Breaking Down Barriers…Building Solutions

BIO Ventures for Global Health

Advance Market Commitments to Stimulate Industry Investment in Global Health Product Development

A Report on the Biotech Industry's Perspective

February 16, 2006

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Executive Summary

New market-based incentive mechanisms are under active consideration by the Group of Eight (G8) governments to stimulate industry investment in global health product development. Under direction from the G7 Finance Ministers, the World Bank and the Global Alliance for Vaccines and Immunization (GAVI) are advising the G7 on the development of the first AMC pilot in 2006.

Under Advance Market Commitments (AMCs), donors make legally-binding commitments to create viable markets for vaccines against neglected diseases such as malaria and HIV/AIDS. BIO Ventures for Global Health (BVGH) supports the AMC concept enthusiastically. Our aim is to ensure that AMC program implementation is both cost-efficient for donors and attractive to industry's most capable innovators. The measure of these programs' success will be increased investment that accelerates the development and accessibility of innovative products for these critical diseases.

In May 2005, following the release of the Center for Global Development's (CGD) report, Making Markets for Vaccines, BVGH issued a strong written endorsement of the AMC concept. At the same time, we prepared a detailed report outlining areas of concern that must be addressed for AMCs to attract capable biotech companies to develop new vaccines for neglected diseases. The report was based upon feedback received from numerous industry executives between 2004 and mid-2005. Building on that initial work, we have held detailed conversations with biotech, large pharmaceutical companies and investors to better understand the likely biotech response to AMCs and determine whether any improvements can be made to enhance the program's likely success. This report outlines the results of our industry discussions and our recommendations for consideration by the G8.

BVGH believes that well-designed AMCs can serve as an important incentive to encourage companies to invest their own resources in research and development (R&D). The successful implementation of an AMC, however, will require extensive effort by the global health community, potential donors and industry to turn these ideas into action.

BVGH has convened meetings and held detailed discussions with more than 50 companies and more than 150 senior executives from a cross-section of the biotech and pharmaceutical sectors. These included companies already committed to developing world markets and capable innovators that might find AMCs attractive if the rewards can compete with other opportunities. We have also talked to investors whose support for such a mechanism is essential to its ultimate success.

These discussions have surfaced several questions about the details of these programs that deserve careful consideration by AMC implementers. BVGH believes that none of these issues is insurmountable, but solutions will depend on a sustained dialogue between industry and potential donors to improve the design and prospects of individual AMC programs.

Biotech companies in general are interested in applying their resources and technologies to developing world markets. They recognize the potential input that biotechnology could have on neglected diseases. Our interviews showed that CEOs are not interested in a windfall from investments in global health problems, but they are interested in fairness, transparency and flexibility. To the extent donor-subsidized markets resemble "real" unsubsidized markets, innovators will be attracted to the opportunities and willing to commit resources and risk capital.

We believe several key principles should guide development of any AMC program:

1. AMCs should mimic market mechanisms to the maximum extent possible;
2. AMCs must be credible and legally-binding, able to withstand the test of time;
3. AMCs should be of a magnitude that meets the hurdle rates for innovators' portfolios; AMCs should be funded at a level that will attract and support multiple competitors over time to drive competition and product improvements;
4. Credible market demand forecasts are essential for sizing market commitments and ensuring companies scale up manufacturing to meet developing world demand; and
5. AMCs are not a substitute for existing push mechanisms.

Our consultations revealed the following key issues for biotech companies in evaluating the value of individual AMC programs.

1. Size of the Market Commitment: The remarkable progress toward design and implementation of AMCs has been welcomed by industry. Industry executives view AMCs as a key component of the collaboration between the public and private sectors. In the course of our discussion, however, industry executives suggested that the AMC commitments, originally proposed around $3 billion, should be "right-sized" to the target markets, the degree of development risk undertaken by industry, and the reasonable expected value of other opportunities pursued by industry. The size of the commitments will be the single most important factor in attracting industry participation.

2. Continued Demand Uncertainty: While a guaranteed market creates certainty around price, it does not reduce demand uncertainty for industry participants. Industry repeatedly emphasized the importance of demand forecasting and the perceived challenges associated with selling products to developing countries. Additional steps to address this risk are critical to an AMC program's success.

3. Long-Run Pricing and Commitments: Under the current design, once the market commitment is exhausted, companies benefiting from the AMC would have to drop the price substantially for designated countries to ensure a sustainable price over the long term. This long-term price is the most difficult term to define at the outset of an AMC program. A long-run price that ends up below the cost of goods, capital and distribution would force industry to sell these products at a loss. No company will commit to a price before they know their manufacturing cost. BVGH recommends against setting a long-run price that might not reflect true capital manufacturing and distribution costs prior to the commencement of pivotal human studies on vaccine candidates. Instead, an AMC should specify a methodology for determining the long-run price when more is known about potential manufacturing costs.

4. Superiority vs. Comparability for Second Entrants: While some industry executives believe that the first to market should be rewarded with some form of market exclusivity that only allows superior products to qualify for the guaranteed price, most pointed to the complexity of making such determinations. Industry is generally more comfortable letting the market sort out these questions. This approach benefits the public sector by attracting multiple suppliers in the marketplace, thus assuring supply and reduced prices over time. BVGH does not support the superiority provision and, instead, recommends that all products that meet the specifications qualify for the AMC.

5. Structure and Function of the IAC: While there were a number of concerns raised by industry about the structure and function of an Independent Assessment Committee (IAC), principal among these was unease over the introduction of a new layer of bureaucracy into a highly regulated environment. BVGH recommends that additional bureaucracy be minimized in the design of an IAC and that the IAC's responsibilities be limited to setting product specifications and certifying that products meet such specifications.

6. Credibility of Donors and Agreements: Industry executives have extensive experience with negotiating and enforcing legally-binding contracts, including product development agreements potentially worth billions of dollars. The greatest concern expressed by industry was in dealing with multiple donors and multiple agreements, and the uncertainty that donor commitments will be fulfilled. BVGH recommends that a single entity such as the World Bank or the Global Alliance for Vaccines and Immunization (GAVI) be the contracting party with the responsibility for holding donors to their commitments.

7. Product Specifications: While BVGH found that most industry executives are comfortable with the idea of product specifications, all cautioned that actual product specifications will strongly affect the attractiveness of an AMC. BVGH strongly recommends that product specifications be set with significant input from industry to assure the practicality and feasibility of such specifications.

8. Milestone Payments or Push Funding: A number of industry executives suggested that the inclusion of milestone payments as an AMC program feature would make such programs more attractive to industry. BVGH believes that, if AMC programs are sized to attract large pharmaceutical companies, the milestone payments that biotech companies would need to participate may be provided eventually by large pharma. However, biotech companies will likely require additional sources of nearer-term funding to bridge the gap between early development and proof of concept.

Conclusion

Vaccines are well-suited as initial targets for AMCs (including high-burden diseases such as malaria, HIV, certain diarrheal diseases and acute lower respiratory infections). Drugs, microbicides and diagnostics may also benefit from similar incentive structures. Regardless of the initial target, however, the biotech and pharmaceutical industries are prepared to meet this formidable challenge. Many companies are eager for new solutions that enable them to apply their technologies toward developing world diseases, and they are excited about the AMC concept. As experience has shown, however, the detailed design of these programs is essential to their success. We firmly believe that industry must participate in the design of these programs.

Donors' shift in thinking toward market-oriented solutions can capitalize on industry's growing interest in global health. AMCs are not a magic bullet to solve all of the barriers limiting industry investment in global health product development. But they are a promising market mechanism for global health and a critical component of the incentives that will attract increasing industry commitment.

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New market-based incentive mechanisms to stimulate industry investment in global health product development are under active consideration by the Group of Eight (G8) governments. Under direction from the G7 Finance Ministers, the World Bank and the Global Alliance for Vaccines and Immunization (GAVI) are now advising the G7 on the development of the first AMC pilot in 2006.

Under Advance Market Commitments (AMCs), donors make legally-binding commitments to create viable markets for vaccines against developing world diseases such as malaria and HIV/AIDS. BIO Ventures for Global Health (BVGH)* enthusiastically supports the AMC concept. Our aim is to ensure that AMC program implementation is both cost-efficient for donors and attractive to industry's most capable innovators. The measure of these programs' success will be increased investment that accelerates the development and accessibility of innovative products for these critical diseases.

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> ***"By restoring appropriate incentives, AMCs can stimulate private research and investment, accelerate the discovery of new vaccines, save lives and contribute to economic development in a cost-effective way."***
>
> ***—Guilio Tremonti, Italian Finance Minister***

* BIO Ventures for Global Health is breaking down barriers that hinder development of new vaccines, drugs, and diagnostics to treat the urgent medical needs of the developing world. Working globally with partners in the for-profit and non-profit sectors, BVGH is building market-based solutions to catalyze industry investment in global health innovations. BVGH devotes its expertise in the business and science of biotechnology product development to improving the lives of people in the neediest regions of the world.

Overview

Creating New Global Health Markets

Innovative medicines are the product of private industry and industry responds to potentially-profitable market opportunities. BVGH acknowledges, however, that looking at the problem of neglected diseases from the standpoint of market incentives is a significant shift in thinking for the global health community.

A new plan announced in late 2004 by Gordon Brown, Britain's chancellor of the exchequer, and embraced in concept by the G8 last June, proposes to create novel market incentives to attract private sector investment in new vaccines for the developing world. Advance Market Commitments (AMCs) would create new, multibillion dollar markets for vaccines targeting diseases such as malaria, HIV and pneumococcus. Momentum for this idea continues to build.

Indeed, at their December 2005 meeting in London, the G7 Finance Ministers agreed to move forward on a pilot for the first AMC. They asked the World Bank and the Global Alliance for Vaccines and Immunizations (GAVI) to advise them on how that pilot should be developed and to provide a prioritized list of vaccine-preventable diseases for the pilot.

Putting AMCs to Work

In the spring of 2005, CGD's "Pull Working Group" published a detailed proposal showing how AMCs can correct the market imbalance.[1] CGD's proposal and a recent report by Italian Finance Minister, Guilio Tremonti, recommending the adoption of AMCs[2] are now serving as the basis for discussion with G8 officials and the World Bank. Several public private part nerships also conducted independent analysis to scope out how AMCs might be designed for their respective diseases.[3] (See Table 1.) Subsequent work by the World Bank has further refined this analysis for the six vaccines under consideration for an initial pilot: rotavirus, human papillomavirus, pneumococcus, malaria, HIV/AIDS, and tuberculosis. BVGH strongly endorses the AMC principles laid out in both of these reports and has spent the last six months gathering extensive industry feedback on the concept.

Under an AMC, donors create new, viable markets by guaranteeing to pay any developer who comes up with an effective vaccine a certain price, up to a specified number of treatments. For example, an AMC could supplement the existing market for malaria vaccines with a $3 billion market guarantee, committing to pay $15 per course of treatment for the first 200 million treatments. Developing countries would be required to contribute a minimum co-pay—perhaps $1—with donors picking up the other $14. Once the $3 billion market commitment is exhausted, the company would have to drop the price substantially for designated countries to ensure a sustainable price over the long term. By that time, the company (or companies) would have made a reasonable return on the investment.

An independent committee would oversee the implementation of the contracts and determine which products meet the pre-set qualifications—qualifications that cannot change throughout the length of the program. Any company that meets the specifications will qualify, allowing them to compete in the marketplace to receive the guaranteed price for each vaccine sale.

Value to Donors and Innovators

Well-designed AMCs can have significant value for donors. They can increase significantly the odds that industry will develop successful products and accelerate the time to development. In addition, while donors must commit to create a market up front, they pay only for success. If no one develops a successful vaccine, donors pay nothing.

Instead, companies assume the risk, investing their own resources to pursue the rewards of an attractive market. They can also help donors leverage their funds by aligning incentives around a problem and encouraging the private sector to compete for the best solution. Finally, they can improve developing world access by ensuring a sustainable supply at an affordable long-run price.

The value to innovators is also strong. AMCs are a significant contribution to the effort to more fully engage the biopharma industry in solving global health issues. They can increase the value of otherwise insufficient markets, creating incentives for companies to invest their own resources toward developing world products. And, if designed right, they can help companies use the price and volume guarantee to justify the investment of substantial capital resources.

Table 1. Proposed AMCs for Malaria and HIV Vaccines

	Sample AMC for Malaria Vaccine (CGD)	Malaria (MVI)[4]	HIV (IAVI)[5]
Design			
Size (NPV)	$3.1b	$3.3b	$3.3b
Price	$15/treatment	$21/treatment	$15–$24/treatment
Quantity	200M treatments	Up to 289M treatments (Africa); (349M total)	200M at $24 or 300M at $15 price
AMC Subsidy	$14/treatment	$15/treatment	$9–$18/treatment
Country Co-Pay	Around $1	$6/treatment	$6 or subject to company discretion; can be revised down to $1
Long-term	$1 or calculated by cost of production	$6/treatment	$6, subject to IAC waiver
Time	Sunsets at 30 years (if no qualifiers) or by certain force majeure clauses	In effect until at least 2025	N/A
Second Entrants	Must be superior to first entrant (unless qualified within one year of first entrant)	All meeting specifications qualify	All meeting specification qualify (must be result of independent R&D efforts)
Eligible Countries	All countries with GNP <$1,000/year with sufficient disease prevalence		All countries with GNP <$1,000/ year or with adult HIV prevalence >5% and per capita income <$5,000
Product Specifications			
Coverage	P. falciparum	P. falciparum	Subtypes A or C
Target Population	0–4 year olds in areas of malaria transmission in Africa	Infants	Adults
Delivery	1–4 doses, EPI schedule preferred	≤3 doses; administer on EPI schedule; can't interfere with EPI vaccines	≤3 does
Efficacy	≥50% of clinical episodes	≥80% for death or severe disease	≥50% for prevention of infection or reduction in rate of disease progression
Duration	≥2 years	≥2 years	5 years
Regulation	Approved by an "Approved Regulatory Country" as deemed by the IAC (US, Canada, France, Mexico, UK, Japan, etc)	Approved by internationally recognized regulatory authority and WHO pre-qualification	Approved by established regulatory body (FDA, EMEA) or WHO prequalification
Safety	TBD, consistent with existing practices by UNICEF and PAHO	Demonstrated Safety and Efficacy	Must meet standards required for regulatory approval
Storage	TBD	Meet WHO standards of "high-stability"	N/A

Background

Scope of the Biotech Industry

Over the past thirty years the biotechnology industry has grown from a few pioneering companies into a major industry of over 4,000 companies that represents one of the most rapidly growing sectors in the worldwide economy. The United States remains the center of excellence and the largest participant, but many countries have identified biotech as an important driver for future economic growth, so that competition in this sector is now worldwide.

The leading companies in the biotech industry now rival pharmaceutical companies in size, revenues and market capitalization. In aggregate, the biotech industry in mid-2005 had nearly $67 billion in revenues, comparable to Merck and Bristol-Meyer Squibb combined, and a combined market capitalization of $492 billion, equivalent to the top four pharmaceutical companies combined.

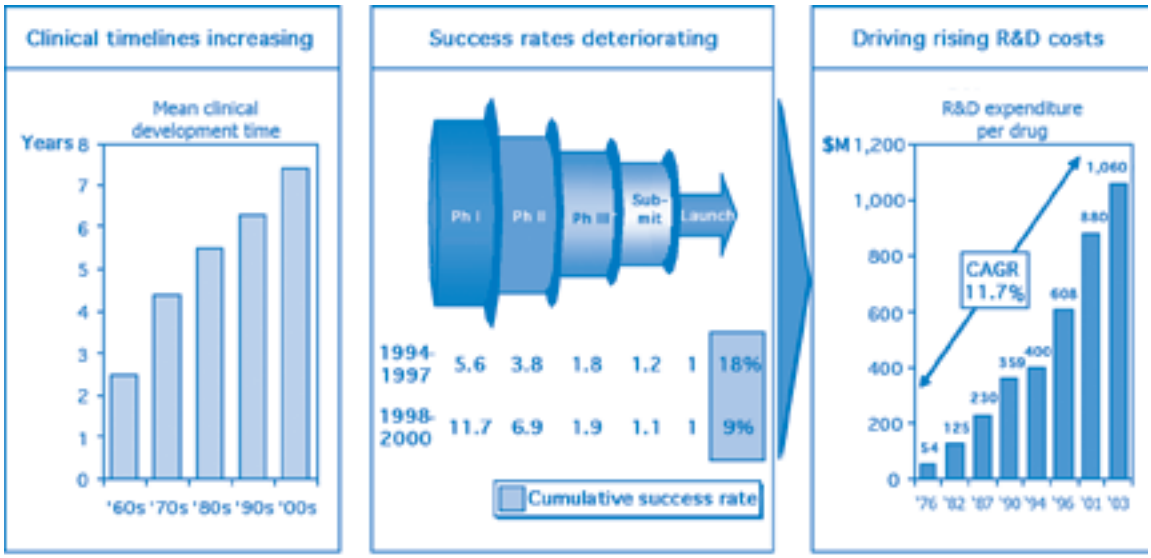
As the large pharma companies have consolidated from 41 companies in 1988 to 16 companies today, their research productivity has declined, and they have become much more dependent on innovation sourced from the biotech industry. By several estimates, as much as 60 percent of the clinical-stage pipeline in large pharma companies today originated in biotech companies, and was in-licensed or acquired by the pharma companies to augment their own internally-generated pipelines. But this in-licensing activity has been matched by a large number of biotech companies that have been successful in raising capital and developing their internal resources to become independent producers and marketers of their own products. As a result, the biotech industry is a critical repository of discovery and development expertise, and it is well-positioned to participate, and indeed lead, the process of innovating and developing vaccines, therapeutics and diagnostics to treat the diseases of the developing world.

Industry Decision-Making Process

Biotech companies are entrepreneurial enterprises with strong pressure from their shareholders to maximize their returns on comparatively limited capital resources. Faced with the high risks of failure and long development timelines, biotech companies make difficult choices about the products in their pipeline to which they can devote scarce financial resources. Companies focus on products that are viewed by their boards and shareholders as most likely to generate a high return on investment.

Unfortunately, drug and vaccine development is extremely expensive and fraught with substantial risks—and both the cost and the risk have been rising steadily over the past three decades. Development of products that make it through to commercialization typically cost between $100–300 million. However, taking into account failures and the cost of capital, the most recent estimates (2003) put the cost of developing a biopharmaceutical product at upwards of $1 billion dollars,

Rapidly Increasing R&D Costs



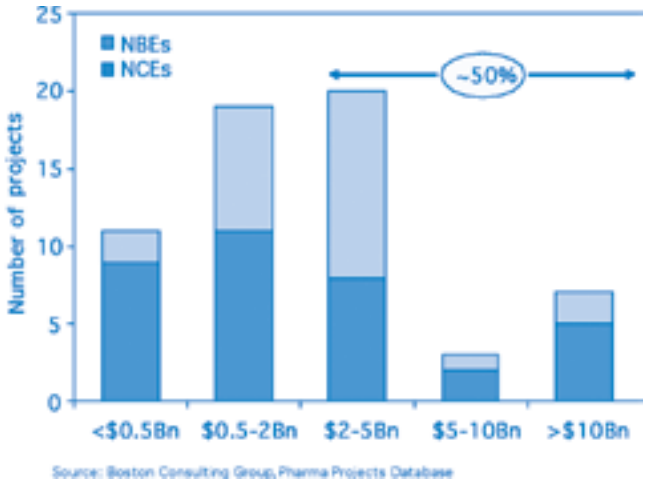
Source: Boston Consulting Group, Tufts CSDD, Parexel, CMR

driven primarily by longer timelines for clinical development and higher attrition rates. At the same time, the market for biopharmaceuticals is exerting much more significant pressure on price.

Biotech companies can be distinguished from large pharma companies in two ways. First, the large pharma companies have tended to pursue development of "blockbuster" drugs with annual market potentials of at least $500 million, and preferably exceeding $1 billion. Biotech companies will tackle smaller markets, but they also favor high value products that potentially offer high profit margins. Analysis of the compounds captured in Pharma Projects Database suggests that more than 80 percent of the novel compounds currently in phase III clinical development are targeted at annual markets of more than half a billion dollars.

Target Annual Market Size

Novel Phase III Compounds



As a general practice, companies follow a portfolio approach, measuring and optimizing value and risk for each opportunity and across their pipeline. Limited resources (both dollars and staff) force them to make tradeoffs regularly. Companies and investors examine four key risk factors when deciding whether to fund research and development: (1) capital risk (e.g. the cost of product development and manufacturing); (2) market risk (e.g. the size of the market, the ability to access that market, expected market penetration and competition);[6] (3) technical risk (including the likelihood of preclinical and clinical success), and (4) regulatory and reimbursement risk.[7] Considering these criteria, companies set priorities for their pipeline, and decide how to allocate management time and the top technical talent in the company.

As companies with technology and development platforms consider devoting resources to global health projects, they will apply these criteria, and the global health products will compete with other projects for markets in developed countries. Immediate questions and concerns that arise include (1) market size, (2) market accessibility, (3) product pricing, and (4) security of intellectual property protection. Because of the significant perceived risk with developing world products, and the extra learning involved in developing an understanding of the markets, distribution channels and regulatory requirements, returns for global health projects must be at least as high as for other product development alternatives.

Barriers to Global Health Product Development

For developing world diseases, lack of credible market opportunities and information on viable markets is a significant barrier to entry for biotech innovators. Biotech companies' reliance on pharmaceutical companies and investors to finance their research and development agenda is critically tied to the convincing demonstration of a future product's market viability. In the case of neglected diseases, the limited purchasing power of developing countries and the poor expected return on investment makes attracting such private capital or pharmaceutical partners particularly difficult. Many companies operating in this space are able to use publicly-supported grants to initiate an R&D program, but their funding often runs out as products approach clinical development.

Further, while direct support ("push funding") reduces the costs and risks of product development, and has been the driving force behind the proliferation of new research and development projects, it, alone, will not lead most companies—particularly the most capable innovators—to allocate sufficient resources, typically in the hundreds of millions of dollars, to develop fully and market these products. These companies are not in business to provide research services in return for cost coverage and a slight profit. More importantly, the cash required for clinical development usually dwarfs what is available through grant support. Because of these issues, only a very small percentage of the capable innovators are researching and developing global health products.

The underlying market opportunity ultimately drives decisions. Companies will pursue developing world projects once they are seen as significant profit opportunities. If the market is seen as sufficiently viable, a company can justify the opportunity cost of allocating capital resources from the R&D and management teams.[8]

Getting the Market Incentives Right to Attract the More Capable Innovators

Large, diversified pharma companies have the capabilities necessary to commercialize health care innovations from universities, public research institutes and, most importantly, biotech companies. Said one executive: "Ninety-nine percent of pharmaceutical innovation takes place outside our company. We have no choice but to access it." Most large drug companies rely on many smaller companies to supply a growing proportion of their development pipeline. Industry analysts estimate that about 60 percent of the current biopharma pipeline is from products initiated in small companies.

Biotech companies, on the other hand, range from very small, private companies with few employees to large, public, multi-billion dollar companies such as Chiron and MedImmune. There are 330 public biotech companies and over 1,100 private biotech companies in the U.S., and nearly 100 public and 1,700 private companies in Europe.[9] Although the top 10 biotech companies have revenues over $1 billion and their market capitalizations total over $281 billion, many of the public biotech companies have market capitalizations under $200 million. Reflecting the long timelines required for biopharmaceutical product development, most biotech companies are still unprofitable and are funded by approximately $20 billion of new equity investment that enters the industry each year. This capital is supplemented by partnership funding from pharmaceutical companies, especially for more expensive, later-stage projects.

The extraordinary diversity of the biotech industry and its track record of innovation are indispensable resources in the search for novel solutions to neglected diseases. Many biotech companies have core competencies in molecular biology, virology, immunology and infectious diseases that are just as relevant to diseases of poor countries as they are to diseases of wealthy countries. Moreover, the leading biotech companies are ideally and, in many ways, uniquely positioned to take discoveries made in academic and research institutes forward into clinical development that would lead expeditiously to registration and launch of new products into the markets that need them the most.

The key to implementing this vision is for biotech companies to view developing world markets as highly attractive and competitive targets to which they will direct their R&D capacity. They will view these opportunities through two lenses: (1) markets that they may be able to address directly, using their own manufacturing and sales forces and (2) perhaps more importantly for global health markets, markets that large pharma companies view as priorities, and that could be opportunities for major partnerships, funding, licensing or even acquisition. In short, "pull" mechanisms such as AMCs can serve as incentives for biotech companies directly or indirectly through collaborations with large pharma companies that decide to put these markets high on their own list of priorities.

As a result, AMCs can work even for early stage projects because larger biotech and pharma companies have tremendous demand for new products to feed their pipelines. They will also acquire earlier-stage technology if the market pull is there. Early-stage investors, in turn, invest in companies with products that can be partnered or acquired by large companies. The value to them comes from the attractiveness of a substantial market that the company can tackle on its own or from sale to a larger company because there is an attractive, well-understood existing market or AMC-enhanced market.

Discussion

BVGH has convened meetings and held detailed discussions with more than 50 companies and more than 150 senior executives from a cross-section of the biotech and pharmaceutical sectors, including companies already committed to developing world markets and capable innovators that might find AMCs attractive if the rewards can compete with other opportunities. We have also talked to investors whose support for such a mechanism is essential to its ultimate success. (See Appendix A for a list of individuals and companies consulted and Appendix B for the methodologies employed.)

Biotech companies in general are interested in applying their resources and technologies to developing world markets. They recognize the potential impact that biotechnology could have on neglected diseases. Our interviews showed that CEOs are not interested in a windfall from investments in global health problems, but they are interested in fairness, transparency and flexibility.

Based on our conversations with these executives, we believe several key principles should guide development of any AMC program:

1. AMCs should mimic market mechanisms to the maximum extent possible;
2. AMCs must be credible and legally-binding commitments able to withstand the test of time;
3. AMCs should be sized to compete with other product opportunities companies face;
4. AMCs should be funded at a level that will attract and support multiple competitors over time in order to drive competition and product improvements;
5. Strong market demand forecasts are essential for sizing market commitments and ensuring that companies scale up manufacturing sufficiently to meet developing world demand; and
6. AMCs are not a substitute for existing push mechanisms.

These discussions have also surfaced several questions about the details of these programs that deserve careful consideration by AMC implementers. BVGH believes that none of these issues is insurmountable, but solutions will depend on a sustained dialogue between industry and potential donors to improve the design and prospects of individual AMC programs. Concerns raised by industry experts include:

1. Size of the AMC market or commitment;
2. Continued demand uncertainty;
3. Long run pricing and commitments;
4. Superiority vs. equivalence of follow-on or second entrant products;
5. Structure and function of the Independent Assessment Committee;
6. Credibility of donors and agreements;
7. Product specifications; and
8. Program milestone payments.

I. Size of the Market Commitment

Proposed Provision: The CGD report concluded that an AMC offering total market revenues of about $3.1 billion (net present value or NPV) could stimulate pharmaceutical companies to invest in R&D.[10] Minister Tremonti's report also estimated the size of the AMC commitment needed for each of the vaccines under consideration (see Table 2). Subsequent analyses conducted by the World Bank have further refined these estimates.

Discussion: Many of the executives consulted by BVGH commented that a total market opportunity of $3.1 billion may be insufficient to change the behavior of industry. This concern merits careful consideration. Market size is arguably the most important issue in the design and implementation of any AMC, both to potential donors and industry participants. Donors will want to tender the minimum amount necessary to attract industry and avoid supporting an industry windfall for developing world products. In contrast, the more experienced vaccine companies, understanding the challenges of operating in these markets and the risk of relying on an untested mechanism, may believe they need a premium above their expected developed market returns. The process of "price discovery" will take time and continued trust building between all parties. To facilitate this discussion, BVGH believes that donors need to employ a transparent, data-driven methodology to establish the minimum market size that will motivate industry to invest in the research and development of new vaccines for any given neglected disease.

When considering a new product opportunity, companies build a financial model, including a discounted cash flow analysis for the new product, incorporating both market size and associated risks.[11] CGD's design for AMCs, however, has primarily relied on historical cost data for drugs. One large pharma executive observed that both historical data and revenue modeling should be considered when assessing the appropriate size of an AMC. BVGH recommends that any AMC include thorough financial modeling preceding the establishment of an AMC, and the models should be discussed and understood by industry.

To be credible, such models must employ well-supported assumptions about cost of capital (discount rate), development costs and product demand forecasts.[12] The need for reliable demand forecasts was emphasized in several of our consultations. Such forecasts not only drive revenue models but capital investment in manufacturing capacity as well. Reasonable demand forecasts are important to attracting industry investment and such forecasts must be available to program participants before the commencement of any large scale clinical studies or the building of significant manufacturing capacity. In addition, development costs should account for the technical feasibility of making the product. Riskier products facing tougher scientific challenges that are farther from the market will require larger markets than less risky, closer-to-market products.

As an alternative, a few executives recommended focusing not on revenue, which is fundamental to discounted cash flow analysis, but on contribution (the profit generated after manufacturing, marketing and administrative costs). While

Table 2. AMC: Commitment Size and Expected Effects

Vaccine	Nominal value ($ billion)	Years to estimated availability	Net Present Value ($ billion)	Nominal yearly contributions by all donors	An AMC would…
Rotavirus	0.8–1.0	2	0.7–0.8	250–320	• influence decisions to expand capacity to meet a larger share of developing country demand; • accelerate access to vaccine.
Human Papillomavirus	0.8–1.0	2	0.7–0.8	250–300	• create incentives to invest in the incremental studies and production capacity to serve developing world.
Pneumococcus	1.0–1.5	4	0.8–1.1	180–270	• create incentives to invest in the incremental studies and production capacity to serve developing world.
Malaria	4.5–5.0	11	2.4–2.6	300–330	• attract additional investment in establishing proof of concept and developing and producing viable products; • influence decisions to expand capacity and accelerate access to vaccine; • encourage investment for second generation products.
HIV/AIDS	5.5–6.0	15	2.3–2.5	240–260	• attract additional investment in establishing proof of concept and developing and producing viable products; • influence decisions to expand capacity and accelerate access to vaccine; • encourage investment for second generation products.
Tuberculosis	5.5–6.0	15	2.3–2.5	240–260	• attract additional investment in establishing proof of concept and developing and producing viable products; • influence decisions to expand capacity and accelerate access to vaccine • encourage investment for second generation products.

Source: Report to the G8 Finance Ministers, London, December 2, 2005.

a given product in a company's portfolio may represent a significant percentage of the company's revenue, it may, due to the product's associated costs, contribute little to bottom line earnings. Products with little or no sales and marketing costs will contribute more to earnings than those with higher costs, as a percent of product revenue. While this would take into consideration significant differences between developed and developing world markets in the costs associated with generating revenue, there seems to be no consensus on whether such costs would be higher or lower.

As another point of comparison, we believe it is helpful to look at the vaccine programs that companies are pursuing today. Table 3 shows current and estimated markets for new vaccines and near-term vaccines that are close to market. Most of these vaccines anticipate annual sales far exceeding $1 billion, whereas the annual sales of a vaccine supported by a $3 billion AMC would be approximately $300 million per year over 10 years.

As donors size AMCs, these numbers provide an important reference point. Donors need demand forecasts as well to develop a realistic understanding of the existing "natural" market for target products before determining whether and how much an AMC needs to enhance the existing market to attract industry investment. Products with stronger developed world markets (including possible travelers and military markets) may need much smaller amounts to supplement the existing market. Products with small developed world markets (such as malaria) or that need to be heavily tailored to developing world needs (possibly HIV) will need larger market commitments.

An initial question for donors to consider is which companies to target with AMCs. We believe that AMCs at a minimum must be attractive to large biopharma companies to spur the interest of smaller biotechs and investors. As discussed in the background section of this report, large biopharmaceutical companies are the investment engine for much of the biotech sector. Newly-marketed products, particularly those for primary-care markets, are typically launched by multi-national firms and are the result of 1) internal R&D projects, 2) acquisitions from or of smaller companies, or 3) partnerships with smaller companies. The exceptions are limited to products that can be developed through smaller clinical development programs and marketed with a comparatively small, specialist sales force. Vaccines, as community-based products, are likely to require the more extensive clinical development and distribution forces of larger pharma companies.

BVGH Recommendations:

- *In addition to historical data, the donor community should employ transparent, data driven financial models when evaluating the appropriate size of any AMC program;*

Table 3. Current and Estimated Global Markets for New Vaccines and Select Vaccines Under Development

Vaccine	Status	Annual Market	Large pharma involvement
Pneumococcus	On market; late-stage development	• Currently >$1 billion, primarily in N. America • Estimate $2.3–$3.2 billion per year by 2010	✓
Rotavirus	On market; late-stage development	• Estimate $1.8–$2.4 billion per year by 2010	✓
HPV	Late-stage development	• Merck estimates $1.55 billion in annual US and EU sales by 2010 • GSK estimates global market of $4–7 billion per year by 2010	✓
Dengue Fever	Development	• Estimate $300–$400 million annual market	✓
Meningitis	Late-stage development	• Currently $275 million per year • Estimate $1.1–1.5 billion per year by 2010	✓
West Nile Virus	Development	• Expected to be low; companies pursuing with push funding to help provide proof of concept for platform technologies	
Cholera	On Market/ Development	• Estimate travelers' market of $400 million per year	

Source: BIO Ventures for Global Health based on industry-reported data.

- *AMC programs should commit to providing demand forecasts prior to the commencement of any large scale clinical studies or the construction of any significant manufacturing capacity;*
- *AMC markets should be sized to compete with markets for current and anticipated products in development by multinational firms; and*
- *The donor community should anticipate AMC commitments may need to exceed the $3.1 billion (2005 dollars) recommended by the CGD if they are to compete with products currently in development by large biotech or pharmaceutical companies.*

II. Continued Demand Uncertainty

Proposed Provision: While an AMC market is defined based on a guaranteed price and volume (creating a minimum total market size), the proposed AMC is not a commitment to purchase a pre-set volume from a successful manufacturer. The burden still rests on the manufacturer to "sell" the product to developing countries in order to benefit from the guaranteed market.

Discussion: While a guaranteed market creates certainty around price, it does not reduce demand uncertainty for industry participants. Several industry executives commented that without sufficient demand certainty, companies will still take a conservative approach to scaling up manufacturing capacity—already a significant problem with today's vaccine market. This demand uncertainty is magnified in the minds of many executives by the uncertainty associated with selling into unfamiliar and unpredictable developing countries. Industry repeatedly emphasized the importance of demand forecasting and the perceived challenges associated with selling products to developing countries. Central to any investment in manufacturing capacity will be the strength of the demand forecast and credible guidance from the global health community.

Policy makers must find ways to reduce the demand uncertainty for manufacturers if AMCs are to fully succeed. This need is particularly acute for an AMC designed for late-stage products.

BVGH Recommendations:

- *Explore where improvements to the existing procurement system can help address continued concerns about demand uncertainty (including moving up the time that procurement contracts are issued and issuing multi-year contracts); and*
- *Help build country demand for AMC products and provide improved demand information to relevant innovators (such as through GAVI ADIPs).*

III. Long-Run Pricing and Commitments

Proposed Provision: In exchange for guaranteed pricing for new vaccine sales up to a certain volume of products, the CGD proposal would require companies that benefit from the guaranteed price to commit to produce and sell treatments for the period following application of the AMC subsidy in eligible countries at a fixed, affordable price.[13] For example, under CGD's proposed contract structure for malaria, in return for a guaranteed price of $15 per treatment for 200 million treatments, companies would be required to provide vaccines to eligible countries at $1 per treatment.[14] In contrast, MVI's proposed AMC for a malaria vaccine calls for a guaranteed price of $21 per treatment and a $6 long-run price. IAVI also proposes a long run price of $6.

Discussion: During our industry consultations, we found no resistance to the *quid pro quo* arrangement of a guaranteed initial price in exchange for lower long-run pricing. Industry is familiar with product price erosion over time due to increased competition. While vaccine products historically have not been subject to generic competition, prices do decline when more than two firms produce competing vaccine products. The inevitability of lower margins over time is accepted by industry as a part of doing business.

However, companies have expressed a range of concerns about the implementation of such a provision in practice. First, it is completely foreign to industry to make long-term supply commitments in the absence of firm demand forecasts and well-defined manufacturing costs. We found no biotech or pharma executives, regardless of company size, willing to commit to a long-run price at the outset of an AMC program before they know their manufacturing costs. Manufacturing costs are typically not known until the company is scaling up products for Phase III clinical trials, and do not stabilize (and become most efficient) for a company until two to three years into product commercialization.

Second, current vaccine technology has become more complex and expensive than that employed in the traditional vaccine market. For example, new technologies such as protein subunit vaccines are more expensive than traditional live, attenuated virus vaccines. In addition, some vaccines, such as those for malaria, are likely to consist of a combination of antigens and proprietary ingredients (such as adjuvants) which may require them to pay royalties to third parties. Such vaccines face increased research and development costs and higher fixed and variable marginal costs.[15] Many in both the

public and private sector now acknowledge that the "pennies per dose" vaccine for more tractable pathogens with complex life cycles and sophisticated defenses against immune response is likely not feasible. Given what we know about future vaccine technology, the $1 price envisioned by CGD is well below likely costs. Long-run prices must allow each company to at least recoup its costs of capital, production and distribution.

Third, companies have expressed concern whether a higher long-term price, such as that proposed recently by IAVI and MVI, would be affordable to developing countries. If the co-payment is too high, countries will not purchase the vaccine. We agree with MVI's conclusion that public sector co-payments may be necessary to fund the long-term purchase of some vaccines even at the lower, long-term price.

Fourth, companies raised concerns about binding themselves to cover long-run supply if demand is too low. To address this concern, IAVI proposes that the Independent Assessment Committee (IAC) waive this requirement for companies that only supply a small share of the market. We support this revision.

Alternatives: In our consultations we explored several alternative approaches to setting the long-run price, including those under active consideration by policy makers. One approach is to use a cost-plus mechanism, where participating firms would agree to reveal their actual costs of manufacturing the vaccine and receive that cost plus a small (10 to 15 percent) margin over and above the cost. This methodology would benefit from the certainty of calculating the manufacturing costs based on actual experience and a known margin at the outset. However, most companies (including all multinationals) consider this data highly sensitive and are reluctant to disclose it to outside parties. While a few biotech executives did express a willingness to share such data in exchange for certainty, we are concerned that such a requirement could severely limit industry participation in an AMC program.

In their work on AMCs, IAVI considered another approach—setting a ceiling price and offering relief in the form of cost-plus pricing if the ceiling price becomes untenable for participating companies. Aside from the issues of cost plus pricing previously discussed, there is some attractiveness to this approach in that disclosure of costs by firms is not required. Firms that are able to work within the ceiling price would never be obliged to reveal sensitive cost information. Also, by setting a ceiling, firms will be required to make choices early on that assure efficient and cost effective manufacturing. By offering relief if the ceiling price becomes untenable, participating firms will not feel trapped by the program and are more likely to participate as a result. The downside to donors is that the long-run price could change, thereby reducing the overall value of an AMC program by failing to assure a sustained supply of vaccine to eligible countries.

Several alternative approaches are currently under discussion by the World Bank and GAVI, which may address some of the hurdles stated above. BVGH believes this issue is not an insurmountable one, but it needs further discussion with both industry and the public sector.

BVGH Recommendations:

- *An AMC should not attempt to set a long-run price at the outset unless the price is based on likely costs of future vaccines and subject to renegotiation at a later time if shown to be unworkable;*
- *Long-run pricing must be sufficient to cover fully-allocated production costs (including costs of maintaining the manufacturing facilities and opportunity costs for their use) and contribute to profitability (even at a significantly reduced margin); and*
- *Many manufacturing arrangements in industry deal with issues of long-term pricing, supply and cost-reduction programs. Donors should look to industry to provide substantive guidance in drafting these provisions.*

IV. Superiority vs. Comparability for Second Entrants

Proposed Provision: CGD's report proposes that second entrants to the market should only be eligible for an AMC if they can demonstrate superiority over the initial product that qualified.[16]

Discussion: While several industry executives strongly believe that the first to market should be rewarded with some form of market exclusivity (i.e. only allowing superior products to qualify for the guaranteed price), most pointed to the complexity and difficulty of making such determinations. For example, how would the IAC determine superiority of a two-dose, oral vaccine that has lower efficacy than a three-dose, parenteral vaccine with slightly higher efficacy? Industry executives were quick to point out that there are even inherent differences in "equivalent" vaccines currently on the market. Industry is generally comfortable competing against similar products and is far more comfortable letting the market sort out product demand. Furthermore, if market demand sets sales, then the first product entrant will gain the initial advantage but not be able to prevent market penetration by a better product.

In addition, there is great value to the public sector of having multiple suppliers in the marketplace. No single firm is likely to be able to supply all the global need for any vaccine. In addition, multiple suppliers can fuel innovation and reduce prices over time.

BVGH Recommendations:

- *AMC programs should not require second entrant products to demonstrate superiority over first entrants in order to qualify for the program.*

V. Structure and Function of the IAC

Proposed Provision: The CGD report calls for an Independent Assessment Committee (IAC) to oversee the arrangements and the implementation of any AMC. Eligibility requirements would be set in advance and could not be raised over time. The IAC would also be responsible for determining eligibility for the AMC.

Discussion: When asked about the structure and function of an independent adjudication committee, industry responses ranged from questioning the necessity of an IAC to recommending that it be modeled on the U.S. Food and Drug Administration. Most executives, however, were concerned with introducing another layer of bureaucracy into an already bureaucratic process and recommended that the IAC have a limited role focused on product specifications and product qualification. To the extent that the IAC is viewed as another regulatory agency that industry needs to deal with, it introduces significant additional risk. Predictability and transparency in decision-making of the IAC are key criteria for attracting potential innovators and investors.

With regard to the composition of an IAC, all executives felt that independence from donors and industry was critically important. The credibility and neutrality of the IAC are paramount. Most felt, however, that reasonable mechanisms exist for appointing such a body and for managing and preventing conflicts of interest.

BVGH Recommendations:

- *The scope of IAC responsibilities should be clear and limited primarily to setting product specifications and determining whether products meet the specifications; and*
- *The IAC should follow the decisions of existing regulatory bodies, including the ability to withdraw eligibility.*

VI. Credibility of Donors and Agreements

Proposed Provision: The essence of an AMC is a legally-binding contract between the program sponsor(s) and participating companies.

Discussion: While there is a consistent low level of concern within industry as to the enforceability of contracts with governmental entities, legally-binding contracts are a routine part of doing business and BVGH received few negative comments during our consultations. There is, however, little interest in having multiple government donors as the contracting parties. Most executives would like to see an intermediary organization as the contracting entity with the responsibility for collecting AMC funds from donors. The organizations most often suggested as the contracting party and/or collector of funds were the World Bank and GAVI.

BVGH believes that the design and implementation of AMCs will be greatly facilitated by the establishment of a secretariat at the earliest possible date.

BVGH Recommendations:

- *A single entity such as the World Bank or the Global Alliance for Vaccines and Immunization (GAVI) should collect donations and hold donors to their commitments; the same, or possibly a separate, entity should serve as the contracting party.*

VII. Product Specifications

Proposed Provision: In order to assure donors real value for the money invested in an AMC program, products will need to meet a product specification to qualify for the price guarantee. Product specifications will be unique to each specific vaccine.

Discussion: To facilitate discussions with industry, BVGH provided executives draft specifications for a malaria vaccine prepared by MVI and for an HIV/AIDS vaccine prepared by IAVI. Both draft product specifications included criteria for technical features such as efficacy, duration and dosage regimen (See Table 1).

Industry executives were actively engaged in evaluating the draft specifications. They made it clear that product specifications will directly influence the success or failure of any AMC. On the whole, most companies were comfortable with the inclusion of product specifications and noted that they

view them in much the same way they do setting the package labeling (product indications) at the beginning of the development process. In fact, most companies expressed support for setting the bar high at the outset, rather than a "race to the bottom," provided that the bar can be lowered if necessary.

Several companies also indicated an interest in being able to apply to the IAC early to determine if alternative product specifications will be acceptable, assuming regulatory approval, before making the commitment to pursue extensive product development. They also expressed a strong interest in reviewing and providing input into the product specifications before they are set since industry is best positioned to understand what is technically and scientifically possible to bring products to the marketplace. BVGH agrees that product specifications will benefit from industry input.

Several executives, however, questioned the need for product specifications, citing already stringent regulatory requirements for vaccines and the industry's interest in, and history of, developing relevant products. While they understand that donors need some assurance that their money would be well spent, they argue that market demand can protect these funds: poor or expensive products will not sell. These and other executives also cautioned against overly burdensome specifications which could have a chilling effect on industry interest in an AMC program.

The purpose of the discussion here is not to provide detailed feedback on the proposed product specifications for malaria and HIV vaccine AMCs, but concerns raised with several specific proposals are worth noting to illustrate the difficulties. First, IAVI's draft AMC for an HIV vaccine proposes that qualifying vaccines must show protection of at least five years to ensure cost-effectiveness at a global level. However, to avoid delaying adoption, they propose that vaccines meet a minimum duration standard of two years to be eligible for purchase but at less than the full price.[17] The balance would be paid retrospectively when additional data demonstrates that the desired standard (5 years) had been met. While we understand their intent, we believe there are significant barriers to implementing the provision in practice. First, there is no precedent for this type of purchase arrangement in the existing marketplace and it raises a host of difficult administration, bookkeeping and tax issues for companies that are likely unworkable. Second, it does not recognize the significant difficulty and costs for companies to conduct detailed post-market studies in low-income countries. We suggest that donors weigh the benefits and costs of vaccine characteristics in the context of likely country demand, and make a clear-cut decision on what it will purchase as part of the program at the time of product licensure. Delays in payment will not be workable for industry.

BVGH Recommendations:

- *Given that product specifications will, in part, determine industry's willingness to participate in an AMC, BVGH recommends that industry have significant input into the setting of specifications.*

VIII. Program Milestone Payments

Proposed Provision: The aim of an AMC is to create a profitable market for a new vaccine where one would not otherwise exist. Since markets do not provide milestone payments during the course of development, neither do AMCs as proposed by the CGD.

Discussion: Foremost in the minds of the majority of executives offering feedback to BVGH was the cost of developing vaccine products and the need for millions of dollars in cash. While this is a shared concern between biotech and large pharmaceutical companies, not surprisingly, the issue was most acute for biotech executives. These executives were quick to point out that AMC programs do not address the need for cash during development.

A number of executives and investors suggested that the inclusion of milestone payments could make AMCs more attractive for early-stage companies and investors, helping offset early cash needs. Early-stage investors, particularly venture capitalists, are looking for returns in a shorter time frame (five to seven years) than the full R&D cycle typical for drugs and vaccines. Yet they invest in very early-stage product concepts because clear progress against a large market opportunity often allows them to harvest the investment via a sale of the young company or shortly after an initial public offering (IPO) where shares are sold to the public.

Some argue that, while milestone payments may create a much-needed revenue stream for companies, if AMCs are structured to appeal to large pharmaceutical companies, they are likely to occur naturally in the new, AMC-created marketplace without sponsor intervention. The smaller players would generally team with the larger ones, just as they do now, with the pharmaceutical partner providing milestones to the smaller companies as part of their deal terms when there is a large market to address. Milestone payments would also change the dynamics for AMCs significantly and ask donors to assume some of the risk—something that may be far less appealing to potential donors. Some donors already assume development risk by funding R&D (so called "push" mechanisms), investing heavily in a number of products currently in development. A combined structure of push funding and milestone payments is significantly more complex and would complicate the AMC structure.

Others, however, question whether it will take too long for large pharma to signal their interest, thereby limiting the impact of an AMC on biotechs. Biotechs need significant capital to conduct pivotal studies, often before large pharma shows any interest. These companies are not convinced that an AMC alone is sufficient to bridge the gap between these costly studies and the point when they can team with large pharma. In addition, for those vaccine companies that aim to be full service companies and take the products to market themselves (or in partnership with an emerging market manufacturer), upfront funding may be critical for their participation.

BVGH believes that, to fully engage the biotech sector in global health product development—and interest investors—some form of payments (through traditional "push" mechanisms) is necessary to supplement any AMC program.

BVGH Recommendations:

- *Ensure that additional push funding is available to bridge the funding gap for early-stage clinical work.*

Conclusion

Keys to Success

Significant progress has been made on all sides to better understand how an AMC mechanism can work. Interest in this mechanism within the biotech community also continues to grow. Several key findings from our discussions with industry are worth highlighting. Most importantly, AMCs are not a magic bullet to solve all of the barriers limiting industry investment in global health product development. Other solutions, including push funding, are needed.

It will also take many years to bring early-stage vaccines to market. To engage industry, donors need to create credible and legally-binding commitments, able to withstand the test of time. Biotech and pharmaceutical companies must be certain that the commitment to purchase will still be there in 10 to 15 years when a new vaccine is eventually developed.

In addition, the market commitment must be the right size. It is safe to assume that the larger the commitment, the more players that will engage. The key for donors is striking the right balance between maximizing the social value of the investment and ensuring broad participation in the program, particularly from industry's more capable players. Analysis by CGD shows that large investments that create new markets for vaccines can have significant social benefit. Industry is prepared to think about target market size even for very early-stage vaccines.

Finally, we share donors' interest in developing a mechanism that ensures long-term access and affordability. Understanding how to address the long-run pricing issue in a way that is workable to industry requires continued dialog and creativity.

As progress on the design of the first AMC pilot continues, we strongly encourage the donor community to continue to engage industry in these discussions. Donors' shift in thinking toward market-oriented solutions can capitalize on industry's growing interest in global health. Ultimately, we believe a continued dialogue between all parties will strengthen any AMC program and increase greatly its ultimate chance of success.

Summary of BVGH Recommendations for Potential Donors

- Employ transparent, data-driven financial models when evaluating the appropriate size for an AMC program.
- Commit to provide demand forecasts prior to the commencement of any large scale clinical studies or the construction of any significant manufacturing capacity.
- Size AMC markets to compete with markets for current and anticipated products in development by multinational firms.
- Explore where improvements to the existing procurement system could help address continued concerns about demand uncertainty (including moving up the time that procurement contracts are issued and issuing multi-year contracts).
- Help build country demand for AMC products and provide improved demand information to relevant innovators.
- Make long-run pricing sufficient to cover fully-allocated production costs (including costs of maintaining the manufacturing facilities and opportunity costs for their use) and contribute to profitability (even at a significantly reduced margin).
- Look to industry to provide substantive guidance in drafting manufacture and supply provisions since many manufacturing arrangements in industry deal with issues of long term pricing, supply and cost reduction programs.
- Allow all products that meet the product specifications to qualify for the AMC program (no superiority provision).
- Limit the scope of IAC responsibilities primarily to setting product specifications and determining that products meet those specifications.
- Create a single entity such as the World Bank or the Global Alliance for Vaccines and Immunization (GAVI) to serve as the contracting party with the responsibility for holding donors to their commitments (or split the IAC and contracting party functions between two organizations that work closely together).
- Allow industry significant input into the setting of specifications since product specifications will have everything to do with industry's willingness to participate in an AMC.
- Ensure that additional funding (push funding) is available to bridge the funding gap for early-stage clinical work.
- Continue to explore AMCs further with industry and understand the potential interaction between push, pull and possibly interim pull (milestone) mechanisms.

Appendix A. Companies Consulted

Acambis
Aeras Global TB Vaccine Foundation
Alloy Ventures
AlphaVax, Inc.
Ardana Bioscience
Ardana PLC
AVANT Immunotherapeutics, Inc.
Bavarian Nordic Group
Baxter Healthcare Corporation
Benitec, Inc.
Biocon India
Bio-Manguinhos/Fiocruz
Biomira Inc.
Biotechnology Industry Organization
Burrill & Company
CancerVax Corporation
Chiron Corporation
Cooley Godward LLC
CV Therapeutics™
DNA Bridges, Inc.
FIT Biotech Oyj Plc.
Genentech, Inc.
GenVec, Inc.
Genzyme Corporation
Gilead Sciences
GlaxoSmithKline
Hawaii Biotech, Inc.
Hollis-Eden Pharmaceuticals, Inc.
Human Genome Sciences
The Immune Response Corporation
Institute for One World Health
Malaria Vaccine Initiative
MaxCyte, Inc.
Maxygen
MedImmune, Inc.
Merck and Company
Mountain View Pharmaceuticals, Inc.
MPM Capital
Nabi Biopharmaceuticals
Napo Pharmaceuticals, Inc.
Nektar Therapeutics, Inc.
Omni Genetics, Inc.
OSI Pharmaceuticals, Inc.
Perseus-Soros BioPharmaceutical Fund
Sanofi Pasteur SA
Serum Institute of Inda
SG Cohen and Co.
Targeted Genetics Corporation
Vaccine Research Institute of San Diego
VaxGen, Inc.
Venrock Associates
Vical, Inc.
Wyeth

Appendix B. BVGH Approach

Biotech Conferences:
BVGH presented the AMC concept at several industry conferences, including The Biotech Meeting at Laguna Niguel (2004), the BIO CEO and Investor Conference (2005) and the BIO Annual International Convention (2004 & 2005). Conference attendees were encouraged to comment on the AMC concept and their feedback is reflected in this report.

Townhall Meeting:
In April 2005, BVGH hosted a townhall-style meeting on global health issues and industry in Palo Alto, California, sponsored by Cooley Godward LLC. Local biotech executives received formal invitations to attend. The agenda included a discussion of the AMC concept and industry feedback is reflected in this report.

One-on-one Interviews:
BVGH conducted one-on-one and group interviews with biotech companies and investors during 2005. Several of the consultations were conducted jointly with IAVI and MVI.

Endnotes

1. Making Markets for Vaccines—Ideas to Action, Center for Global Development Advance Market Commitment Working Group, Washington, DC, 2005.

2. Giulio Tremonti, Minister of the Economy and Finance, Italy. Advanced Market Commitments for Vaccines: A New Tool in the Fight Against Disease and Poverty. Report to the G8 Finance Ministers. London, December 2, 2005.

3. Advance Market Commitment for Malaria Vaccines: A Discussion Document from the PATH Malaria Vaccine Initiative dated September 9, 2005; An Advance Market Commitment for AIDS Vaccines Accelerating the Response from Industry: for review and comment dated September 8, 2005.

4. MVI employed industry-standard financial modeling to estimate the AMC size for malaria.

5. IAVI grossed-up the CGD AMC size recommendation, based on the technical difficulty associated with HIV/AIDS vaccine development.

6. For large pharma, expected revenue is $500 million to $1 billion per year. For emerging biotechs, the number is still in the several hundred million.

7. In the case of AMCs, reimbursement and regulatory risk could include the risk of "changes in the rules", changes in the "payment situation", changes in the "success criteria," or the adjudication process. Payments that are predictable and transparent vastly lower the risk assessment—a critical issue when deciding to start a project.

8. Add to this the fact that these diseases are still not well understood, the science is complex, and the prospect of discovering a successful new treatment or vaccine remains risky. For every five product candidates that enter clinical trials, statistically only one will emerge successfully. This combination of high market risk and high technology risk—whether real or perceived—has preempted, indeed prevented, active industry involvement.

Further, sizeable markets alone are not enough. Companies face significant hurdles developing products in uncertain markets where they have limited or no experience. Weak public health infrastructure and distribution systems in these countries make it difficult to test lead drugs and vaccines in clinical trials or get successfully-developed products to those that need them. Navigating multiple regulatory systems to pursue product registration in disease-endemic regions also presents a host of complex challenges. In addition, few adequately understand who the purchasers are and how the procurement process works. To further complicate the picture, the developing world is not a singular concept, so market approaches may vary dramatically by country. Because of all this uncertainty, and the costs involved in developing sufficient expertise to operate in these markets, all but the largest pharmaceutical companies have expressed that developing world markets must be even more compelling than others to lead them to pursue development.

9. Ernst and Young, Beyond Borders: The Global Biotechnology Report 2005. EYG No. CW0006.

10. The use of NPV here is unconventional. As we understand the CGD report's use of the term, NPV is used here to mean the total net sales over the future life of a vaccine in 2004 dollars. When looking at the source material for the CGD report, Grabowski, *et al.*, Returns on Research and Development for 1990's New Drug Introductions *Pharmaco-Economics 2002;* 20 (Suppl. 3): 11–29, the authors, using conventional methods for discounted cash flow analysis, calculate the average NPV for the 118 drugs analyzed at $45 million in year 2000 dollars.

11. Analysis currently underway at the World Bank employs similar methodology.

12. These are admittedly complex models that are very sensitive to certain variables, particularly discount rate (cost of capital) and development costs. Grabowski, *et al.* used an 11% discount rate in their models based on four capital asset pricing models (CAPMs) for the industry. This 11% rate does not include an expected 3% long-run inflation rate, making a 14% nominal rate realistic for these models. Interestingly, the authors found that the hurdle rates in 2001 for six pharmaceutical firms ranged from 13.5% to over 20%. The authors also tackled the development cost variable, concluding that the capitalized research and development costs for the mean new chemical entity in their 1990 to 1994 sample was $686 million (year 2000 dollars). Recent estimates of the current cost of R&D for a new chemical entity exceed $1 billion. MVI projects the development costs of a malaria vaccine at close to $1 billion.

13. CGD report at 4.

14. *Id.* at 33.

15. MVI document

16. The report contains an exception to this requirement if the second entrant qualifies within the first year of the initial product to qualify for an AMC.

17. IAVI report

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