100 for the complete series of three shots. The vaccine used a chemical purification technology that resulted in a high-quality but high-cost product, specifically targeted to health workers and other high risk individuals in industrialized countries. As was noted afterwards, "only after the companies were successful at producing such a Hepatitis B vaccine did they realize that the real need was not in the West but in the countries of Asia and Africa".[69]

In 1986, a group of experts in HepB formed the International Task Force on Hepatitis Immunization, with the goal of creating supply and making the case for integration of a HepB vaccine in the developing world. The Task Force's objectives were to lower the price of the vaccine by transferring technology to lower cost producers, and convincing developing countries and the international health community that HepB control through immunization of infants should be a top priority.

The use of pilot projects in developing countries was central to the Task Force's efforts, to prove that the product could be successfully integrated into immunization programs with positive results. These demonstration projects would prove to countries that HepB immunization was both possible and worth doing, and prove to industry that demand could exist at the right price, in the hope of creating incentives to supply at that price.

In 1987, the Task Force designed and piloted its first project in Lombok, Indonesia. They solicited international tenders for supply of the vaccine; the tender required that bidders offer Indonesia the same price once it introduced the vaccine nationwide and offer the same price to other developing countries. The winner was Korean Green Cross which – capitalizing on advances in lower cost production technology – offered to supply at $0.95 per dose, dramatically lower than the prevailing market rate of $15-30 per dose.

[69] *Asian Development Bank, 2001*

This low price fundamentally changed the nature of the HepB market. Through the late 1980s further demonstration projects followed, and the Task Force provided assistance to several countries developing international tenders. By 1992 a number of Asian countries, including China, Thailand, Indonesia, the Philippines and Mongolia, had introduced HepB into their routine immunization programs. The price dropped as low as $0.65 per dose in 1991.

In parallel, a Recombinant DNA vaccine was introduced in the late 1990s, by Merck and SmithKline Beecham at prices near $40 per dose. Competition with the plasma-derived vaccine drove prices down, and developing country manufacturers also began to supply low-income markets at drastically lower prices. Prices dropped to just over $1 per dose for the recombinant product by the early 1990s.

In 1992, the World Health Organization (WHO) recommended that all countries incorporate Hepatitis B into their routine immunization schedules by 1997. Since then, price has continued to be a major barrier to the introduction of HepB vaccine in the developing world (even at a low of $0.30 per dose for the monovalent vaccine, it was 3-5 times more expensive than older vaccines like DTP and measles[70]). Still, the availability of low cost supply has kept the price decreasing and the market reasonably robust; more recent support from GAVI and the Vaccine Fund has accelerated introduction in many of the world's poorest countries. As of 2001, nearly 100 countries provide the HepB vaccine as part of their routine campaigns, but more than 60 percent of the world's children[71] – largely the poorest of the poor – still did not receive this potentially life-saving vaccine (Widdus, 2000 and WHO, 2003).

From the time a Hepatitis B vaccine was available on the market, it took five years to begin a concerted global effort to bring the vaccine to the developing world; ten years to reach even double-digit coverage in South East Asia; and eleven years to convince the WHO to make a universal recommendation for use. This lag in introduction and uptake means a decade of lives lost. The public sector and the developing world were largely caught by surprise with the availability of this effective but expensive vaccine and had to start from scratch in 1981 by creating both supply and market demand. HepB can be seen as a success story in some sense – prices did drop and the product was introduced with some success – but it is a story that leaves room for improvement.

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[70] See Global Alliance for Vaccines and Immunization, 2001 for details.

[71] Global reported coverage in 2002 was 44 percent (WHO-UNICEF estimate 32 percent). In WHO's Africa region, 25 percent (6 percent); Americas 74 percent (58 percent); South East Asia 12 percent (9 percent). World Health Organization, 2003

A.2 The Haemophilus influenzae type b (Hib) experience

Since the late 1980s, highly effective vaccines against Hib have been licensed and widely used in the industrialized world.[72] The effect has been dramatic – incidence of invasive Hib disease has fallen by more than 90 percent in those countries. Yet in the developing world, Hib runs largely unchecked, because very few countries use these vaccines in routine immunizations. In 2001, only 77 countries of 191 WHO member states had introduced Hib vaccine, and most of those represent introduction in North America, Europe and Latin America. The vast majority of countries in South East Asia and Africa have still not introduced the vaccine. It is estimated that around half a million children die every year from lower respiratory tract infections caused by Hib, which could be prevented by a vaccine we already have.

Cost is commonly cited as a significant barrier to introduction of Hib vaccine. Even at the 2000 price of $2 per dose for a three-dose schedule, Hib is significantly more expensive than traditional vaccines. In this sense, the cost barrier is analagous to the experience with the Hepatitis B vaccine. Perhaps more important for Hib, however, is the fact that many governments are simply not convinced that the disease is a problem in their country. Despite being a major cause of bacterial meningitis and pneumonia in young children worldwide, the Hib bacterium is difficult to isolate without invasive procedures – all pneumonia, the most common result of the Hib bacteria, looks alike, so doctors and public health professionals rarely diagnose Hib as the cause of disease or death.

By the mid-1990s, international efforts to increase children's access to Hib vaccines in the developing world began in earnest. These efforts, led by a number of scientific and public health champions, centered on establishing and communicating the burden of Hib disease. In The Gambia and West Africa, between 1993 and 1995, researchers assessed the impact of a Hib conjugate vaccine on the incidence of pneumonia overall in a double-blind trial involving over 40,000 infants, and concluded that one in five episodes of severe childhood pneumonia in The Gambia was Hib-related. Researchers in Chile have performed similar studies with very similar

[72] Until the late 1980s, the only available Hib vaccines were based on the polysaccharide, or sugary, capsule of the bacterium. These vaccines were protective in older children and adults, but not in infants – those at greatest risk of infection – because their immune systems could not respond. The new generation of conjugate vaccines contain two components: the Hib polysaccharide capsule and, attached to it, a carrier protein antigen such as tetanus toxoid which stimulates a strong T-cell related immune response from the infant immune system. Several Hib conjugate vaccines have been licensed, including combinations with DTP and DTP plus Hepatitis B. For further details see P. Brown, forthcoming.

results. As a result, a handful of countries outside the established industrialized economies pioneered the introduction of Hib vaccine – mostly in Latin America and some in Africa.

In 1998 the WHO published a position paper recommending use of Hib conjugate vaccines in routine infant immunization programs. Two years later, a Hib vaccine trial similar to those in Latin America and Africa was undertaken in Lombok, Indonesia with the aim of increasing awareness and uptake in Asia. Uptake today remains low – the WHO[73] estimates 9 percent (12 percnet reported) in the South East Asia region in 2002.

Given the growing body of evidence on the burden of disease and the still disappointingly low rates of uptake, GAVI has set itself a target of introducing Hib vaccine to 50 percent of high-burden, low-income countries by 2005. If they achieve this target, they will still reach only half the people who need this vaccine most, more than 25 years after it was made available.

[73] WHO, 2003

Appendix B: Draft Term Sheet for Framework Agreement.

1. Parties: One or more nongovernmental, grant-making organizations (such as the Gates Foundation) or governmental grant-making organizations (such as USAID) (each, a **"Funder"**)[74] and one or more pharmaceutical or biotech companies[75] that will work within the Framework (as defined below) to develop eligible vaccine(s) (each, a **"Developer**").

[74] The Framework and Guaranty Agreement term sheets were designed to accommodate a variety of Funders, despite the fact that there are substantial differences between governmental and nongovernmental organizations in areas such as funding capacity and ability to contractually commit to the Guaranty Agreement. There were discussions regarding mechanisms for ensuring that Funders are and remain bound by their financial commitments under the Framework and Guaranty Agreements. In the end, the Working Group concluded that traditional commercial mechanisms for ensuring compliance, such as letters of credit or escrow arrangements, would be unattractive to potential Funders as they would result in increased transaction costs and unnecessarily tie up funds that could be made available for more immediate opportunities. Instead, the Working Group elected to implement a bilateral contract structure, which would permit the Developer to pursue standard contract remedies, such as money damages and specific performance, if the Funders fail to satisfy their financial commitments.

[75] The Framework and Guaranty term sheets were designed to allow participation by both pharmaceutical companies and biotechnology companies. The Working Group considered, but did not incorporate, an alternative funding system recommended by a few of the biotechnology companies interviewed that would provide for interim payments, upon the achievement of certain predetermined milestones, to create incentives for research and early-stage development activities and encourage venture capital investment in emerging companies committed to the Framework.

2. Purpose: Create a legally binding series of agreements[76] that guaranties the developer(s) of a [____] vaccine[77] that meets the requirements set forth in the agreements a specific price for each qualified sale of the vaccine in certain designated developing countries (the **"Framework"**). The Framework Agreement will clearly state the goals and objectives of the Framework with regard to the target disease, the eligible countries and the affected populations.[78]

3. Benefits to Funder: Fulfills the Funder's philanthropic mission (or a statutory or regulatory mandate, in the event Funder is a governmental organization) by giving Developers an economic incentive to (a) select and implement R&D projects that are likely to lead to vaccines developed specifically for diseases found primarily in developing countries, and (b) establish manufacturing capacity for production of such vaccines.

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[76] Initially some thought was given by the Working Group to establishing the Framework Agreement as a form of unilateral agreement. A unilateral agreement is an offer by one party, the offeror or in this case the Funder, which only becomes a contract when it is accepted by the other party, the offeree or in this case the Developer. A unilateral agreement permits the offeror is withdraw its offer prior to acceptance, and what constitutes acceptance is not always clear, particularly in this context. This risk, it was thought by the Working Group, might create too much uncertainty for the Developer and thereby dilute the effect of the commitment. The Framework Agreement as reflected in term sheet would be bilateral agreement, which would be binding on the Funders as soon as one or more Developers sign on.

[77] The Working Group initially intended that the Framework and Guaranty Agreement term sheets would be used for both late-stage and early-stage vaccine candidates. However, on further consideration, the Working Group decided that a form approach did not make sense, given the fact that specific Developers and Eligible Vaccines had been identified for Rotavirus, and the recognition that each Developer had specific needs and objectives. Instead, the Working Group recommended that the Developers and the Funders directly negotiate long-term supply or other appropriate arrangements to ensure reliable, affordable supply to meet the long-run needs of Eligible Countries, while providing appropriate rewards for the vaccine developer.

[78] Each Framework Agreement will establish a specific price for qualified sales of an Approved Vaccine, by supplementing the "base price" paid by a vaccine purchaser (e.g., UNICEF) up to a certain dollar amount. The purposes of the Framework Agreement are to: 1) attract private sector R&D through market-oriented approach; 2) to use donor dollars to reward success without micro-managing research process; 3) shape type and pace of product development; and 4) to complement existing push programs.

4.	**Benefits to Developers:**	Establishes a specific price for all eligible sales of the vaccine in developing countries that allows the Designated Supplier (as defined below) to cover, over the term of the agreements, R&D costs as well as manufacturing costs and to make an acceptable return on its investment. The guaranteed price will be based on a per-patient dosing regimen to provide the required prophylactic benefit and will paid on all eligible sales up to the maximum number specified in the Guaranty and Supply Agreement (the **"Maximum Guaranteed Amount"**). For example, if a course of 3 immunizations are required to provide the necessary immunity, the guaranteed price is $20 and the Maximum Guaranteed Amount is 250 million, then the Developer would receive the guaranteed price of $20 only upon an eligible sale of all three doses comprising the course of treatment. If the Developer's total eligible sales equal the Maximum Guaranteed Amount, 750 million doses, or 250 million courses of treatment, then the Developer would be entitled to a guaranteed payment of $5 billion.[79]

[79] The Working Group discussions led to the conclusion that the price guaranty should be for "per course of treatment" rather than "per dose." This approach provides incentives to ensure that all doses of multiple dose vaccines are administered, and encourages the development of vaccines requiring fewer doses where scientifically possible.

5.	**Principal Responsibilities of the Funder:**	Funder shall (a) upon satisfaction of the conditions precedent set forth in Section 7, enter into a Guaranty and Supply Agreement (in the form attached to the Framework Agreement) with one or more Designated Supplier(s) (as defined below),[80] (b) fund the operation of the Independent Adjudication Committee (as defined below) in accordance with budgeted amounts, (c) indemnify the members of the Committee for claims and losses arising out of the performance of their duties under the Framework Agreement and the Guaranty and Supply Agreement,[81] (d) retain the Contract Administrators (as defined below) to administer the Framework in accordance with budgeted amounts, (e) maintain in strict confidence any confidential business information submitted to it by the Developers, and (f) agree to be bound by decisions of the Committee acting within the scope of its authority.

[80] Until a vaccine is approved under the conditions set forth in Section 7 of the Framework Agreement term sheet, the Funder is only required to commit to the Framework Agreement, and fund the functions of the Independent Adjudication Committee. Once an Approved Vaccine is identified, the Developer has the right, and the Funder the obligation, to enter into the Guaranty Agreement with respect to that product.

[81] The Framework Agreement is designed so that the members of the Independent Adjudication Committee owe certain duties in performing their functions equivalent to the duties of the director of a Delaware corporation. Consistent with this duty, the indemnification of the members of the Independent Adjudication Committee may exclude intentional misconduct or actions that are conducted in bad faith or for personal gain.

6.	**Principal Responsibilities of Developers:**	Each Developer shall (a) provide confidential reports to the Independent Adjudication Committee on the progress of its development efforts at the times specified by the Committee (it is contemplated that these reports would be high-level annual status reports at the outset and would increase in frequency and detail as the development efforts advance),[82] (b) provide such technical information as may be reasonably requested by the Committee in order to confirm that the conditions precedent set forth in Section 7 have been satisfied, and (c) agree to be bound by decisions of the Committee acting within the scope of its authority.
7.	**Conditions Precedent to Obligations of Funder:**	It shall be a condition precedent to Funder's obligation to enter into and perform its obligations under the Guaranty and Supply Agreement that the vaccine meet (a) the technical specifications outlined in Section 8 below, and (b) the usability requirements outlined in Section 9 below.[83]
8.	**Technical Specifications:**	For a vaccine to meet the technical specifications it must, subject to Section 10, satisfy the approval, safety and efficacy requirements set forth in Schedule A.

[82] Developers may provide confidential information to the Independent Adjudication Committee in two circumstances. First, Developers would submit progress reports to the Independent Adjudication Committee reports during the term of the Framework Agreement. These reports were thought by the Working Group to provide a way to evaluate the effectiveness of the mechanism during the research and early-development periods. These reports, if not promising, may permit the Funder to withdraw from the Framework Agreement under Section 25 of the term sheet. Second, for those Developers seeking to participate at a later date, the Framework Agreement requires some evidence that the Developer has a technology or expertise with scientific promise for the development of an Approved Vaccine.

[83] Although the Framework Agreement is designed to create an enforceable bilateral contract between the Developers and the Funders, the Funders would not be obligated to enter into the Guaranty Agreement until a product is tendered that meets certain minimum technical specifications, such as approval of both the product and its manufacturing process by a qualified regulatory body and certain safety, efficacy and use requirements.

9. Usability Requirements: For a vaccine to meet the usability requirements it must, subject to Section 10, satisfy the dosage, means of delivery, storage, shelf life and other requirements set forth in Schedule A.

10. Waiver of Conditions Precedent: After the effective date of the Framework Agreement the Independent Adjudication Committee may (by a 2/3 vote of its members or at the direction of the Funder) waive or modify the technical specifications or usability requirements in a way that does not materially increase the cost of performance for a Developer. For purposes of illustrating the foregoing, if a specification called for 60% effectiveness, the Committee could, by a 2/3 vote of its members, reduce the requirement to 50% effectiveness, but could not increase it to 70% effectiveness under this provision.[84]

[84] Because there was concern that the Developer should be assured that the Funder could not change the rules of the game after the Framework Agreement was entered into, technical requirements cannot be changed to increase the burden of those requirements, unless there is a significant change in circumstances with respect to the disease that would significantly reduce the need for a vaccine or undermine the specifications, such as a dramatic decrease in disease prevalence, a significant change in disease transmission or progression or a major advancement in treatment. As noted below, these types of changes would be subject to judicial review. Technical requirements may be decreased, however, at the discretion of the IAC.

11.	**Testing and Acceptance:**	The Developer shall submit the vaccine to the Independent Adjudication Committee for testing and acceptance. The Committee shall be responsible for making determinations with respect to whether a vaccine tendered by a Developer satisfies the conditions precedent set forth in Section 7, provided that the IAC shall have the right to delegate this responsibility to one or more third-parties that it determines: are qualified to make such determinations and are independent and unbiased, such as, for example, the World Health Organization's prequalification process. Further, the Committee shall have the right to retain one or more consultants or rely on the actions of governmental or other third parties, such as the United States Food and Drug Administration, in making its determinations. In addition, the Committee shall have authority to grant waivers of, or make modifications to, the application of specific technical specifications or usability requirements as provided in Sections 10 and 22.
12.	**Designated Supplier:**	If the Independent Adjudication Committee determines that the conditions precedent have been satisfied (or if the conditions that have not been satisfied are waived or modified) then (a) the vaccine submitted by the Developer to the Committee shall be deemed an **"Approved Vaccine,"** (b) the Developer of the Approved Vaccine shall be deemed a **"Designated Supplier,"** and (c) the Funder and the Designated Supplier shall enter into the Guaranty and Supply Agreement within thirty (30) days of the date of the final, written determination of the Committee.[85]

[85] As noted above, the Framework Agreement is designed to be self-executing with respect to the Funders, providing the Developers with the right to enter into the Guaranty Agreement on the terms specified in the Framework Agreement. The Framework Agreement is also designed to permit more than one Developer to receive funds under the Guaranty Agreement. For the reasons discussed in the Guaranty Agreement, the Working Group determined not to pursue a winner-take-all approach. The Working Group intends that the terms should distinguish between those Developers who are second because they are simply copying the First Developer's vaccine and those who are second because their independent research program happened to take longer.

13. Composition of Independent Adjudication Committee:

The Funder shall establish a committee (the **"Independent Adjudication Committee"** or the **"Committee"**), which shall be comprised of not less than [5] members. Members of the Committee will have expertise in the following fields: (a) immunization practices, (b) public health, (c) vaccinology and vaccine development, manufacturing and commercialization, (d) pediatric and internal medicine, (e) social and community attitudes on immunization, (f) economics, (g) contract law and (h) the vaccine industry, in each case, as applicable, with developing country perspectives. Members of the Committee shall serve a term of [_] years. Vacancies on the Committee will be filled by the remaining members of the Committee.

14. Actions of the Committee:

Each member of the Independent Adjudication Committee shall have one vote. Fifty percent of the members of the Committee, rounded up, shall constitute a quorum. Except as provided in Sections 10, 20 and 22, all decisions of the Committee will be made by majority vote of the members at a meeting at which a quorum exists.

15. Duties of the Committee:

The Committee will (a) seek to identify independent, unbiased and expert-qualified institutions and procedures to assist with determining whether a product meets the technical specifications and usability requirements and that can provide ongoing review of product safety and efficacy and manufacturing, (b) if necessary, designate Approved Regulatory Countries and Approved Manufacturing Countries from time to time, (c) evaluate products presented by Developers to determine if they satisfy the conditions precedent, (d) at its discretion or at the direction of Funder, waive or modify the application of specific technical specifications or usability requirements pursuant to Section 10, (e) if requested or as necessary, conduct multiple bilateral or multilateral meetings with Developer(s) in order to provide information about testing and acceptance procedures, waivers and modifications to the conditions precedent, market demand and supply forecasting, disease epidemiology and other relevant information, (f) using the standards specified in Schedule B, determine whether subsequent vaccines are superior to the original Approved Vaccine, whether for certain target populations, epidemiological conditions or otherwise, and designate new Approved Vaccine(s) and new Designated Supplier(s), (g) after an Approved Vaccine has been designated, monitor the sales and use of such Approved Vaccine for ongoing compliance with the technical specifications and usability requirements set forth in Sections 8 and 9 and decertify any vaccine that is not in material compliance with such specifications and requirements, and (h) determine whether the technical specifications and usability requirements set forth in Sections 8 and 9 or the Maximum Guaranteed Amount or Funder's other payment obligations under the Guaranty and Supply Agreement should be modified in whole or in part based on force majeure criteria pursuant to Section 22.

16.	**Duties of Committee Members:**	Each member of the Independent Adjudication Committee shall, in the exercise of its authority under the Framework Agreement, have the same fiduciary duties (including duty of care and duty of loyalty) as the director of a Delaware corporation.[86]
17.	**Contract Administrator:**	The Funder shall retain one or more individuals (each, a **"Contract Administrator"**) to implement the decisions of the Independent Adjudication Committee and to perform such other administrative, support and other tasks as may be assigned by the Committee, subject to the approved budget for administrative expenses.
18.	**Budget:**	The parties will agree on a budgeting process to ensure that the reasonable expenses of the Independent Adjudication Committee and the Contract Administrators will be reimbursed by Funder. [87]

[86] The duties of a corporate director under Delaware Law are the duty of loyalty, the duty of care and the duty of good faith. The duty of loyalty requires the director to place the corporation's interests above his or her own. The duty of care requires the director to act with certain minimum level of skill and deliberation. The duty of good faith requires that a director not act with bad faith, or engage in intentional misconduct.

[87] A Funder's obligation to reimburse the Independent Adjudication Committee is subject to the requirement that its expenses be reasonable. A Funder may want to give further consideration to mechanisms that would permit it to regulate the cost of the IAC without compromising the IAC's independence.

19.	**Addition of New Developers to the Framework:**	During the period beginning on the effective date of the Framework Agreement and ending [36] months thereafter, one or more entities may become parties to the Framework Agreement (*i.e.*, Developers) upon written acceptance of the terms of the Framework Agreement by such entity. Thereafter, additional entities may become parties to the Framework Agreement upon (a) written approval by the Committee if the new entity has technology or expertise that shows promise for the development of an Approved Vaccine, and (b) written acceptance of the terms of the Framework Agreement by the new entity; provided that no entity may become a party to the Framework Agreement with respect to a product after it commenced clinical trials for such product without the consent of the Funder.[88]
20.	**Addition of New Designated Suppliers:**	The Independent Adjudication Committee may (by a 2/3 vote of its members and using the standards specified in Schedule B) determine that a newly developed vaccine satisfies the conditions precedent in Section 7, subject to its waiver and modification authority, and is superior to the previously selected Approved Vaccine, whether for certain target populations or epidemiological conditions or otherwise. Upon such a determination by the Committee, the Developer of the newly developed vaccine shall have the right to become a party to the Guaranty and Supply Agreement, whereupon the Developer of the new vaccine shall be deemed a "Designated Supplier" and the new vaccine shall be deemed an "Approved Vaccine." The addition of new Designated Suppliers and Approved Vaccines shall, in each case, be subject to the original Maximum Guaranteed Amount set forth in the Guaranty and Supply Agreement.
21.	**Reserved Rights of Developer:**	Developer reserves all rights, and the Framework shall not apply, to sales of any Approved Vaccine (a) outside the eligible countries identified in the Guaranty and Supply Agreement, and (b) in the military or travelers markets.

22.	**Force Majeure**	In the event that there is a substantial change in circumstances with respect to the [disease] in the countries identified in the Guaranty and Supply Agreement, including, without limitation, its incidence, its characteristics or methods for its treatment or prevention, such that the technical specifications outlined in Section 8, or the usability requirements outlined in Section 9 no longer achieve the original objectives, the Committee shall have the right (by a 3/4 vote of its members), using the criteria set forth in Schedule C, to (a) modify the technical specifications or the usability requirements, as applicable, (b) reduce the Maximum Guaranteed Amount or the Funder's other financial obligations to reflect changes in the number of eligible countries or the incidence of untreated [disease] in those countries, or (c) terminate the Framework Agreement. Unlike other decisions of the Committee, these decisions shall be subject to judicial review by an appropriate forum to determine whether the Committee abused its discretion.[89]
23.	**Representation and Warranties:**	[TBD]
24.	**Indemnification and Insurance:**	[TBD]

[89] The Framework Agreement for an early stage vaccine could be in force for a decade or more before a vaccine candidate is presented for final review to the Independent Adjudication Committee. Accordingly, a force majeure provision permitting the Funder to alter the Framework Agreement based upon extraordinary events has been included. The force majeure clause would void or alter the Framework Agreement in the event of major changes to technology, disease epidemiology, etc. that make a vaccine either inappropriate or unnecessary or that would require a change in the specifications that would be more burdensome to the Developers. These determinations are subject to judicial review.

25.	**Term and Termination:**	The term will begin on the date that [__] Developers have executed the Framework Agreement (the "Effective Date") and, unless earlier terminated pursuant to Section 22 or this Section 25, continue until the [_____] anniversary of that date, unless a Guaranty and Supply Agreement has been entered into prior to such anniversary in which case the term shall continue until the later of such anniversary and the expiration or earlier termination of the Guaranty and Supply Agreement. Funder shall have the right to terminate the Framework Agreement (a) after the [_____] anniversary of the Effective Date if no Developer has commenced GLP toxicology studies for a product that shows reasonable promise to become an Approved Vaccine, (b) after the [_____] anniversary of the Effective Date if no Developer has commenced clinical trials for a product that shows reasonable promise to become an Approved Vaccine, (c) after the [_____] anniversary of the Effective Date if no Developer has commenced a pivotal clinical trial designed to demonstrate that a product meets the technical specifications and the usability requirements for an Approved Vaccine, (d) after the [_____] anniversary of the Effective Date if no Developer has filed an NDA or other comparable filing for a product that meets the technical specifications and the usability requirements for an Approved Vaccine, and (e) after the [_____] anniversary of the Effective Date if no Developer has entered into a Guaranty and Supply Agreement with respect to an Approved Vaccine.[90]
26.	**Remedies in the Event of Breach:**	[TBD]
27.	**Dispute Resolution:**	Arbitration under AAA rules in NY, NY.

[90] The Funders have the right to terminate the Framework Agreement if certain interim milestones have not been achieved in a timely manner. This provision is included to provide the Funders with an early out if the Framework does not appear to be stimulating productive research and development activities. This would permit Funders to pursue other, more-promising opportunities.

28. Governing Law: New York law.

29. Waiver of Immunity: If the Funder is a sovereign, it will (a) acknowledge that the transactions are subject to private commercial law, and (b) waive sovereign immunity.

30. Other Provisions: Other covenants, terms and provisions as requested by legal counsel to Funder or the Developers.

31. Exhibits: Guaranty and Supply Agreement

Schedule A to Term Sheet for Framework Agreement (Malaria)

I Technical Requirements

A. Indication:

1. Prevention of clinical episodes of Plasmodium falciparum malaria in infants and young children.

B. Target Population:

1. 0 – 4 year olds in areas of malaria transmission in Africa

C. Efficacy Requirements

1. Prevent at least 50% of clinical episodes of malaria due to P. falciparum

D. Duration of Protection

1. At least **duration to be specified** with no qualitative or quantitative exacerbation of subsequent disease

E. Interference

1. No interference with other pediatric vaccines

F. Regulatory Approval and Quality Control

1. Regulatory approval of a product, with labeling that meets or exceeds the other technical specifications and usability requirements set forth herein, in one or more of Canada, France, Germany, Italy, Japan, [Mexico], Spain, the United Kingdom, the United States, [others] and such other World Healthy Organization (WHO)-qualified countries with regulatory standards and procedures that are at least equivalent to those in the foregoing countries, as the Independent Adjudication Committee may designate from time to time (each, an **"Approved Regulatory Country"**). The Committee shall have the right to remove any Approved Regulatory Country if its regulatory standards and procedures change after the effective date of the Framework Agreement or the date that it was approved by the Committee, as applicable.

2. Manufacture of product in one or more of Canada, France, Germany, Italy, Japan, [Mexico], Spain, the United Kingdom, the United States, [others] and such other WHO-qualified countries with regulatory standards and procedures that are at least equivalent to those in the foregoing countries, as the Independent Adjudication Committee may designate from time to time (each, an **"Approved Manufacturing Country"**). The Committee shall have the right to remove any Approved Manufacturing Country if its regulatory standards and procedures change after the effective date of the Framework Agreement or the date that it was approved by the Committee,

as applicable.

3. In lieu of one or both of the foregoing requirements, the Committee may rely on an independent, unbiased, expert third party (*e.g.*, the WHO) to determine that the product meets or exceeds the other technical specifications and usability requirements set forth herein, and to ensure that the facilities where, and conditions under which, the product is manufactured are in compliance with Good Manufacturing Practices and other applicable international standards with respect to the manufacture, holding and shipment of vaccines, in each case throughout the term of the Guaranty and Supply Agreement.

II Usability Requirements

A. Dosage:

1. 1 to a maximum of 4 immunizations; EPI schedule preferred

B. Route of immunization:

1. Any, provided conducive to use on a large scale in Eligible Countries as defined in the Guaranty and Supply Agreement

C. Presentation:

1. Multi - dose vials

D. Storage

1. **to be determined**
2. Two years shelf life

E. Safety Requirements

to be specified, consistent with existing practices by UNICEF and PAHO

Schedule B to Draft Term Sheet for Framework Agreement (Malaria)

Standards and Criteria

1. Standards for Addition of New Designated Suppliers

[*Insert*]

2. Criteria for Termination of Funder's Payment Obligations

[*Insert*]

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Appendix C: Draft Term Sheet for Guaranty & Supply Agreement

1. Parties: Funder(s) and one or more Designated Suppliers.[91]

2. Purpose: Guaranty that the Designated Supplier(s) receive a specific price[92] for each sale of the Approved Vaccine[93] if the sale qualifies as a Qualified Sale (as defined below) and the Approved Vaccine is purchased for use in an Eligible Country (as defined below), provided that the Designated Supplier commits to supply the Approved Vaccine to Eligible Countries to meet their requirements.[94]

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[91] The Framework and Guaranty Agreement term sheets were designed to accommodate a variety of sponsors, despite the fact that there are substantial differences between governmental and nongovernmental organizations in areas such as funding capacity and ability to contractually commit to the Guaranty Agreement. There were discussions regarding mechanisms for ensuring that sponsors are and remain bound by their financial commitments under the Framework and Guaranty Agreements. In the end, the Working Group concluded that traditional commercial mechanisms for ensuring compliance, such as letters of credit or escrow arrangements, would be unattractive to potential Funders as they would result in increased transaction costs and unnecessarily tie up funds that could be made available for more immediate opportunities. Instead, the Working Group elected to implement a bilateral contract structure, which would permit the Developer to pursue standard contract remedies, such as money damages and specific performance, if the Funders fail to satisfy their financial commitments. The Guaranty Agreement term sheet would permit a single Funder, multiple Funders or a system where a lead Funder parcels out participations to sub-Funders. Some of the potential Funders considered by the Working Group include private foundations, developed country governments and international organizations.

[92] The Guaranty Agreement is designed so that price for each Qualified Sale could vary. For example, a higher payment could be made in the early years to permit the Developer to recapture R&D costs and capital investments in manufacturing capacity more rapidly, with lower payments in the later years.

[93] The Working Group determined that a price guaranty, rather than a minimum quantity guaranty, would be the basis for the incentive. See Chapter 4 for an explanation. The pricing structure can be designed to provide substantial insurance against demand risk for prospective vaccine developers so as to yield a net present value of revenue comparable to commercial products even under pessimistic uptake scenarios.

[94] Sufficient vaccine must be made available to satisfy the requirements of all Eligible Countries. A Developer could not select a few Eligible Countries where it wishes to offer the vaccine or cease to supply vaccine once the price supplements cease to apply.

3.	**Principal Responsibilities of Funder:**	Guarantor will, subject to Sections 7 and 13 below, irrevocably and unconditionally guaranty that the gross price paid to a Designated Supplier shall be not less than the price set forth in Schedule A (the **"Guaranteed Price"**) for each Qualified Sale of the Approved Vaccine up to the maximum number of sales specified in Schedule A (the **"Approved Maximum"**)[95]; provided that (a) the Base Price is not less than the amount specified in Schedule A, and (b) the Approved Vaccine is purchased for use in an Eligible Country. The **"Base Price"** is the amount actually paid, directly or indirectly, by the purchaser of the Approved Vaccine.[96]
4.	**Principal Responsibilities of Designated Supplier:**	The Designated Supplier will (a) use commercially reasonable efforts to create awareness of the availability of the Approved Vaccine in the Eligible Countries in order to meet the public health requirements in the Eligible Countries,[97] (b) [use commercially reasonable efforts to] establish manufacturing capacity for the production of the Approved Vaccine that is sufficient to meet the public health requirements for the Approved Vaccine in the Eligible Countries,[98] (c) obtain and maintain World

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[95] The Approved Maximum and the Guaranteed Price can be set to yield desired revenue. Price guaranties are on a per treatment--*e.g.*, course of immunization--basis, rather than a per dose basis.

[96] A Base Price concept, similar to a co-payment, was introduced to create an incentive to help ensure that qualifying vaccines are not wasted and that payments are not made for unusable vaccines. If countries, or other donors, are required to make a minimum investment in an Eligible Vaccine, then there is greater likelihood that appropriate quantities of the vaccine will be procured and that those quantities will be administered.

[97] Although the Designated Supplier has responsibility for generating awareness of the availability of Approved Vaccines in Eligible Countries, the Working Group, as noted above, recognized that the Funders must also share in this responsibility.

[98] It is critical that the Designated Supplier have adequate manufacturing capacity to meet all of the requirements of the Eligible Countries, not just the Approved Maximum amount of product. The Guaranty Agreement requires that the Designated Supplier use commercially reasonable efforts in this regard, but a higher standard, such as best efforts or an absolute obligation, may be preferable in certain circumstances. In addition, as noted below, consideration needs to be given to the contract remedy if the Designated Supplier fails to establish adequate

Health Organization (WHO) prequalification (or any substitute qualification determined by the Committee) for the Approved Vaccine,[99] and those facilities used in its production, as well as any local authorizations and approvals necessary to market and sell the Approved Vaccine in the Eligible Countries, including by complying with all adverse event reporting requirements and providing ongoing evidence of product and production safety and regulatory compliance, (d) provide the Committee with copies of all written communications to or from, including all filings or submissions to, and summaries of all oral communications with, the WHO or any other relevant regulatory agency with respect to the Approved Vaccine, (e) in connection with the marketing, distribution and sale of the Approved Vaccine, comply with the U.S. Foreign Corrupt Practices Act and all other applicable law,[100] (f) provide information as reasonably requested by the Committee from time to time in order to confirm ongoing compliance with the technical specifications and usability requirements set forth in Sections 8 and 9 of the Framework Agreement, (g) agree to be bound by decisions of the Committee acting within the scope of its authority,[101] and (h) continue to supply product to Eligible Countries to meet their requirements as provided in Section 8.

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manufacturing capacity, or otherwise meet its supply requirements, under the Guaranty Agreement, particularly once the Guaranteed Price has been exhausted.

[99] The Working Group recognized that it would be extremely costly to create an Independent Adjudication Committee that was fully capable of evaluating, approving and monitoring the Eligible Vaccines and their ongoing production. Accordingly, the Framework and Guaranty Agreements permit the IAC to rely on third parties and their procedures, such as the WHO and its pre-qualification process.

[100] Compliance with the Foreign Corrupt Practices Act was imposed to alleviate concern that illegal payments might be used to generate demand. Obviously, the purpose of the AdvancedMarkets mechanism is to generate orders for vaccines that will be used, not to simply to generate orders for vaccines.

[101] The Working Group recognized the tension between the need for certainty in the determinations of the Independent Adjudication Committee and the need for some review. Court review was deemed impractical in most circumstances. Instead, the goal is to create an IAC that would be viewed as independent by all participants in the Framework, but which is subject to review in its most important decisions.

5. Qualified Sale: The sale of the Approved Vaccine for use in an Eligible Country shall be deemed a **"Qualified Sale"** if it meets the criteria set forth in Schedule B, as modified from time to time by the Independent Adjudication Committee. In the event of a conflict between Funder and the Designated Supplier over whether a particular sale of the Approved Vaccine satisfies the criteria for a Qualified Sale, the matter shall be referred to the Independent Adjudication Committee, whose decision shall be final and binding on the parties.

6. Eligible Countries: Each of the countries listed in Schedule C shall be deemed **"Eligible Countries"**). Schedule C may be revised from time to time by the Independent Adjudication Committee in order to (a) add countries whose per capita GDP (as determined by [_____]) is less than [$____], or (b) remove countries whose per capita GDP (as determined by [_____]) is greater than [$____].

7. Cap on Total Commitment [and Termination of Commitment]: The total payment obligation of Funder pursuant to the Guaranty and Supply Agreement, including all payments and distributions to the initial Designated Supplier and any additional or replacement Designated Suppliers, shall (a) not exceed, in the aggregate, [$_____] (the **"Maximum Guaranteed Amount"**), and (b) be subject to termination or modification by the Independent Advisory Committee pursuant to Section 22 of the Framework Agreement. [Schedule C of the Framework Agreement sets forth the assumptions underlying the calculation of the Maximum Guaranteed Amount and the criteria for adjusting it if the number of Eligible Countries is materially reduced or a force majeure event occurs.]

8. Supply The Designated Supplier shall supply all requirements of the Approved Vaccines in Eligible Countries during Funding Term as provided herein and, thereafter, for a period of [10] years, or such longer period as the Designated Supplier may determine (the "Supply Term"), at a price not to exceed (a) if the Designated Supplier has received payments for the sale of the Approved Vaccine in Eligible Countries (the **"Gross Sales"**) in amounts, in the aggregate, greater than [$_____] (the **"Minimum Gross**

Sales Amount"), then the lesser of [__] percent of its fully burdened (without recapture of research and development) costs and expenses to manufacture the Approved Vaccine and [$___] per Dose (as defined in Schedule B), and (b) if the Designated Supplier has not received such payments in such amounts, then the per-Dose amount in clause (a) shall be increased by [__] percent only until the aggregate Gross Sales for the Approved Vaccine equals the Minimum Gross Sales Amount, whereupon the increase in this clause (b) shall cease to apply. [102]

9. Intellectual Property: The Designated Supplier shall own all right, title and interest in and to the Approved Vaccine; provided, however, if the Designated Supplier fails to supply Approved Vaccine in the Eligible Countries as required in Section 8 during the Funding Term or the Supply Term and, in any event, within 2 years prior to the expiration of the Supply Term, the Designated Supplier shall grant Funder, or its designee, a non-exclusive, irrevocable, perpetual, license (with the right to sublicense) solely to make, have made, use, sell, offer for sale and import the Approved Vaccine in any Eligible Country, but Funder shall not have rights to any other products and shall have no rights outside the Eligible Countries, except the right to make and have made Approved Vaccine for use in Eligible Countries. The license grant shall be royalty-free, unless the Designated Supplier has not been paid the Minimum Gross Sales Amount, in which case such grant shall be subject to a royalty of [__] percent of net sales until such time as the aggregate royalty payments to the Designated Supplier equal the product of (a) [__] percent, multiplied by (b) the amount, if any, by which the Minimum Gross Sales Amount exceeds the aggregate Gross Sales of the Approved Vaccine,

[102] The Guaranty Agreement requires that the Developer continue to make Approved Vaccines available even after the Funding Period expires on a cost-plus basis subject to a cap. If there are multiple Developers, the cap will be increased for a limited time for any Developer that does not receive a certain minimum percentage of the Maximum Guaranteed Amount during the Funding Term, which amount is defined as the Minimum Gross Sales Amount. The increase will cease to be effective, and the cap will return to the predetermined amount, once the Developer's aggregate sales equal the Minimum Gross Sales Amount. The Minimum Gross Sales Amount is intended to be a rough proxy for a return on the Developer's investment in the Eligible Product, but cannot exceed 100% of the Maximum Guaranteed Amount.

whereupon such vaccine will be fully-paid and no further royalties shall be due. [103]

10. Representation and Warranties: [TBD]

11. Indemnification: The Designated Supplier will defend and indemnify the Funder and the members of the Independent Adjudication Committee from all claims and losses arising out of or related to (a) the use of the Approved Vaccine, including claims and losses for physical or mental injury (including death) and (b) infringement or misappropriation of intellectual property.[104]

12. Term: The Guaranty and Supply Agreement shall begin on the date that the Committee designated the first Approved Vaccine and continue through such time as the Maximum Guaranteed Amount has been paid (the **"Funding Term"**), and, thereafter, until the end of the Supply Term, unless earlier terminated pursuant to Section 12.

13. Termination: The Guaranty and Supply Agreement may be terminated by either party in the event of a material breach which is not cured within 30 days of notice thereof from the non-breaching party.

In addition, Funder shall have the right to terminate the Guaranty

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[103] If the Designated Supplier of an Eligible Vaccine fails to meet its supply requirements under the Guaranty Agreement, it would be required to grant the Funder, or its designee, a non-exclusive, royalty-free (except as necessary to provide the Designated Supplier with the Minimum Gross Sales Amount, as described above) license to exploit the Eligible Vaccine only in Eligible Countries. Although less than ideal, this is intended to make the relevant technology available to the Funder if the Designated Supplier breaches its obligations under the Guaranty Agreement. However, because this provision may not provide much of an incentive not to breach, especially if a Designated Supplier has already received the Maximum Guaranteed Amount and because, even with this license, there could be a disruption of supply, potential Funders may wish to consider other penalties that would disincentivize a Designated Supplier from breaching, such as liquidated damages provisions.

[104] Indemnification was deemed to be particularly important to attract qualified members to serve on the Independent Adjudication Committee. It is contemplated that this indemnification would be similar to that which is provided for directors and officers of corporations.

and Supply Agreement (a) with respect to a particular Designated Supplier in the event the Independent Adjudication Committee determines that the Approved Vaccine of that Designated Supplier no longer satisfies the technical specifications and usability requirements set forth in Sections 8 and 9 of the Framework Agreement, or (b) in the event of a force majeure event as determined by the Independent Advisory Committee as set forth in Section 22 of the Framework Agreement.[105]

14. Addition of New Designated Suppliers: If the Independent Adjudication Committee determines (by a 2/3 vote of its members and using the standards specified in Schedule B of the Framework Agreement) that a newly developed vaccine is superior to the previously selected Approved Vaccine, whether for certain target populations or epidemiological conditions or otherwise, and the Developer of the newly developed vaccine elects to become a party to the Guaranty Agreement, the Developer of the new vaccine shall be deemed a "Designated Supplier", the new vaccine shall be deemed an "Approved Vaccine" and the new Designated Supplier shall have the right to compete with the original Designated Supplier to make Qualified Sales of the new Approved Vaccine in the Eligible Countries under the Guaranty Agreement.[106] The addition of new Designated Suppliers and Approved Vaccines shall, in each case, be subject to the cap on Sponsor's total commitment set forth in the Section 7.

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[105] A force majeure provision permitting the Funder to alter the Guaranty Agreement based upon extraordinary events has been included. The force majeure clause would permit the IAC to void or alter the Guaranty Agreement in the event of major changes to technology or disease epidemiology that render a vaccine either inappropriate or unnecessary. For example, if advances in pesticides substantially reduced the incidence of malaria in Eligible Countries, then the Funders financial obligation would be reduced accordingly.

[106] The Working Group devoted considerable discussion to the question of whether more than one Developer would be permitted to receive payments under the Guaranty Agreement. On the one hand, the Working Group felt that it was important to preserve incentives for product improvements and that it would be important to use superior products should they be developed. On the other hand, the Working Group was concerned companies might be less willing to risk large investments in early research if they faced the prospect of entry of "me too" products offering no significant advance over the original vaccine. However, many of the industry participants interviewed by the Working Group indicated that they would prefer to have multiple suppliers over a winner-takes-all approach.

15.	**Remedies in the Event of Breach:**	[TBD]
16.	**Dispute Resolution:**	Arbitration under AAA rules in NY, NY
17.	**Governing Law:**	New York law.
18.	**Waiver of Immunity:**	If the Funder is a sovereign, it will (a) acknowledge that the transactions are subject to private commercial law, and (b) waive sovereign immunity.
19.	**Other Provisions:**	Other covenants, terms and provisions as requested by legal counsel to Funder or the Designated Supplier.

Schedule A to Draft Term Sheet for Guaranty and Supply Agreement

Base Price, Guaranteed Price and Approved Maximum

A. Base Price. The minimum Base Price shall be an amount not less than [$__] per Dose (as defined in Schedule B).

B. Guaranteed Price.

C. Approved Maximum (quantity of vaccine in Doses).

* * *

Schedule B to Draft Term Sheet for Guaranty and Supply Agreement

Criteria for Qualified Sales

A. Buyer Criteria.

1. Buyers Included. Qualified Buyer include (a) UNICEF, (b) WHO, (c) Pan American Health Organization, (d) any individual Eligible Country that is purchasing for the benefit of the public sector or local non-profits, and (e) and any other buyer approved by the Independent Adjudication Committee.

2. Buyers Excluded. A pharmaceutical company, acting directly or indirectly thorough one or more intermediaries, shall not qualify as a Qualified Buyer.

B. Sales Criteria.

1. Course of Treatment. A single course of treatment, regardless of the number of individual immunizations, required to provide the desired efficacy and duration of protection shall be deemed a single "Dose" and shall constitute a single sale. For example, if 3 immunizations over a period of 2 years are required to achieve the desired efficacy and duration of protection, then the sale of all 3 immunizations, one Dose, shall be required to constitute a Qualified Sale.

2. Bundled Sales. In the event that the Designated Supplier bundles the sale of the Approved Vaccine to a purchaser with the sale or licensing of another product or service of the Designated Supplier or its affiliates, the Designated Supplier shall reasonably assign prices to (allocate revenue amounts between) the Approved Vaccine and such other products or services sold or licensed by the Designated Supplier or its affiliates to the purchaser, in accordance with the terms set forth in Exhibit B1 in order to ensure that the Designated Supplier has attributed a reasonable and equitable portion of that sale to the Approved Vaccine.

3. No Top Up. The Designated Supplier shall not seek or receive any additional compensation or value for the sale of the Approved Vaccine in an Eligible Country other than compensation from the purchaser in the form of the Base Price and the compensation from the Funder under the terms of the Guaranty and Supply Agreement; provided, however, that the Designated Supplier may seek and receive additional compensation or value if (a) additional Funders are added to the Guaranty and Supply Agreement by amendment, or (b) approved by the Independent Adjudication Committee in writing.

4. Use in an Eligible Country. If the Approved Vaccine is purchased for use in a particular Eligible Country, the Designated Supplier must have a reasonable expectation that the Approved Vaccine will actually be used in such Eligible Country. For purposes of illustrating the foregoing, if UNICEF, as it presently operates, certifies that a country has certain requirements for the Approved Vaccine, then the Designated Supplier will have a reasonable expectation that such requirements of the Approved Vaccine will actually be used in such country.

C. Other Criteria.

[*Insert other criteria*]

* * *

Schedule C to Draft Term Sheet for Guaranty and Supply Agreement

Eligible Countries

[*Insert list*]

* * *

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