

Valuing Industry Contributions to Public-Private Partnerships for Health Product Development

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Initiative on Public-Private Partnerships for Health



Initiative on
Public-Private
**Partnerships
for Health**

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© Initiative on Public-Private Partnerships for Health, Global Forum for Health Research
Published by The Initiative on Public-Private Partnerships for Health,
Global Forum for Health Research, May 2003
ISBN 2-94 0286-09-4

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Glossary of Abbreviations

ABPI	Association for British Pharmaceutical Industries
BD	Becton Dickinson
CRO	Contract Research Organizations
DFID	UK Department for International Development
GATB	Global Alliance for TB Drug Development
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
IAVI	International AIDS Vaccine Initiative
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
IGH	Institute for Global Health
IND	Investigational New Drug
IOWH	Institute for One World Health
IP	Intellectual Property
IPR	Intellectual Property Rights
IPPPH	Initiative on Public-Private Partnerships for Health
LDC	Less Developed Country
MMV	Medicines for Malaria Venture
MSF	Médecins Sans Frontières
MVI	Malaria Vaccine Initiative
NIH	National Institutes of Health
NPV	Net Present Value
PATH	Program for Appropriate Technology in Health
PPP	Public-Private Partnership
PR	Public Relations
R&D	Research and Development
TB	Tuberculosis
TDR	UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases
UCSF	University of California, San Francisco
WHO	World Health Organization

1. Introduction

1.1 Background

The Initiative on Public-Private Partnerships for Health commissioned researchers from the Institute for Global Health (IGH) at the University of California, San Francisco, to evaluate the contributions that private industry has made — both compensated and “in kind” — to public-private partnerships (PPPs) involved in the development of new treatments for diseases prevalent in the developing world, including HIV/AIDS, tuberculosis (TB), malaria and lesser known neglected diseases such as Chagas disease. This paper presents the findings of this study and makes recommendations for future collaboration with industry.

The findings are based on primary and secondary sources. The team conducted in-depth interviews with industry representatives and experts, PPPs and foundations. Detailed responses from an IPPPH-administered survey supplement the information gathered in these meetings. Secondary research included literature searches, analysis of databases on PPP deals and analysis of press releases.

1.2 Overview

Evidence that PPPs are getting “good value” in return for their payments to private industry is beneficial to both PPPs and industry. PPPs can use the results to support their decisions to contract with private industry, and to help leverage additional funding from public and non-profit funding sources. Industry can use the results to support two claims: first, that they are participating in a global and multi-sectoral effort to accelerate R&D for new drugs and vaccines to tackle neglected diseases; and second, that they are making significant, valuable contributions to the deals done with PPPs (i.e. not just drawing scarce resources away from the public sector).

In **Section 2**, we briefly examine the organization of the R&D process and the division of labour

between the public and private sectors. Changes in this process over the past 20 years, especially with the entry of many small, specialized biotechnology research companies, the move by major pharmaceutical companies to contract out many more stages of the process and the development of contract research companies to fill demand gaps have important implications for the PPP model. Together they make the theoretical concept of a “virtually” organized, publicly funded, privately conducted research entity more of a practical reality.

In **Section 3** we review different methods applied in the for-profit world for structuring and assessing the value of business deals. These methods provide the tools needed to assess and compare the value of deals done by PPPs with private companies.

In **Section 4**, following the identification of categories of contributions that companies might make to PPPs, we present six illustrative case studies. Categories of contributions include:

- licensing out of a compound for the PPP to develop
- working under contract on a new product based on PPP specifications
- participation on an advisory board
- provision of technology and scientists to work on a specific project.

The former two types of contributions are more likely to be compensated than the latter two, which are often made in kind (non-compensated). In each case, we describe the kind of deal involved and highlight the value of the role played by industry. We then distinguish between contributions stipulated in the contract and those that are made in kind.

Section 5 includes the general findings, together with a number of recommendations from companies in the life sciences industry on ways of improving collaboration between PPPs and the private sector. The conclusions are presented in **Section 6**.

1.3 Definitions

In order to estimate the value of industry contributions, it is necessary to distinguish between those that are compensated and those that are made in kind. Compensated contributions by industry are those in which a PPP pays industry for goods or services in a contractual agreement or business deal. The contributions made to PPPs by industry in return for a payment are the ones most likely to be reported in press releases and financial statements. These contractual arrangements are the same as transactions that occur between two business entities under normal market conditions, with two key exceptions: in some cases, industry provides goods and services to PPPs at cheaper rates than it would charge a pharmaceutical or biotech company for the same market transaction; in other cases, industry makes outright in-kind contributions for which it expects no monetary compensation. For industry, the motivation may include a sense of corporate social responsibility and a willingness to act in the interest of the “public good”. It may also be based on expectations of positive public relations — a motive often referred to as “enlightened self-interest”¹.

Regardless of the motivation for such actions, these in-kind contributions represent value to the PPPs, even though it is often difficult to measure in financial terms. In-kind contributions, such as hours worked, technologies made available or contract work completed, are easier to value than in-kind contributions such as the presence of an influential

scientist or CEO on an advisory board or the fact that work by experienced private companies gets done more quickly and effectively than if PPPs had to rely solely on public sector organizations with limited experience of drug development.

We also distinguish between PPP deals involving “*shared*” partnerships (in which each partner contributes approximately 50% of the cost of the project) and those based on “*contract*” partnerships (in which the industry partner agrees to provide only what is specified and compensated through the contract). In a contract partnership, the PPP drives the strategy and product criteria and designates the milestones. The study revealed that big pharmaceutical company partners are much more likely to participate in shared partnerships (as equal partners) than are smaller biotech companies. In some cases, pharmaceutical companies’ in-kind contributions have matched the value of the PPP investment, making them equal partners, each contributing 50% of the value. Biotech partners are less able to contribute in kind and most of the work they do is likely to be fully compensated in the PPP deal. Both types of partnership have advantages and disadvantages. While shared partnerships with pharmaceutical companies offer PPPs greater value in the form of in-kind contributions, they also involve the loss of some control over the direction of the project. And while contract deals enable PPPs to retain full control of the project, they also have to put in over 90% of the money.

¹ Ariel Pablos-Mendez, personal communication.

2. Changing patterns in pharmaceutical R&D and their implications for PPPs

2.1 Recent trends in the R&D process

Developing a new drug is a complex, expensive and risky process. It requires the mobilization and coordination of different kinds of expertise and activities over a protracted period of time. It can easily take over 10 years to turn a viable idea into a pharmaceutical product. The average cost of bringing a new drug to market is estimated at US\$800 million—US\$1 billion. And despite great advancements in technology in specific stages of the R&D process, the success rate has not improved significantly. The chance of a drug candidate passing through all the hurdles from the development of an idea to the launch of an approved product is one in 100 at best. Although companies have become better at finding leads, they still have problems developing products that are stable, safe and efficacious².

Over the past 20 years, the structure of the pharmaceutical industry has gone through several major changes. Before the arrival of the biotechnology industry, drug development was conducted primarily by R&D groups within a small number of large, fully-integrated, global pharmaceutical companies. The development of biotechnology companies challenged both the traditional methods used to discover a drug and the way R&D was organized. Biotechnology companies have been successful in identifying novel molecules, usually proteins, and their contribution has been centred on the first four stages of the R&D process (Figure 1-page 4). However, only a handful so far have demonstrated the ability to take a product through the development process and on to the market without the help of big pharmaceutical companies. Today, the majority of biotechnology companies depend on external funding sources, few are earning any revenue, and only a small percentage of them are breaking even.

A process of specialization according to stages in the product lifecycle has now started to evolve. Pharmaceutical companies, in an effort to ensure returns on investment in line with shareholders' expectations, increasingly seek out deals with biotechnology companies to co-develop products and/or to serve as the sales and marketing arm once a product has been approved for market. With company valuations by Wall Street driven primarily by the expectation that blockbuster drugs will be developed, deals with biotech companies, in theory at least, enable pharmaceutical companies to increase the scope and diversity of their research operations. Meanwhile, biotechnology companies are dependent on pharmaceutical companies to provide the vast resources and expertise needed to take a drug right through from research to market (Figure 1: stages 5-11).

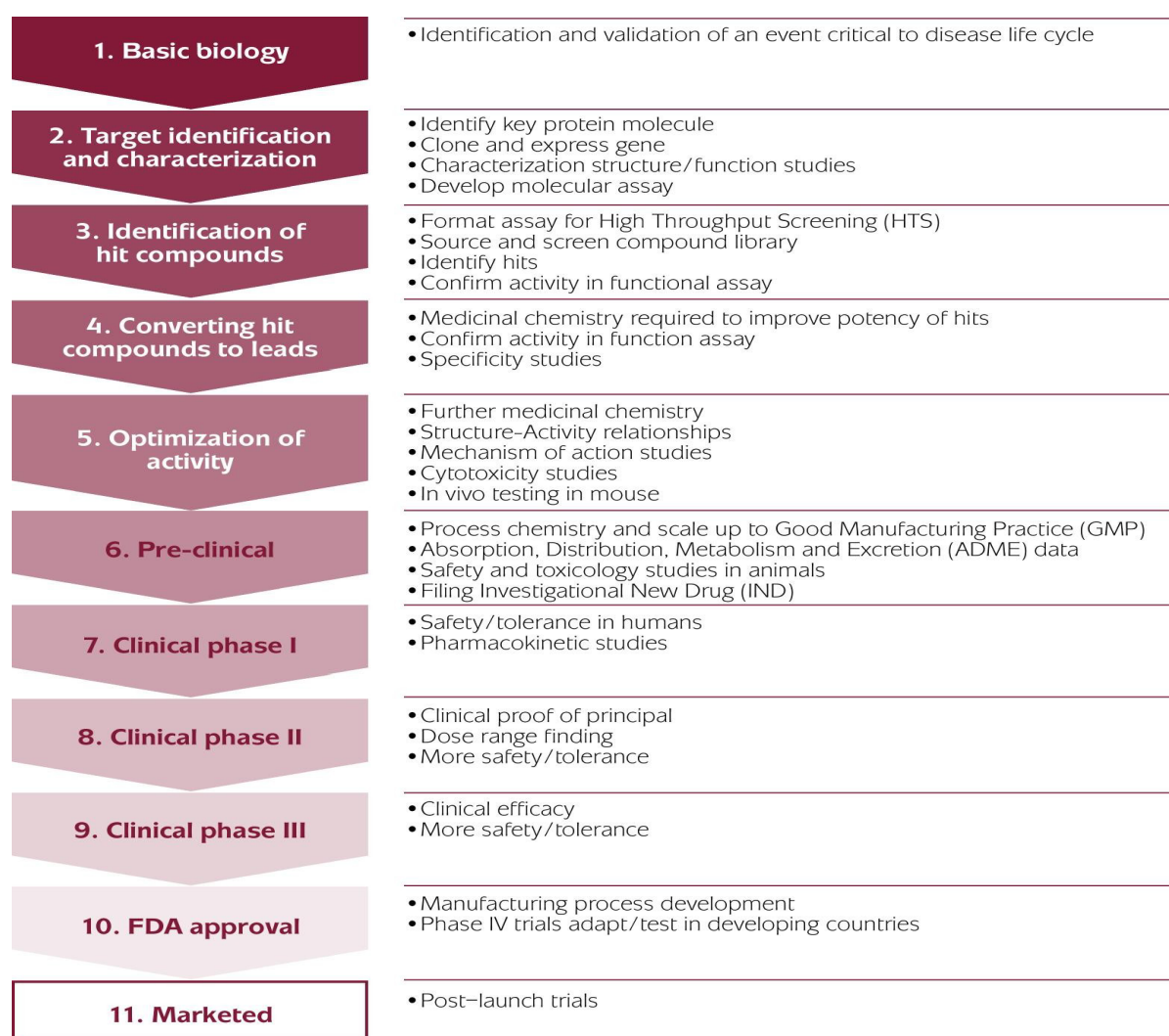
These types of deals are the lifeblood of the biotechnology industry. More than half of the biotech drugs approved in 2000 were either co-developed or marketed by pharmaceutical companies. "Of the 15 protein-based drugs that generated sales in excess of US\$200 million in 1999, most were either co-developed with pharmaceutical companies or licensed out to major companies for development and marketing"³.

From the pharmaceutical companies' standpoint, it is estimated that by 2005, more than 50% of their revenues will come from products that were discovered, researched and developed outside their organization. Through a learning-by-doing process, both pharmaceutical and biotech companies have developed sophisticated expertise in business development. Once an overlooked group that worked on market research and competitive intelligence, business development groups have evolved as key players in many pharmaceutical and biotech companies. Today, good business

² Society for Medicines Research (SMR)-www.prous.com/smr01.

³ Ernst and Young, 2001, 68.

Figure 1. The drug R&D process



development directors are a scarce and much sought-after resource.

Meanwhile, company deals are not limited to pharma/biotech. There are pharma/pharma and biotech/biotech deals as well. According to Ernst and Young surveys, smaller biotech companies often prefer to work with other, albeit larger, biotech companies to improve the chance that their product takes priority in the partner's pipeline.

2.2 Product development PPPs⁴

Up until now, the life sciences industry — comprising pharmaceutical companies, biotechnology companies, diagnostic manufacturers and medical device/equipment companies — has contributed to product development for neglected diseases in a fragmented and relatively unsustainable way. In some cases, new interventions for neglected diseases have been discovered serendipitously during clinical trials. Elsewhere, discoveries have been made through trial and error, by using products approved for alternative applications, including some initially developed for animal use (e.g. benznidazole and nifurtimox to treat

⁴ Drawn from Kettler and Towse "Public-Private Partnerships for Research and Development: Medicines and Vaccines for Diseases of Poverty", OHE. 2002.

Chagas disease and ivermectin to treat onchocerciasis). In general, these neglected disease products rarely took priority either in researchers' time or company resources — suggesting that product development may have taken longer than necessary and that the projects risked being dropped on grounds of competition for resources rather than lack of efficacy.

Product development PPPs have been established to ensure that viable projects involving neglected diseases are adequately funded and their progress accelerated. All have a similar mission: to make strategic and targeted investments in companies and academic or institutional research centres to develop pipelines of drugs and vaccines to treat or prevent diseases of poverty. The PPP managers are responsible for ensuring that the projects are given priority.

Among the product development PPPs are initiatives such as the Malaria Vaccine Initiative (MVI), Medicines for Malaria Venture (MMV), International AIDS Vaccine Initiative (IAVI), the Institute for One World Health (IOWH) and the Global Alliance for TB Drug Development (GATB). Key founders and funders of these PPPs include the Gates Foundation, the Rockefeller Foundation, the World Health Organization (WHO), the Association for British Pharmaceutical Industries (ABPI), the International Federation of Pharmaceutical Manufacturers' Associations (IFPMA), the World Bank, Médecins Sans Frontières (MSF) and a number of governments (e.g. the UK and the Netherlands). Table A (page 6) lists some of the prominent PPP deals.

Individual PPPs employ different strategies for funding, management and R&D. Most are based on some version of a “virtual R&D model” where the PPP manages the R&D process but funds external partners to conduct the work. These organizational differences reflect disease-specific differences in the scientific challenges, the existence or absence of treatments in the pipeline or on the market, and the existence of a disease-focused industry infrastructure on which to draw.

Examples of these differences include:

- MMV works only on malaria drugs and seeks to balance a portfolio in terms of risk and opportunity by investing in early discovery, preclinical and development projects. To date, MMV has relied on large company or academic-led teams to conduct its work. All the academic

projects involve company team members. MMV, for example, provides financing, contacts and process advancement assistance. It has made a strategic decision to work, wherever possible, with a major pharmaceutical company – an essential partner, it maintains, for the manufacture, regulatory approval and distribution of any successful drug candidates. Although MMV does not seek to own a compound outright or to control the entire worldwide intellectual property rights (IPR), it does insist on receiving the exclusive marketing rights for the malaria product in low-income countries where the disease is endemic.

- GATB aims to acquire TB compounds on licence and to establish and manage a “virtual” team to develop each new product, drawing on the expertise of different companies, Contract Research Organizations (CROs) and institutes. The strategy is based upon a concept promulgated by a number of private biotech companies.
- IAVI seeks to “own” or co-own the HIV vaccines and supporting technology in which it invests. Companies, to date all small biotech companies, conduct the scientific research and development work in cooperation with one or more academic research centres, under IAVI contract. The scientific community working on AIDS vaccines is itself unsure of what approaches are most likely to work, especially for the strains of the disease that prevail in the developing world. As a result, IAVI is investing in a range of different delivery and vector technologies in order to determine the most effective approach. IAVI will have to provide support for any successful technologies throughout the R&D process, unless it can attract a major vaccine producer to take over the development process — an implicit but so far not an explicit component of its product development strategy.
- IOWH seeks to acquire drugs for all parasitic diseases on licence – ideally those already at the investigational new drug (IND) stage or later – and bring them through clinical trials to market. The small staff manages product assessment and clinical trials through a combination of in-house scientific skills and outsourced or contracted research in the country of the clinical trials. IOWH has an explicit goal to help build up and use manufacturing and testing facilities in the developing world.

Table A. A selection of PPP deals

<i>PPP</i>	<i>Industry Partner</i>	<i>Project</i>
Global Alliance for TB Drug Development	Chiron	Chiron licensed out PA824. GATB will proceed with preclinical and clinical development.
Medicines for Malaria Venture	Bayer	Bayer will conduct work to discover and develop improved artemisinin derivatives for the treatment of uncomplicated, non-severe malaria.
Medicines for Malaria Venture	GlaxoSmithKline (Philadelphia)	Modify a class of inhibitors (being exploited for osteoporosis) and apply them to a malaria drug target identified by Univ. California at San Francisco researcher Dr. Phil Rosenthal.
Malaria Vaccine Initiative	Apovia	To complete all development work and regulatory processes required for ICC-1132-a pre-erythrocytic malaria vaccine candidate-to proceed into clinical trials.
Malaria Vaccine Initiative	GlaxoSmithKline Biologicals	To demonstrate the safety, immunogenicity, and protective efficacy of RTS,S -a pre-erythrocytic malaria vaccine candidate- in children in malaria-endemic countries.
Institute for One World Health	Celera	Celera licensed out CRA-3316 for Chagas disease. IOWH will leverage a network of non-profit and government resources to get the drug to market.
International AIDS Vaccine Initiative	AlphaVax	Apply AlphaVax's ArVä delivery technology to an antigen identified at the University of Cape Town. Contract not renewed in 2002.
International AIDS Vaccine Initiative	Becton Dickinson	Charitable contribution of funding and equipment. Separate R&D collaboration on flow cytometry for HIV vaccine includes Becton Dickinson (BD) performing in-house flow cytometry services.
International AIDS Vaccine Initiative	Therion	Test HIV genes in MVA virus constructed from HIV subtype C with Therion's delivery technology. Therion will manufacture doses for early trials, then transfer the technology to an Indian firm.
International AIDS Vaccine Initiative	Targeted Genetics	Apply Targeted Genetic's AAV gene therapy technology to a vaccine based on the HIV subtypes most prevalent in east and southern Africa.

2.3 Implications for PPPs of changes in the R&D process

Changes in the organizational structure of R&D within the life sciences industry have important implications for product development PPPs and their industry partnerships. First, the growth and variety of deals and partnerships within the industry underline the fact that PPPs need industry partners to succeed. Even fully integrated pharmaceutical companies look to outside industry partners to help with specific tasks along the R&D process.

Second, a precedent already exists for the pursuit of R&D by way of partnerships across companies and organizations. A number of biotechnology companies have experimented with “virtual” R&D, including DevCo Pharmaceuticals, Pozen Inc., Arachnova Limited and Fulcrum Pharmaceuticals. Initial successes have shown that skilled negotiators and project managers are vital in the early success cases, giving credibility to the “virtual” approach that most PPPs have adopted.

Thirdly, the promotion of business development departments within companies means that when doing deals with industry, PPPs are negotiating with a new breed of professional skilled in making deals. In anticipation of working with these business development experts, it is essential that PPPs understand the companies’ goals and expectations, as well as the environment in which they operate. Most small to medium biotechnology companies do not have significant revenues (many have no marketed products), are not yet breaking even, and find funding extremely difficult to obtain. These companies are under intense pressure from their shareholders to meet earnings expectations. As a

result, an effective business development executive has to become a skilful, well-connected negotiator, and an often over-worked risk manager for the company’s portfolio.

This does not mean that the company and its representatives do not, at some level, share a philanthropic interest to work with the PPPs to improve health in developing countries. Rather it suggests that business development executives are under significant constraints and will assess a potential PPP deal in the same way as they would a commercial deal i.e. whether the deal has the potential to earn a reasonable return for the company over and above the costs incurred.

In view of this, it is essential that PPPs make a business case to their potential industry partners and construct a deal that includes something that each partner will value. Value for the industry partner can come from assets other than money, such as positive public relations (PR), proof of technology, data, training, know-how and introductions to new markets. These benefits are more or less attractive to a company depending on that partner’s specific needs at the time the deal is struck. However, without a strong business case, and a win/win proposition, a PPP deal will be difficult to construct, or will be difficult to sustain as soon as other more pressing projects or opportunities arise for the industry partner.

As a first step towards evaluating company contributions to PPPs, it is useful to consider the methods used in the for-profit sector to assess the value of deals between companies and between companies and public/academic organizations.

3. Deal structures and value assessment methods

3.1 Asset valuation: valuing contributions to deals

When evaluating deals in the life sciences industry it is essential to keep in mind the fundamental rule of market economies that the value of an asset is dictated by demand. The following section outlines a number of empirical methods for valuing a product or a deal. They can be used as tools to help estimate ranges but cannot be expected to produce a definitive answer. Ultimately, the value of an asset is dictated by what the market will bear, not by the cost of production.

We focus first on the different theoretical approaches used in commercial opportunities where a potentially lucrative market can be estimated. Then we examine how each method might be applied in situations where a commercial market does not exist, as in the case of many of the PPP deals.

3.2 Valuing the asset

An extensive literature exists on the elusive subject of valuing an asset or contribution. Although some authors have tried to establish “scientific” formulas for valuation, it is not an exact science. The following should be used as a set of tools and guidelines to structure the negotiation between partners. Four different methodologies are commonly used to value an asset/contribution: (i) net present value; (ii) resource cost analysis; (iii) historical data; and (iv) cost of the next best alternative. Other theoretical approaches, such as option pricing have been omitted here as they are of little practical use in assessing PPP deals.

3.2.1 Net present value approach

The approach most commonly applied to deals involving commercial entities is the calculation of the net present value (NPV). This method entails estimating the future cash flows generated by the

asset and adjusting the value of those cash flows for the risk, costs and time involved in achieving them. This approach is most often used when the asset that is being valued is, or is likely to be, a marketed product or service. NPV is less likely to be used to value expertise, human resources, or a non-marketed contribution. The key to this process is estimating the cash flow⁵ the asset will generate. Each entity participating in the deal will need to determine if the investment that is required, combined with the expected risk, is justified by the potential “return”: in this case, cash flow generated over the life of the asset.

To calculate the NPV of a particular investment opportunity, we need to consider some basic rules of finance. The first rule is that a dollar received today is worth more than a dollar received tomorrow. This is based on the assumption that a dollar can be invested today in safe securities that will return more than one dollar in the future. Therefore, when evaluating any investment, it is important to consider whether the dollar invested today in a given investment opportunity will generate a greater return than investment in safe securities. The expected rate of return from a safe investment is called the *riskless rate*. For instance, if we were to invest US\$100,000 in government securities with a guaranteed return of US\$102,000 in one year, our riskless rate would be 2%:

Expected Return from riskless investment (riskless rate) = (expected profit/investment) = US\$2,000/US\$100,000 = 2%.

⁵ Cash Flow is the result of inflows and outflows over a period of time (month, quarter, or year) and can be defined in a number of ways. A typical and simple measure of cash flow is to take net income (revenue less all costs) and add back any depreciation, amortization, and other non-cash charges (as given in the income statement). Generally speaking, cash flow is the best measure of a company’s ability to continue operations, make capital investments, service its debt, and pay dividends to its investors.

An investor's "hurdle", or "discount" rate should be higher than the riskless rate of return because they are presumably taking risks by investing in other opportunities and should be compensated for this. In other words, an investor would not invest in an alternative, potentially more risky investment if it did not return more than 2% each year. The hurdle rate is set by each individual or company and is defined as its estimate of an attractive rate of return. The more risky the investment, the higher the return must be, as a risky investment is discounted significantly. This supports the second rule of finance: a safe dollar is better than a risky one.

These rules apply to biotech companies, as well as to any company or individual making an investment. Senior management must look for investment opportunities for their organizations which will maximize returns over a given period of time. This is because individual and institutional investors who have invested their own or their clients' money in these companies expect to maximize their respective returns. To determine if a company is making a sound investment, the company calculates the NPV of the future cash flows the project/asset they are investing in will generate, i.e. they will estimate what the predicted future cash flow is worth in today's dollars by discounting the projected dollars back to the current year based on the number of years and the hurdle rate they have set for investments. Net present value is then the present value of the expected future cash flows minus the cost of the investment.

This NPV approach is best suited for deals where there is a well-defined market for a product. Each partner can evaluate the future sales and development risks on their own and is able to focus on the areas of disagreement as they work towards a creative solution that protects both parties sufficiently.

Implications for PPPs

When considering a deal between a PPP and a commercial entity, the Net Present Value approach could be effective, bearing in mind that the business development team within a pharmaceutical company is likely to approach a PPP deal with exactly the same mindset as it does a commercial deal. So, for instance, a PPP needs to think about a company's NPV model for a particular opportunity. When the commercial market is very small, it is difficult to get a positive NPV, or make

an attractive return on investment. Therefore, a PPP must reduce the risks for industry partners to ensure the NPV is positive for products with limited markets (e.g. products for neglected diseases affecting primarily poor populations). This could be accomplished, for example, through the PPP providing up-front funding of early research, fixing profit margins or guaranteeing sales volumes, reducing expenses by sharing costs, or speeding up drug registration through government partners. If the PPP can reduce the risks associated with the development of the product, the NPV model can become attractive again.

3.2.2 Resource-based analysis approach

Under this methodology, the contribution/asset is valued by measuring the time and effort that goes into its creation. This method is most often used when the cash flow of the future product is difficult to project (i.e. the product is at a very early stage), or when the contribution is not a major component of the final product.

For instance, a newly formed proteomics company may wish to access the flow cytometry services of a major corporation for a single process that they are running. The challenge is to derive the estimated value of flow cytometry contribution towards the advancement of the science. In this situation — with no defined market and no understanding as to how critical the services contributed will be for the end goal — how does the proteomics company value the contribution of the flow cytometry services to the creation of their product?

One possible approach would be to measure the contribution based on the resources, time, materials and personnel that have been dedicated to or invested in providing the flow cytometry services. By using a formula that estimates the cost of labour in that market at a specific skill level or at the rate that the service is offered generally in the market, the companies can negotiate a value for the contribution. The more "customization" that is required, the more likely the estimation of time and effort to complete the deal will vary.

This approach can be used for any situation where one company provides a service or difficult-to-value asset to another, most commonly when that asset contributes to a product that is yet to be completed (i.e. there is not yet a market to help value this input). This allows one company to estimate the

“value” of their contribution based on the time and resources required to perform the task. How that company gets compensated for the contribution (cash, equity or debt) will depend on the case and negotiations.

3.2.3 Comparables data approach

For each type of deal, there is often a comparable deal that has already been done in a related area. These comparable deals set a baseline for determining the value of a new deal. This method of using comparable deals as a benchmark for negotiations saves time and starts all parties at a similar place. However, negotiations can then get stalled by differences over the extent to which the benchmark case is comparable or different.

For example, one of the new classes of compounds currently in development for the treatment of osteoporosis is based on parathyroid hormone (PTH) analogues. It is believed that this class of compounds may not only slow the rate of bone loss (as do existing anti-resorptive agents) but could actually regenerate bone. A handful of companies are working on this new technology. However, most projects (with the exception of Eli Lilly, which has a product in pre-registration with the FDA) are still in the preclinical or early human trials.

In this particular disease area, it is difficult for a company to find a partner willing to make a significant investment in a still very risky preclinical compound. Therefore, companies with similar compounds, such as NPS Pharmaceutical, Emisphere, and Beaufour Ipsen should, in theory, anticipate a challenging deal environment. However, circumstances changed in April 2002, with just one deal. At this time, Unigene, a company which also has a PTH analogue in preclinical development, signed a licensing deal with GSK that, according to BioWorld (Biotechnology News and Information Source) is valued at US\$150 million. This amount is comprised of up-front payments, milestone payments and royalties in exchange for Unigene granting GSK worldwide rights to market the technology.

With this deal finalized, other companies with a similar approach now have a comparable deal with which to leverage for negotiations with potential partners. Both parties, of course, will try to use this additional information in their favour. For the small developer of a PTH analogue, they now can explain why their technology is better than

Unigene’s and why they deserve a better deal than US\$150 million, creating a floor for valuation. By contrast, the potential licensing partner can argue that Unigene’s product, unlike the others, is an oral formulation and therefore a better and more valuable asset. This Unigene and GSK deal could actually create a ceiling for valuation (not just a floor).

Regardless of how the data is used, comparables do provide additional information that helps put some boundaries around valuation of the asset. However, this methodology should be considered as just one of the components, not the entire picture. When used in combination with an NPV valuation, and/or resource-based valuation, a more complete picture can be assembled about the value of the technology.

Implications for PPPs

When considering the role of comparables in PPP negotiations with pharmaceutical and biotechnology companies, it is possible that over time these comparables could become more valuable. For instance, once more deals have been done for malaria, tuberculosis and AIDS vaccines or in specific functional areas such as development or manufacturing, the PPPs will be better equipped to handle negotiations, drawing on experience from their own or other PPP deals. Until that time, PPPs face a difficult challenge in finding commercially-oriented comparables that can be applied to the non-profit sector.

3.2.4 Cost of next best alternative approach

Another possible method for valuing a deal is to compare the cost of the next best alternative. In any deal negotiations, a “walk-away” value is established. For instance, if a company has an interesting technology that appears to be important for a neglected disease, that company may be the final judge on what the best price for the technology is. In the absence of a comparable or NPV value, PPPs have problems assessing whether the company is offering a good deal or not. For instance, in the example above, if Unigene demanded US\$200 million up front for their technology, and GSK was not willing to pay this amount, their next best alternative would be to use a different type of hormone analogue (inferior to PTH), for which they might only be willing to pay US\$100 million. If there were no other PTH analogues in development, GSK would probably just walk away

from osteoporosis altogether and find a new product in another market.

Since PPPs focus on products with no significant markets for financial returns, there are relatively few companies that can provide a “next best alternative.” A PPP may find only one company that has developed a leishmaniasis product that seems to have any significant therapeutic value — leaving the PPP with no option but to do a deal with this company if it wants to gain access to the technology. Thus doing a deal with that particular company can never be measured objectively as a good or bad investment, since “walking away” is not an option.

Under this scenario, the PPP must consider what happens if a deal is not struck, or how that money might be otherwise spent to further their objective. Evaluating all other options and their cost is an important ingredient in the evaluation of any deal that is on the table.

3.3 Converting these valuation approaches into a deal

All of these approaches can be useful in constructing a deal. Successful negotiators often experiment with each of these tools prior to entering into a negotiation, each with different sets of assumptions and scenarios: the best case, the most probable and the worst case. This helps the negotiator to understand how their potential partner might approach the issues.

The key to success in deal making is to anticipate and understand what a future partner will want from the deal. In addition, it is important to note that a partner’s needs, and what they value, can change over time. For example, if a pharmaceutical company has recently received adverse publicity, they may value the positive public relations (PR) that could come out of a PPP deal more than they would at another time.

4. PPP Deals

4.1 Characterizing industry deals with PPPs

PPPs operate in an environment where negotiations bring together parties with different expectations and motivations. In a commercial deal, both companies are driven to seek the greatest financial return with the least amount of risk. But in a PPP-to-company deal, the motives are less clear cut. While to some extent, companies are motivated to do a PPP deal in order to contribute to social returns, by definition, the stronger motivating factor is the pursuit of commercial returns. All companies face challenges when participating in a PPP deal. For a publicly traded company⁶ these include pressures from the shareholders to develop financial business cases to justify the costs of a small or non-existent return and to demonstrate that, in undertaking a PPP project, the company will not be exposed to any added legal or liability risk. Companies do not want to do anything that will expose them to major technology or legal risks, such as pushing through a project that would not stand up to U.S. regulatory requirements.

Small private companies that depend on raising start-up, venture capital and public funding to advance their pipeline enjoy even less flexibility to follow through on a PPP deal. Private venture capitalists, like public shareholders, expect a high rate of return from the biotech companies in which they invest. Even if the deal comes with resources to finance the neglected disease project, venture capitalists worry that the company's researchers will get distracted from their primary mission – to bring them and other investors an attractive return on their money to compensate them for their risk capital.

Industry contributions to PPPs have largely been restricted to well-defined deals on specific projects⁷. However, the amount of time and resources committed varies greatly between pharmaceutical companies and biotech companies. Large companies are better placed to “donate” people, technology, and know-how to support a PPP project. By contrast, a small biotech company can rarely afford to devote any resources over and above those tied into the funded contract. In the case of small companies with a single technology, PPP funding may actually cover a considerable percentage of direct project costs.

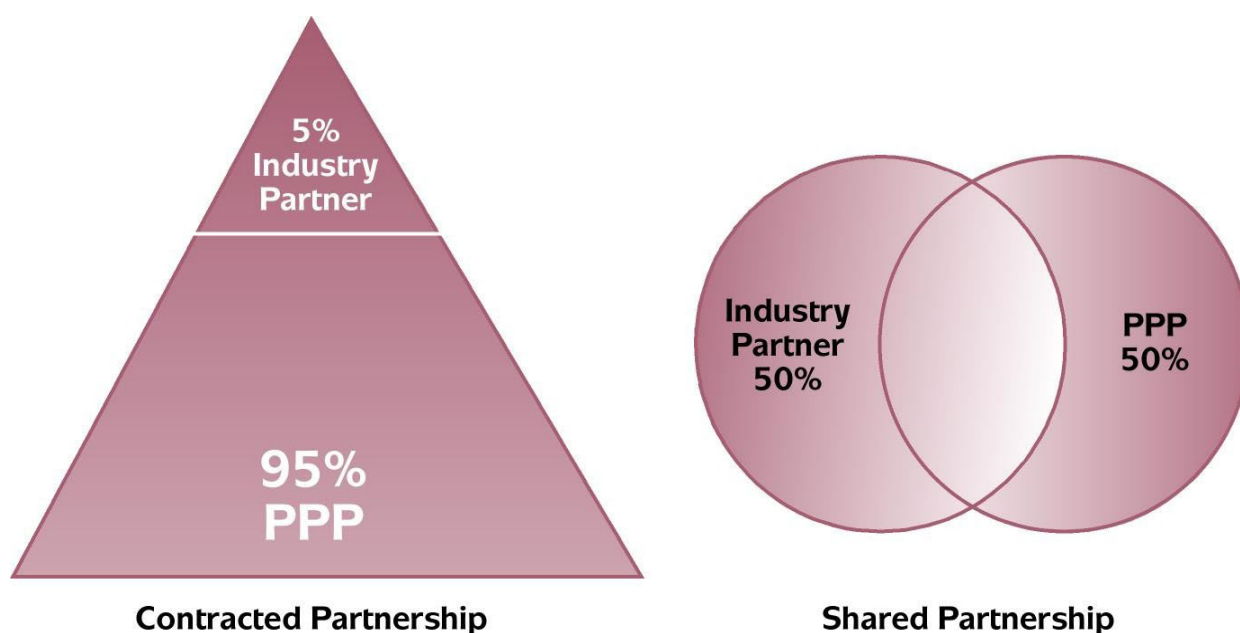
Meanwhile, companies differ in their individual perception of the motivation and potential benefits from participating in PPPs. In view of their significant wealth and role as global citizens, large pharmaceutical companies, for example, arguably have greater incentives to build community support and good PR through contributions to PPPs. Small biotech companies are less able to align their strategic decisions with the needs of PPPs. Their limited cash flows, resources and capacity and often narrow IP and product portfolio mean they have to focus on securing funds and protecting their IPR.

Figure 2 (page 13) provides a simplified depiction of the types of relationships PPPs have established with companies. In a shared partnership, the in-kind contributions of industry approach the value of the PPP's financial investments. In its simplest depiction, each partner contributes up to 50% of the partnership resources. In a contracted partnership, the industry partner contributes the work that has been contracted for, but little else. This does not discount the value of the research and work done under this contract. What we are highlighting here is *who is paying for the deal* (in kind and in cash).

⁶ A publicly traded company has stock traded on a stock exchange open to the public to purchase and is subject to federal reporting regulations.

⁷ GSK is the only exception. It is engaged in multiple deals with a single PPP – MMV in this case, some of which were, however, initiated by previously separate companies that were merged.

Figure 2. Public-Private Partnerships based on resource contribution to deal



Both types of partnerships have advantages and disadvantages. In the shared partnerships, PPPs gain the value of in-kind contributions, but give up some control over the design and direction of the project. There are issues such as the targeted patient profile, countries and pricing, where the PPP and the industry contributors can have differing opinions. In shared partnerships, a negotiated settlement can often be reached.

One example of this is the malaria project to develop “LAPDAP+Artesunate”. In this case, GSK is a partner alongside WHO, the UK Department for International Development (DFID) and MMV. GSK contributes invaluable in-kind resources, is managing most of the work, and retains liability for the product. However, as bearer of that liability, GSK is unwilling to take on the risk of testing the product in pregnant women, despite the priority the global health community, and MMV in particular, has placed on testing and developing new malaria treatments for this patient group. In order for MMV to advance these tests, they will probably need to take back control of the project (including the liabilities) and contract out the work to other partners, most likely at market rates.

In a contracted deal, the PPP retains control but at the cost of a significant increase in management time and R&D costs. Even assuming that PPPs can

identify relatively inexpensive contract researchers and manufacturing partners in the developing world (a talent still to be tested), they will need to pay for additional staff to manage and monitor the project and for consultants to address expected and unexpected issues that experienced, participating industry partners would probably know how to deal with (and would do in-kind as part of their contribution to the project).

4.2 Categories of contributions

As with any life sciences company-to-company deal, a PPP-company deal involves a combination of monetary and in-kind contributions. In this case, the money comes almost exclusively from the PPP and in-kind resources come from all parties. For the work to proceed, both parties need to feel that the anticipated return warrants the investment.

In the PPP deals, industry is sometimes willing to contribute more for free or at a discounted rate than they would in a purely market transaction. Industry deserves credit for these contributions, the value of which has, in most cases, not yet been determined. As PPPs look to renew current funding commitments and to raise additional public or philanthropic monies, they need to be able to demonstrate estimates of companies’ in-kind

contributions. In so doing, they can validate their strategic decision to work with private industry. Both public and non-profit donors are more likely to be willing to give if they understand that industry's contribution has been significant and sometimes beyond the reported contracted deal.

The industry contributions that we present in our case studies broadly fit into two categories: goods and services.

Goods

- Compounds
- Tools and technologies, such as reagents, vaccine delivery technologies, compound libraries, or assays
- Equipment.

Services

- Advisory board participation
- Personnel time and expertise (project management, clinical trials)
- Technology services
- Access to proprietary data and information
- Functional or scientific expertise
- Opportunities for an exit strategy.

4.3 Case studies

The analysis of each deal is structured in four sections. First, we describe the overall deal with a focus on contributions from industry to the partnership. Second, wherever feasible, we estimate the value of the companies' contributions, distinguishing between the goods and services components. Third, we assess the extent to which the PPP has benefited from in-kind contributions over and above what the companies were paid and contracted to do. Finally, we draw lessons for future PPP deals.

Case 1. Industry expert serving on an advisory or scientific board

A company representative donates his/her time and expertise to the governing boards or scientific advisory committees of the PPP. The PPP boards work together with the management team to design the PPP's strategy and make key staff appointments,

and are responsible for ensuring that the organization pursues its stated goals effectively. The PPP Scientific Advisory Committee advises the board on scientific issues and technical oversight, particularly in selecting projects to fund and in developing the R&D strategy and portfolio.

In each case, the industry adviser spends on average three to four full days per year in meetings with the PPP and is called upon to provide advice and time as needed throughout the year. Although PPP board and advisory members are unpaid, travel expenses are sometimes covered. In other cases, the adviser's company agrees to meet the costs.

Valuing industry contributions

The historical data approach is useful in valuing this type of contribution from industry. This involves looking at the compensation a board member would receive for performing a similar job in a for-profit organization and using it as a proxy for the monetary worth of the industry expert's time which the PPP is getting for free. A 2001 Towers Perrin study based on proxy filings from 250 S&P 500 companies shows that the mean annual cash and stock compensation for a non-employee corporate director is US\$118,337, of which US\$49,000 is paid in cash. A non-employee corporate director for a for-profit company probably contributes more time, for example 5%-10% or 10-20 days a year. If we estimate a rate of US\$11,000 per day compensation, that suggests that the maximum value of the industry's contribution to the PPP board is in the order of US\$44,000-US\$60,000 for four to six days.

In addition to the value of the forgone compensation, there are other, less easy to value contributions that an adviser will make to a PPP beyond traditional advice. For example, she provides introductions to potential industry partners and legitimacy to the PPP organization they represent.

Lessons learned

While it is difficult to assess the value of the contributions that individual industry representatives have made to PPPs, the calibre of the individual board members demonstrates the seriousness of industry's commitment to these organizations. The fact that the industry representative is not compensated means that all their time is considered an in-kind contribution.

Table B. Selected examples of pharmaceutical and biotech executives who serve on PPP boards or scientific committees

<i>PPP</i>	<i>Board Members from Industry</i>
GATB	Dr. Gail Cassell, Vice President of Infectious Diseases, Eli Lilly and Company, USA. Seán Lance, Chairman, President and CEO of Chiron, USA.
IAVI	Dr. R. Gordon Douglas Jr, Former Vice President, Merck & Co., Former President, Merck Vaccines, USA. Lee C. Smith, Former President, Levi Strauss International, Former Board Chair, Leadership Coalition on AIDS, USA. Sir Richard Sykes, D.Sc., F.R.S. Former Chairman, GlaxoSmithKline, UK.
MMV	Prof. Trevor Jones, Director-General, The Association of British Pharmaceutical Industries, UK.
<i>PPP</i>	<i>Scientific Advisory Committee Members from Industry</i>
GATB	Dr. Ken Duncan, Manager of the Action TB programme and Leader, Mycobacterial Infection Research, GlaxoSmithKline Medicines Research Center, UK. Dr. John Horton, ex-GlaxoSmithKline.
IAVI	Dr. Michel De Wilde, Aventis Pasteur Inc. , USA. Ian Gust, M.D. Director, Research and Development, CSL Limited, Australia.
MMV	Dr. Simon Campbell FRS, Chemist, ex-Head of Worldwide Drug Discovery and Development, Europe, Pfizer. Dr. Tanjore Balganes, Biologist with specialist expertise in infectious diseases. Head of Research and Development, Astra-Zeneca, India. Dr. Yves Ribeill, Chemist with experience of malaria through earlier work as Head of Anti-infective Chemistry Research with Rhône-Poulenc Rorer France, now President and CEO, Scynexis Chemistry and Automation Inc., USA. Dr Dennis Schmatz, Biologist with expertise in parasitology, including malaria. Executive Director, Human and Animal Infectious Disease Research, Merck Research Laboratories, USA. Dr. David Wesche, Clinical Pharmacologist with expertise in malaria from previous position with Walter Reed Army Institute of Research, currently with Pfizer Global Research and Development, USA.

Case 2. Multi-tiered equipment deal: Becton Dickinson (BD) and IAVI

Becton Dickinson (BD) makes a flow cytometry machine that analyses cells in suspension to evaluate the expression of antigens in specific cells to see how these cells respond to disease agents (infectious or malignant processes). The instrument evaluates the cytokine response to see if the cell is stimulated by the antigen of interest (i.e. whether the cell can mount a good immune response to the disease agent). The technology can be used to evaluate prophylactic vaccines by measuring a blood cell's protective immune response to the vaccine — providing researchers with a good idea of a vaccine's effectiveness at an early stage in a human trial.

In 2001, IAVI announced its plan to create a “state-of-the-art” core laboratory from which to coordinate the evaluation of AIDS vaccine candidates as they complete the different stages of human trials at sites worldwide. The laboratory is also designed to provide developing country scientists with training and access to the most modern equipment.

In order to obtain the flow cytometry machines for use in the laboratory, IAVI and BD negotiated a deal which provides benefits — both cash and in kind — to both parties involved. The deal was helped by long-standing good personal relationships between two key personnel within IAVI and BD.

The deal has four separate but inter-related components:

- **Charitable donation:** BD Corporate is to donate US\$500,000-US\$1,000,000 a year in charitable contributions to IAVI. In 2002, IAVI received a US\$1,000,000 cash contribution from BD, which it plans to use for the core laboratory in London. The fairly complex application process required to access these funds was helped by the fact that BD was not just donating money to IAVI but also intended to collaborate in R&D. The cost to BD of the contribution is partially offset by the amount of tax savings since the company is not liable for tax on the money it donates to IAVI.
- **R&D collaboration:** BD will offer IAVI deep (approximately 40%) discounts on their technology (instruments and reagents) and services. IAVI has contracted to buy approximately eight flow cytometry machines from BD. In return, IAVI will share the data collected from using the BD assay on people at risk or living with

HIV/AIDS — data which it would otherwise be difficult to obtain. The data will enable BD to determine how their assay performs on prophylactic vaccines. BD retains first right of refusal on any assay (for any indication) and for any results from this deal. If the R&D collaboration produces good results, this may lead to approval by the US Food and Drug Administration (FDA) for a new indication and new product for BD to market. In addition, IAVI will be training researchers from all over the world in the use of BD products — thereby helping develop new long-term markets for these products.

- **Donation of equipment:** BD donated an Automated Cell Analysis System (flow cytometer) to IAVI's London laboratory (US\$100,000 at list price). In return, BD will receive a tax deduction and ensure that more developing world researchers are trained in the use of their products.
- **Additional R&D collaboration:** As in the item on R&D collaboration above, BD is giving IAVI a significant discount on their in-house flow cytometry services (running samples from IAVI primate studies). In return, BD is given the rights to keep the data they analyse.

Benefit to IAVI

Monetary

- US\$1million charitable contribution.

Goods in kind

- Equipment US\$100,000
- Value of equipment discount over US\$300,000.

Services in kind

- Over US\$100,000 service discount
- State-of-the-art core lab
- Expertise
- Training/product support.

Benefit to BD

Monetary

- US\$100,000 tax deduction.

Goods in kind

- Equipment purchased from BD US\$450,000.

Services in kind

- US\$150,000 services contracted from BD
- Assay data on people with HIV/AIDS
- IP that comes out of deal
- Favourable public relations.

Valuing benefit to IAVI

While several methods can be used to measure the value of BD's contribution to the IAVI deal, certain parts of the contribution are easier to value than others. We know the approximate cash value of the charitable contribution, the equipment, and the equipment and service discounts. Since these cash flows/discounts will be offered over the course of several years, we can apply a discount rate and use the *Net Present Value* approach to value the contribution. The cash value of this contribution would still work out to be over US\$1.5 million. In addition, BD has made several additional (less tangible) contributions which are much more difficult to value.

The value of a state-of-the-art core laboratory might be measured using the *Next Best Alternative* approach, i.e. its value would be the cost of IAVI completing a similar deal with the best alternative partner, with a premium added to compensate for the fact that the deal was not done with the preferred partner (BD). This premium accounts for the value of the BD brand and/or the extra functionality that makes BD the first choice.

The value of BD expertise could also be determined using the *Next Best Alternative* approach, provided this expertise exists elsewhere. Alternatively, the value could be determined using the *Cost Build-up Approach*. Here the key question is: how much would it cost IAVI to develop its own expertise in this area? This could cost several thousand person hours to replicate the expertise of BD employees, together with the additional costs of overheads and equipment needed. To get some idea of what the person hours could cost, consider that a senior R&D director at a major device company can earn up to US\$200,000-US\$300,000 a year.

Value of "excess" contribution

BD clearly provided excess value in both goods and services - beyond what was stipulated in the contract. The value can be divided into good and services components. The goods components include: the US\$1 million cash donation; US\$100,000 in donated equipment; and over US\$400,000 in equipment, service and discounts, which is offset by over US\$500,000 in discounted equipment and services that IAVI has contracted to purchase from BD. In addition, IAVI is gaining access to a state-of-the-art core laboratory as well as expertise and training/product support, which must be included in the additional value provided above the contract price.

The fact that this deal took place at all is largely due to the time and effort spent by representatives from BD's business development, R&D and legal departments. Meanwhile, the company's commitment to helping IAVI advance its research goals also has intangible value for IAVI.

Lessons learned

- Asking an industry partner for money alone could be ineffective; there must be a good, strong strategic business case for the company as well. In this case, the charitable contribution would have been difficult to obtain outside the context of the equipment contract and R&D agreement.
- It is important to understand the constraints of a commercial company with shareholders that dictate behaviour. For example, BD Corporate was the only entity able to give a charitable contribution; this type of funding is unlikely to come out of the operating budget of one of the subsidiaries.
- It is important to identify at least one strong, well-respected internal "champion" within the industry partner. The science is complicated and the nature of the deal, particularly as it relates to neglected diseases in developing countries is not always easy to explain or garner support for. Completing such deals requires a strong champion both for the negotiation and implementation of the deal.
- Each side must gain something of value from the deal.
- It is difficult to value some in-kind contributions and intangible benefits; they may change over time depending on current demand for the benefit.

Case 3. Biotech R&D under contract: IAVI deal with AlphaVax

AlphaVax has developed a "platform" technology for vaccine delivery that is not disease-specific. In this deal, IAVI contracted with AlphaVax to make use of this "vector" technology to carry genes encoding antigens that provoke an immune response to the strain of HIV that is prevalent in South Africa. IAVI originally agreed to provide US\$4.6 million in funding over three years to AlphaVax to test and develop this technology up to the point of manufacture for clinical trials, including subcontractual work at the University of Cape Town and the University of North Carolina.

In addition to the potential use of their technology as a platform for proprietary HIV vaccines, the deal offered AlphaVax an opportunity to build up infrastructure and move their technology into the clinic, without having to rely on private investment. If a vaccine was successfully developed as a result of this project, AlphaVax committed to make it available at a target price of 10% above the production cost. In addition, IAVI would retain “march in” rights, obliging AlphaVax to subcontract vaccine manufacture to eligible alternative suppliers if AlphaVax could not meet their bids.

At the time the deal was signed, the project represented the only significant research project at AlphaVax. It was also one of IAVI’s first deals. Shortly after initiation, project goals were modified to target initiation of Phase I trials within three years as part of IAVI’s emphasis on accelerating development. In mid-2002, during an interim one-year contract extension prior to renegotiation of a second phase of the partnership, IAVI terminated the arrangement, reflecting differences in development and regulatory philosophy between the two organizations.

Benefit to IAVI

- Implementation and management of in-house and subcontracted research, development and GMP manufacturing support
- In-kind contributions of about US\$2.7 million to support overhead and indirect costs for the project
- Private sector “validation” of the IAVI partnership model.

Benefit to AlphaVax

- Scientific validation of the technology’s potential
- Over three years of funding (totaling US\$9.4 million) to test and develop the technology in order to move the technology into the clinic (the funding support for this program was picked up by the NIH following cessation of IAVI contributions)
- An opportunity to prove and advance their platform vaccine technology and organizational capability in the HIV/AIDS field as well as for other commercial vaccine applications.

Value of “excess” contribution

Although AlphaVax were paid to do the work on this project, they were not paid for the approximately US\$2.7 million (AlphaVax estimate)

in overhead expenses associated with this project. By our definition, these overhead expenditures are considered to be “excess” contribution by AlphaVax.

Lessons learned

Because this deal was one of the first for both AlphaVax and IAVI, two very young organizations at that time, there was a lack of “deal-making” experience on both sides⁸. Also, there were few, if any, prior examples for new “partnerships” to draw upon. A number of key issues were not spelled out in the original contract, and these later proved to raise difficulties:

- There was an unresolved conflict over responsibility for overhead costs. Because AlphaVax is such a small company and the IAVI project accounted for 75%-80% of their workload, AlphaVax maintained that the cost of the facility and other overhead expenses should be covered in the deal or defrayed by other participants in a broader multi-partite partnership. However, IAVI has a policy of funding only projects, not general company development, and was concerned about the possible dilution of its influence in a broader partnership. When forging a deal with a small company with limited products and infrastructure, the issue of responsibility for overhead costs must be agreed on in advance and clearly spelled out in the contract.
- IAVI viewed AlphaVax as a start-up company with limited capability and expertise, and felt compelled to assert more project direction and outside consultation. For their part, AlphaVax viewed IAVI’s understanding of the development process as “arm’s-length” and sometimes unrealistic, and their management practices as unhelpful if not counter-productive. In reality, both parties’ perceptions largely reflected the early stage of their respective organizational development and maturation.
- In this deal, the confidentiality and control issues were ill-defined, particularly for a small company that is dependent on a single technology. IAVI expected a level of transparency and involvement in day-to-day decisions about technology or regulatory and product advancement strategies which AlphaVax could not accept — especially

⁸ Both organizations have progressed considerably since the time of the original negotiations. The authors and IPPPH appreciate their agreement to let others learn from their experiences.

in view of the involvement of competitors in IAVI's scientific and project review structures and the creation of a new IAVI partnership with a direct AlphaVax competitor. More time should have been spent in working out how to deal with these issues within the relationship. This issue is less of a problem for larger biotech and pharmaceutical companies which have either a "stable" of technologies or a technology which has limited potential beyond the partnership.

- Because AlphaVax has a platform technology, the intellectual property issues are more difficult than they would be for a compound with limited application and no global commercial potential. If IAVI moved AlphaVax's technology to a manufacturer in a developing country, this could potentially threaten the integrity of their intellectual property, including know-how and trade secrets. This threat, together with the prospect of cost transparency, acted as a disincentive to potential deals with other companies interested in HIV products.
- Because of IAVI's emphasis on speed of development and accountability, they tended to view the partnership as a form of contract R&D. As a result, they expected to have significant control over decisions and involvement in the development process. However, AlphaVax were not only contributing their only technology to the partnership, they were also paying for most of the overhead costs for a project with an unprofitable product target. In view of its proprietary and competitive considerations, AlphaVax saw the relationship as more of a grant-based partnership and believed that control and confidentiality were indispensable.

Case 4. Shared development partnership with pharmaceutical company: MMV/ Bayer Deal

In 2001, Bayer and the Medicines for Malaria Venture (MMV) signed an agreement involving the completion of preclinical development and the subsequent development of a new malaria medicine based on the active ingredient Artemisone. The new substance, for which Bayer holds patent rights, is from the artemisinin natural product class. The product is the result of a Bayer-funded research alliance in the mid to late 1990s between Bayer and the Hong Kong University of Science and Technology.

Studies in monkeys have shown that Artemisone is well tolerated and non-neurotoxic. They have also demonstrated that it is 20 to 30 times more effective and much faster-acting than existing products. The project team is therefore aiming for a short duration therapy of one to three days. Clinical trials are scheduled to begin in early 2003, while the first market launch of Artemisone tablets is planned for late 2005.

In this partnership, Bayer assumes responsibility for managing the remaining preclinical and clinical studies and MMV has agreed to fund this work. On the basis of their knowledge and experience of pharmaceutical development, Bayer and the project team decide how best to conduct the work, whether in-house or via contractors, as is common for the development of a product that is driven by humanitarian need rather than commercial imperatives. Late clinical development in malaria-endemic regions will benefit from WHO access to the health systems and patient groups in those developing countries and from the supervisory experience of both WHO and MMV. Bayer will manufacture the product for clinical trials. The company already have a production facility which meets standards for Good Manufacturing Practice (GMP), and the scale-up process for active ingredient is already under way. The project team were free to choose contractors for manufacturing but found that the quality/price opportunities were better in-house. Once the product is approved, MMV will seek WHO support for monitored distribution through the health delivery system in developing countries. An "affordable" price will be negotiated at a later date to ensure that the drug is available to all who need it. Bayer will also market the product in the industrialized countries.

Bayer is contributing a promising development product, back-up compounds, development and project management know-how, infrastructure and overheads in kind. In Bayer's toxicology department, a screening method was developed to ensure the selection of candidate compounds that are free of neurotoxic potential. Some 80-90 people are currently involved in the project, most at Bayer and the rest in partner institutions in Hong Kong, Brisbane and London or in contractual laboratories (e.g. for pharmacokinetic or metabolism investigations). However, they work in different projects at the same time — making it difficult to estimate the equivalent number of full-time employees involved. Up until 2001, the researchers

in Hong Kong were responsible for the discovery chemistry, involving the design of stable, tolerable and efficacious compounds. In cooperation with Bayer process chemists and analytical staff, they will continue to provide chemical support to the synthetic development process as it moves towards the final GMP manufacturing conditions. During clinical development, strategic decisions (e.g. which patient populations to target, where to conduct the clinical trials, and with whom to work in the field) will be made jointly. A first meeting of clinical experts is scheduled for early 2003. In the meantime, Bayer is conducting the appropriate toxicology and animal studies to determine whether this drug can be safely administered to young children and pregnant women — two of the most vulnerable groups for malaria.

Benefit to MMV

- Intellectual property rights for one of the most promising antimalarial compound classes to date and development compounds for multiple applications as antimalarials
- Preclinical and clinical development know-how
- Experience in management of in-house and contractual project resources
- Resources for development, manufacturing and marketing
- Project funding is treated as donation: no payment for company or institution (e.g. university) overheads outside direct project work.

Benefit to Bayer

- Budget for development
- Expertise on specific needs of “orphan” drug development
- Contact with WHO and access to public health systems and clinicians in malaria-endemic regions.

Lessons learned

This project has benefited from a dedicated project team, led by an in-company project coordinator who has been involved with the compound since the early discovery research phase and has fought for it within the company. All project team members are involved on a voluntary and part-time basis. Their motivation in contributing their expertise to development of a new malaria product is to help save lives in low-income countries which lack the resources needed to combat the disease effectively.

This motivation, together with freedom from organizational conflict over internal funding priorities is key to the success of the project.

Case 5. Product licensing: GATB/Chiron

The Global Alliance for TB Drug Development has signed a deal to license a chemical compound (PA-824) from Chiron Corporation for an undisclosed amount. GATB will seek partners to develop the compound for treating TB. In the deal, Chiron agreed to waive any royalties from sales in low-income countries, but retains a “grant-back” option to make and sell the medicine in wealthier countries. GATB has full rights in the developing world, including over pricing, and is allowed to find another partner should Chiron choose not to take up the project again in the late clinical trial, manufacturing, and distribution stages.

At the time of deal, the drug had been optimized but required further preclinical work before an IND could be granted. GATB paid relatively little up front for the compound, but is responsible for funding and managing the remaining preclinical stage and all of the clinical work. Some of these steps will depend on access to Chiron scientists, which was granted in the agreement. A decision on “grant-back” rights to sell the drug in high-income countries will depend on the results of efficacy and safety tests, which GATB will fund and manage. Chiron’s motivation for entering into this deal was partly to reduce the risks involved. If it decides to exercise the grant-back option, it will have to pay GATB for all the development costs. However, if the tests fail, it will pay nothing. If the product is successful, GATB gains a partner for large-scale clinical trials and manufacturing and Chiron acquires a drug at low risk for use in large and lucrative TB markets.

Benefit to GATB

- Rights to compound at a discounted price (undisclosed amount)
- If the product is successful, the deal provides GATB with an exit strategy whereby Chiron will fully fund development both retrospectively and prospectively. However, if the product fails, GATB will not be reimbursed.
- Access to Chiron researchers and information to help support preclinical work and the transition of the product to GATB.

Benefit to Chiron

- Cash in return for the product licence
- Assuming the risks involved in early stage research – an appropriate role for the public sector to play
- Allows industry to benefit with grant-back option.

Valuing benefit to GATB

The value of Chiron's discount on the price of the compound could be estimated by looking at comparable deals for a similar preclinical compound. However, this is difficult as TB is a relatively small market (up to US\$800 million according to GATB estimates) and not many commercial deals have been done in this area. Based on a McKinsey study that looked at the licensing arrangements of the top 12 pharmaceutical companies with biotech companies, the average upfront payment for a preclinical compound is US\$2 million with US\$15 million in "milestone" payments. In the hepatitis C market, for example (valued at over US\$1 billion), Rigel licensed an antiviral programme to Questcor for US\$1 million (in cash and stock payments up front), together with a potential US\$10 million in milestone payments. This helps put an upper limit on the value of PA-824.

The opportunity for an exit strategy is extremely valuable. If the product is successful, the value of the exit strategy is the cost of development to the point at which Chiron licenses the product back from GATB (retrospectively), and potentially the cost of conducting clinical trials and manufacturing of this product. If Chiron (or another large company) does not come in to take over the product, GATB would need to spend the hundreds of millions of dollars it would cost to conduct clinical trials and manufacture the product.

The value of access to researchers is also difficult to determine since this expertise would be difficult, if not impossible, to get elsewhere.

Value of "excess" contribution

Chiron's excess contribution is still to be determined. If a market existed for this product, the excess contribution would be the discount they were willing to offer to GATB. Based on comparables for licensing other compounds, this is probably less than US\$1 million in an up-front payment and US\$10 million in milestone payments.

Since the product was "on the shelf", we assume there was no competitive market for this product. Chiron's excess contribution will come into play when and if Chiron licenses the compound back from GATB and invests significant resources in taking the product forward. We might also be able to look at a resource-based approach to determine how much money Chiron has invested in the R&D to date.

Lessons learned

- Incentives must be aligned. If the product is de-risked for Chiron, it may be motivated to step back in to conduct the late stage development and manufacturing work. Meanwhile, GATB gets what it wants with a modest up-front payment and a chance of getting reimbursed.
- Until a product has been granted an IND and undergone early human trials, it will be very difficult for PPPs to find an industry partner to commit to finishing the work.
- For GATB to succeed, it cannot operate on a year-to-year funding model. The Alliance needs sufficient funds to contract out the steps necessary to advance the product. This is true for any product development partnership that has a portfolio approach over several or more years.

Case 6. Compound donation: IOWH/Celera

Celera donated development and commercialization rights for CRA-3316, for all parasitic diseases in all markets, to the Institute for OneWorld Health (IOWH). IOWH will first seek to develop it for a new treatment for Chagas disease.

CRA-3316 is a cysteine protease inhibitor that was discovered, screened and optimized by three chemists at Khepri (acquired by Axys in 1996; Celera acquired Axys in June 2001) with some funding from NIH. James McKerrow at UCSF, also funded by the NIH, did early work on the project and developed the assay. Khepri "donated" its cysteine protease inhibitor library. Many of these compounds had already been pre-screened against the target enzyme of the Chagas parasite. The additional assay work and subsequent *in vivo* experiments, performed by McKerrow, identified CRA-3316 as the best compound for subsequent development. Jim Palmer, a medicinal chemist at Khepri, patented an optimized version as CRA-

3316. Much work continued on the compound after the Axys takeover of Khepri as the compound was under consideration for many different indications.

McKerrow and UCSF's contribution ended when the candidate was patented. It became the company's responsibility to develop it or license it out. With the takeover of Axys by Celera, it was decided to give IOWH an exclusive licence to develop the compound for parasitic infections in humans, free of any royalty fees or cash payments. IOWH has agreed to sponsor all development activities, including production of drug substance, IND-enabling safety studies and Phase I clinical trials. IND-enabling studies of CRA-3316 are currently under way at the National Institute of Allergies and Infectious Diseases (NIAID) at the US National Institutes of Health (NIH).

Through making a contribution of this kind, Celera gained the benefit of good public relations, at a time when they needed it. It also gave the company an opportunity to demonstrate that they now had in-house capability to translate technologies into products, in part through the purchase of Axys. It remains unclear whether the work led and funded by IOWH will produce leads to other, possibly more lucrative, applications of the same compound (as is the case with the cysteine protease inhibitor under development between UCSF and GSK for malaria and osteoporosis).

Benefit to IOWH

- Licence to CRA-3316 for all parasitic infections in all markets.

Benefit to Celera

- IOWH has committed to develop CRA-3316. This includes completing a large Phase III clinical trial, and seeking regulatory approval of the drug in India. IOWH has recently raised US\$4.2 million from the Gates Foundation for this purpose.

Valuing Celera's contribution

Assuming Celera is not going to further develop CRA-3316 for any other indication, a *Cost Build-up* approach could be used to determine the value of the licence to IOWH. In this case, we would look at how much it cost Celera to develop the compound to the point where it was licensed out i.e. the identification, optimization, patenting and development of CRA-3316. Celera estimates that it took three chemists three years to develop the family of compounds — equivalent to nine full-time employees at US\$250,000 a year. In addition, the assay and *in vivo* pharmacology work adds up to an additional nine full-time employees at a similar rate of pay. Therefore, the total value of the work (the research and the advancement in the basic field) would be almost US\$4.5 million. As Chagas was the most promising of the indications that were tested, it is likely to be the only one taken forward. As a result, the actual value of the compound today is likely to be less than the approximately US\$4.5 million it took to develop it.

Value of excess contribution

This would be the total value of the compound as described above since IOWH has not paid Celera anything.

Lessons learned

- Personal relationships between the lead researchers involved were essential in getting the research to the current stage.
- Celera needed “proof of concept” of development work — a major factor in encouraging them to take the compound as far as they did.
- In choosing to partner with a biotech company at the “right” time, PPPs can offer both proof of concept and positive public relations — something a company cannot buy.
- It is easier to negotiate a deal for a product for diseases such as Chagas disease, which has only a limited market.

5. Conditions that might motivate greater company engagement

Despite the investments and contributions that over 20 companies have made towards PPPs, companies — especially large multinational corporations — continue to express real concerns about working in these disease areas. In the course of this study, company representatives highlighted four key issues: the unsolved access problems (and no clear policy strategy for resolving this); negative public relations regardless of what they do; unresolved IPR issues; and difficult scientific hurdles.

The fact that poor patients in the developing world do not have access to many approved, off-patent and “affordable” drugs for infectious diseases acts as a major disincentive for companies to contribute more resources towards the development of new tools. Some companies now maintain that, instead of increasing their R&D efforts, the best way of making a contribution to global health is to enter into more collaborative drug donation programmes that include on-the-ground testing and infrastructure building to ensure that existing products reach the patients who need them.

At the same time, controversy over the provision of HIV drugs in Africa and other low-income countries — in which industry is largely cast as the villain — have made companies anxious about increased pressure to give products away. Meanwhile, companies continue to receive criticism and attacks even if they do so. Companies need help from PPPs, the Gates Foundation and others to ‘depoliticize’ the access issue. Overall, large companies feel their efforts to improve global health are neither acknowledged nor appreciated.

Unsurprisingly, companies expressed more interest in participating in R&D projects in diseases with modest-sized paying markets such as hepatitis A and C, and pneumonia, and in operating in regions where some infrastructure for delivery and treatment already exists. Like PPPs themselves, companies are looking for “quick hits” and early

successes that could serve as a catalyst for more partnerships and increased company involvement. Pharmaceutical companies need to know that money and advocacy will back the project that they get involved in.

The challenges involved in designing effective products to fight neglected diseases should not be underestimated and may in some cases be greater than the disincentive of small markets and uncertain public relations environments. In addition to solving the scientific challenges posed by the parasites, viruses and bacteria, the products must be useful for patients with limited access to health services (a patient seen once may never return), some living in tropical conditions and most surviving on poor and inadequate diets, without clean water or acceptable sanitation. And as with every disease, the R&D process is complicated and expensive. It takes a lot of resources to develop a drug, and there is a very low probability of success.

A number of companies also commented that while “virtual” R&D is better than nothing, it is also very difficult to control, as it depends on the PPP managers keeping a diverse number of actors to a time and priority schedule without any real means of recourse should one or more of the players pull out or disappoint at a critical juncture in the project.

Company recommendations to PPPs for encouraging greater contributions from industry:

- Advertise the specific package that PPPs can offer to minimize companies’ risk in a project and maximize the reward of contributing to the PPP’s mission.
- In order to identify possible “quick hits” and expand the use of company resources, pursue a strategy of starting with drugs known to be safe or that have already been used in humans for a different indication. One company, for example, expressed a willingness to allow scientists or PPPs access to their libraries of “safe compounds”.

- Make an effort to ensure that companies receive appropriate credit for their contributions and, wherever possible, take steps to defuse the politics surrounding the “access issue”. Companies are agreeing to contracts that include affordable access provisions. This too needs to be acknowledged.
- PPPs must anticipate the stages in the R&D process where company partners will need support and what form that assistance will take. Industry, broadly defined, has expertise in discovery and development but not, for the most part, in developing countries. In the case of clinical trials, for example, while they are knowledgeable about how to design, run and monitor the trials, they run the risk of being seen as exploitative when they attempt to conduct these trials in the least-developed countries. In this case, they can advise but PPPs will have to lead the clinical trials.
- Industry in general can play a greater advisory role at the scientific, preclinical, and clinical stages, than they are currently doing.
- Greater effort should be taken to tap into the network of experienced retired scientists and company clinicians who have valuable expertise to share either on contract or voluntarily to PPPs. If an organized “fellowship” programme was established, companies might be willing to allow more of their staff to make specific contributions to PPPs.

6. Conclusions

To date, companies have made valuable in-kind contributions to public private partnerships — contributing time and resources over and above those agreed in a paid contract. But it is difficult to place a monetary value on some of the less tangible items, such as “experience”, “credibility”, “programme management” and “time savings”, which the large pharmaceutical companies bring to each project. The non-compensated contributions of large companies — including time, technologies and networks — are perhaps more visible. However, small companies, which can least afford to do so, are also making contributions (e.g. in the form of covering overhead costs).

As to whether the PPPs have received “good value for money” by selecting to work with the private sector, they often have little choice since public institutions lack the experience and resources needed to conduct certain stages in the R&D process. Looking ahead, PPPs can learn from past experience to seek out deals that offer a company genuine opportunities to promote its own for-profit strategy while at the same time advancing the PPP’s global health mandate. This “win-win” situation will boost the relative priority of the neglected disease project within a company’s portfolio. None of the deals we have looked at were made as goodwill gestures. Almost all of them make good business and strategy sense for the company, as well as for the not-for-profit entity. This is an important requirement for a partnership which must be sustainable over the lengthy R&D process. In the event that the partnership turns out to be an unsuccessful arrangement for both sides (e.g. IAVI/AlphaVax), the partnership will dissolve.

The most difficult to value of the in-kind contributions, but arguably the most important, is that of “staying in the game”. Through deals and partnerships, PPPs are encouraging key private players to continue participating in efforts to target neglected diseases. This is important in that it

retains some of the human, technical and physical infrastructure necessary to conduct R&D for neglected diseases within the private sector. In addition, PPPs look towards the private pharmaceutical companies to complete the R&D process for products coming through their pipeline, i.e. to conduct or assist with manufacturing and distribution. It is expected that companies will find these projects more “attractive” at this downstream end once the PPPs have taken on much of the risks and costs. The amount of time and commitment that a company gives to the neglected disease project, as a percentage of the company’s total portfolio, decreases as company size increases. Small biotech companies, for example, may be allocating as much as one-third to one-half of their resources towards a PPP deal because the contract with the PPP is generating a significant amount of their cash flow.

Biotech companies have unique technologies to contribute to PPPs, but they also bring a unique set of demands. Since biotech companies can only “create themselves” and their technology once, they may be more likely to enter into a partnership to prove their technology. However, they cannot afford to fail. To date, few biotech companies have proved to be capable of bringing products through the pipeline and on to the shelf. Therefore, partnerships in the later stages of the development process need to focus on pharmaceutical and CRO partners instead.

The future success of PPPs involved in neglected diseases will depend, to a large extent, on whether they can expand the pool of potential partners and retain those with the skill and commitment to conduct manufacturing, large scale clinical trials and multiple-country regulatory approval applications, and help with the distribution involved. Scale has much to do with conducting these later stages of the development process well and today much of the capacity resides in the private sector. As PPP

pipelines mature, partnerships will become ever more dependent on doing deals with large, established multinational companies.

A still-to-be-tested theory is that major companies will step in to take over the responsibility for projects once they reach the relatively less risky, albeit expensive and complex (from a coordination standpoint) late stages of clinical development and large-scale manufacturing. To date, only a few companies, notably GlaxoSmithKline, have made a sizeable commitment to projects in late-stage development. Many companies still have credible doubts about the ability of PPPs to “deliver” i.e. to succeed in getting products to patients. And experience so far suggests that, as the product advances, the company requires greater involvement in the strategic development of those projects. This will inevitably limit the ability of PPPs to pursue their specific, narrow objectives.

Ultimately, PPPs should be judged on their ability to deliver new products to patients who desperately need them. The ability to do productive and effective deals with industry, an invaluable player in the R&D process, is an essential step in this process but should not be viewed as an end in itself. While a high percentage of products — and partnerships — will inevitably fail, many are likely to become good “win-win” deals for all the parties involved.

Appendix

List of Interviewees

- Ian Boulton, **GSK**
- Maria Freire, **GATB**
- Burkhard Fugmann, **Bayer**
- David Gold, **IAVI**
- Victoria Hale, **IOWH**
- Chris Hentschel, **MMV**
- John Horton, **ex-GSK and GATB**
- Trevor Jones, **ABPI**
- Wayne Koff, **IAVI**
- Robin Krause, **Patterson, Belknap, Webb & Tyler**
- Sean Lance, **Chiron**
- Vernon ‘Skip’ Maino, **BD**
- Kristen Manion, **BD**
- James McKerrow, **UCSF-PSG**
- Charles Moehle, **Chiron**
- Wayne Montgomery, **Celera**
- Melinda Moree, **PATH/MVI**
- Solomon Nwaka, **MMV**
- Sean O’Connell, **Chiron**
- Jim Palmer, **Celera**
- Dennis Panicali, **Therion**
- John Pender, **GSK**
- Edward Pollack, **IAVI**
- Robert Ridley, **TDR**
- Joelle Tanguy, **GATB**
- David Ubben, **MMV**
- Michael Venuti, **Celera**
- Craig Wheeler, **Chiron**
- Richard Wilder, **Powell, Goldstein, Frazer & Murphy LLP**
(now with **Sidley, Austin, Brown and Wood LLP**)
- Peter Young, **AlphaVax**