Venture Capital and Global Health

A discussion paper in preparation for the September 2005 Workshop

Financing Global Health Ventures

Organized by Commons Capital and CIMIT/MAP
Authors:

Elizabeth Bailey, Meg Wirth and David Zapol

Acknowledgments:

Funding for this paper was provided by The Bill and Melinda Gates Foundation and the conceptualization of the paper was influenced by multiple exchanges with Hannah Kettler. Thanks to Josh Ruxin and Columbia University’s Earth Institute for providing space and support for part of this work. Discussions with Reuben Abraham, Thomas Atterstam, Yanis Ben-Amor, Cathy Clark, Lisa Conte, Magdalene Cook, Jonathan Donner, Rob Fogler, Michael Free, Charles Gardner, Jacqueline Kohr, Rustom Masalawala, Carol Nacy, Willy Osborn, Jason Salter, Paul Wilson and many others informed the paper.
Table of Contents

Executive Summary 4

Introduction
The Limitations of Venture Capital for Global Health
Global Health Market Risk
Lack of Momentum in Global Health Markets
Shortage of Intellectual Capital in For-Profit Global Health
Traditional Venture Capital's Need for an Early Exit
High Return Expectations
Mitigating Risk through Syndication
The Emerging Field of Double Bottom Line and Social Venture Capital
Next Steps

A Preface on Terminology 6

Introduction 8

Part I: Why Has Venture Capital Failed Global Health? 9

An Overview of the Venture Capital Model: Market, Momentum and Management
An Overview of the Venture Capital Model Continued: Fund Structure
Conclusion

Part II: Can Double Bottom Line or Social Venture Capital Offer Any Solutions For Global Health Innovation? 16

What Is 'Double Bottom Line' or 'Social' Venture Capital?
Social/DBL Venture Capital and Global Health
Foundations as Global Health Investors
Conclusion

Part III: Next Steps 20

Markets
Momentum
Management
Fund Structure
Other

Appendix A: Examples of Equity-Financed Global Health Innovations 21

Appendix B: A Case Study of Napo Pharmaceuticals 22

Company Financing History

Endnotes 24
Executive Summary

Introduction

In September 2005, a group of approximately 50 individuals representing various stakeholders will convene in Cambridge, Massachusetts to discuss the role of venture capital in global health innovation. This paper was developed as background for this workshop and seeks to explore why traditional venture capital (VC) has largely been unavailable to companies that are developing products for neglected diseases and global health markets. In addition, it begins to explore whether double bottom line (DBL) or social venture capital may be a better model to provide equity financing to these types of companies.

The Limitations of Venture Capital for Global Health

Venture capital has made a significant contribution to the health care industry in the developed world in the form of accelerated innovation, extending and improving the quality of life, and generating strong returns for investors. However, despite the fact that the venture capital model is predicated on a high risk tolerance, global health investments appear to present too many unfamiliar risks to VC investors. Specifically, venture capitalists look for:

- large and growing markets in excess of $1 billion;
- momentum to help get a product through development; and
- a proven management team.

Unfortunately, these basic criteria are often not met in the context of global health businesses.

Global Health Market Risk

Global health markets have not been well defined or characterized, and this uncertainty around their size, growth, segmentation and general dynamics has created a formidable obstacle to traditional venture investing. Although some efforts have been made to better delineate global health markets, estimates vary widely and more work needs to be done in this area to give funders greater clarity on prospective investments. In the meantime, some companies have pursued a 'dual market strategy' where their products have a demand in both the developed and developing world in order to meet the large and growing market criterion.

Lack of Momentum in Global Health Markets

While public-private partnerships (PPPs) have recently created a flurry of activity in neglected disease drug development, there has been markedly less activity regarding commercialization and distribution for such products. Areas such as regulation, reimbursement, procurement and distribution remain under explored, thereby creating additional risks for the already wary VC investor.

Shortage of Intellectual Capital in For-Profit Global Health

VCs look to invest in companies led by experienced entrepreneurs who have a proven track record with venture investors. Because the global health and venture capital communities have not collaborated extensively up to this point, 'seasoned' executives with skill sets from both fields are rare.

Traditional Venture Capital's Need for an Early Exit

The fundamental structure of a VC fund also creates obstacles to global health investing. In particular, the life cycle of a fund is anywhere from seven to ten years which encourages exiting investments in the two to five year timeframe in order to generate strong financial returns for the fund's investors. This relatively short time horizon in the context of long biotech development timelines often means that investors exit an investment long before a product gets to market. In a developing market context, this creates a potential problem for the ultimate commercialization and distribution of global health products.

High Return Expectations

The need for quick exits is in part driven by the expectation of strong financials returns, where a shorter time to exit often yields a higher internal rate of return (IRR). VC investors can look for returns as high as 60%, especially given that there is an expectation that many deals will ultimately return nothing. Venture capitalists typically believe that these kinds of return expectations are unachievable given perceived smaller markets, with less momentum and relatively inexperienced entrepreneurs. Moreover, the private and public markets that provide liquidity for traditional biotech investors are not readily apparent for companies...
Mitigating Risk through Syndication

One of the strategies VC funds use to mitigate risk is syndication—investing alongside other venture funds. While this was not a priority in the Internet boom of the late nineties, it is now the dominant practice in the industry. In the second quarter of 2005, 81% of the 167 biotech and health care venture deals were syndicated with at least two venture funds. This desire for co-investment creates a vicious cycle for global health companies; if few to no venture firms are investing in global health ventures, then even a progressive-thinking VC investor that sees an opportunity may ultimately have to pass because of an inability to attract other investors into a syndicate.

The Emerging Field of Double Bottom Line and Social Venture Capital

Double bottom line and social venture capital refer to for-profit and non-profit equity financing vehicles with explicit social and financial return expectations. This new model may offer a better option for companies developing novel products for global disease, as it adds important social criteria to the investment equation. Most of the social/DBL funds operate like traditional VC funds in terms of identifying experienced entrepreneurs, creating viable business models, co-investing with other VC firms and managing their investments through board seats. However, the desire for positive social impact can sometimes have important implications in terms of financial return expectations.

A few social venture funds that have targeted the priorities of global health in their investment strategies have mainly adjusted their return expectations. Acumen Fund, Programs for Appropriate Technologies in Health (PATH) and the Rockefeller Foundation's ProVenEx are three such examples. ProVenEx was able to achieve an exit for its investment in Biosyn, a microbicide development company, which was sold to a public company (Cellegy).

Other organizations are in various stages of conceptualizing new global health focused VC funds. These include:

- ASM Resources: The for-profit venture arm of the American Society for Microbiology has designed a fund concept that enables the participation of multiple foundations in a single venture fund to allow for alignment of foundation investment and mission.

- Commons Capital: A DBL venture fund that has primarily invested in socially responsible health care companies that focus on the domestic market is exploring a new for-profit venture fund in the areas of diagnostics and devices (with a particular emphasis on women's health).

- The Foundation Strategy Group: The consulting groups Social Investment Fund for Health Care Delivery would invest in private companies in developing countries targeting downstream distribution and delivery of health care products to be used by the poor in urban and semi-urban areas.

- PATH: This non-profit organization is exploring a social venture fund or other financing vehicle, leveraging its existing capabilities in technical collaboration, co-design and development, licensing, policy harmonization and market development, to get high impact primary health care products through the value chain and into widespread use.

These funds will need to make significant inroads into better understanding markets for new products, finding global health and business experienced entrepreneurs, developing viable investment vehicles and strategies, and generating new options for exiting investments, in order to achieve strong financial and social returns. In addition, foundations, as potential investors for these funds, will have to decide what types of financing vehicles will align best with their internal mission and organizational practices, and have the most promise for delivering needed global health products to the developing world.

Next Steps

Because the existing and proposed social/DBL venture funds present more questions than answers at this point, the Financing Global Health Ventures workshop is intended to refine these inquiries and begin to develop solutions to the problem of global health innovation.
A Preface on Terminology

The stakeholders brought together for this workshop—namely ‘venture capitalists’ and ‘philanthropists’—do not necessarily speak the same language. Even within their worlds, there is often disagreement and debate on essential terms. While we acknowledge the importance of terminology and note that this workshop will not resolve such disagreements, we want to ensure that we begin with a common set of overall concepts. This section lays out certain key terms as we use them in this paper and plan to use them for the workshop.

Blended value. The idea that the value created by an organization is fundamentally indivisible—meaning that ‘economic value’, ‘social value’ or ‘environmental value’ are simply parts of one essential value. Blended value builds upon and transcends the concepts of the double and triple bottom lines (defined below).

Double bottom line (DBL) investing. Financing vehicles (such as venture funds) with explicit social and financial return expectations. Some argue that DBL investing holds social and/or environmental value generation as a primary goal. Social venture capital and program-related investments are types of DBL investing.

Equity. Ownership of a company which is sold in order to provide cash for a growing company. Unlike debts (loans or bonds) which require full repayment plus interest, equity appreciates and depreciates based on the firm's value. For example, stocks are publicly traded equities and are thought to reflect the underlying value of the firm. Because equity defers all payment to the investor until the time of sale, it is a preferred form of capital for early-stage companies that use cash to invest in R&D and do not have dependable revenues to ‘maintain’ debt.

Global health ventures. We use this term somewhat loosely to imply companies (potential or actual) which target neglected diseases (defined below) and health problems of the poor in the developing world—including but not limited to HIV/AIDS, malaria, TB, Chagas disease, leishmaniasis, etc.. We note also that health issues like acute respiratory infection, maternal mortality, malnutrition and sexually transmitted infections disproportionately affect the poor—thus such issues should also be included in efforts to spur innovation in this field. The term ‘global health’ could also encompass non-communicable diseases including cancer, heart disease, diabetes and others that are not the primary focus of this paper.

Internal Rate of Return (IRR). A present-value-based measure used for determining the compounded annual rate of return on investments held for a time period of one year or more.

Neglected diseases are defined as seriously disabling or life-threatening diseases for which treatment options are inadequate or do not exist. These largely communicable diseases primarily affect people in developing countries. A distinction is made between neglected diseases like malaria and TB in which pharmaceutical companies might have a marginal interest and ‘the most neglected diseases’ which almost exclusively affect people in developing countries who are too poor to pay for treatment—illnesses like Chagas disease, schistosomiasis, onchocerciasis, African trypanosomiasis and leishmaniasis.

Program-related investments (PRI's). Investments by a foundation to support an activity related to the philanthropy's strategy. Though they are usually structured as loans, PRI's can be equity investments as well. By employing the foundation's assets as investments with financial returns, this form of investment acts as a 'recyclable grant': the financial returns can be reinvested for other charitable purposes effectively augmenting a foundation's overall dollars. By definition, rates of return on PRI's must be below market on a risk-adjusted basis, and most are set at very low interest rates. PRI's were created via a 1969 tax act—with a recent surge in PRI's as an investment vehicle occurring in the late 1990's and continuing in tandem with the growing interest in venture philanthropy.

Public-private partnerships (PPP's) are defined in the ‘global health space’ as public-health-driven, not-for-profit organizations that spur drug development for neglected diseases in conjunction with industry groups. Examples of PPP's in this space include: Medicines for Malaria Venture (MMV), the International AIDS Vaccine Initiative (IAVI), the Global Alliance for TB Drug Development (GATB) and the Foundation for Innovative New Diagnostics (FIND).

Social venture capital. A financing vehicle that invests in for-profit companies in a wide range of
sectors with explicit social and financial return expectations. Within this definition there exists a spectrum of types of social venture capital funds – varying from those with minimal emphasis on the financial returns to those that expect traditional market returns on investments as well as some level of social returns. Social venture capital is a type of double bottom line (DBL) investing.

**Stages of investment.** An inconsistency arises when discussing 'stages' of investment across the global health and venture capital communities: 'Early-stage' or 'later-stage' investment could refer to the age or stage of a company or to the stage of **product** development (e.g., R&D, pre-clinical, Phase I trials). Because this report is focused on the potential role of venture capital in global health investments, we have outlined very general terminology that corresponds with the stages of *company* development. It is also important to note that there is no consensus on this term even among investors. This is compounded by the fact that industry data is self-reported.

**Triple bottom line (TBL) investing** focuses corporations not just on the economic value they add, but also on the environmental and social value they add – and destroy. At its narrowest, the term is used as a framework for measuring and reporting corporate performance against economic, social and environmental parameters. For brevity in this paper, we use the term DBL to include TBL as well.

**Venture capital** refers to equity investments in new or young companies. Venture capital is a subset of private equity, often included in the term 'alternative investments' by institutional investors such as foundation endowment managers. Private equity also includes other non-debt, relatively illiquid (i.e. can't be easily bought or sold like public stocks) investments such as timber, oil and gas, real estate or management buyouts.

**Venture philanthropy.** A model for charitable giving that arose in the 1990’s based on the application of venture capital investment principles to social investments. Funders 'invest' not just money but energy and expertise in the organizations they support. Venture philanthropists manage a ‘portfolio’ of organizations and seek to increase its social impact by providing management support and expecting results and accountability from the organizations they fund. Venture philanthropy focuses on leadership, bold ideas, developing strong teams, active board involvement and long-term funding. Market-based mechanisms are used to bring 'ideas' and 'products' to scale.

**Figure 1**

<table>
<thead>
<tr>
<th>Private Investment Stages Track Company Growth for Health and Biotech</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(usual sources of capital)</strong></td>
</tr>
<tr>
<td><strong>Seed</strong></td>
</tr>
<tr>
<td>Often before a product or company is formed: friends and family and government/foundation research grants.</td>
</tr>
<tr>
<td><strong>Start-up</strong></td>
</tr>
<tr>
<td>Company is ready to conduct business, no revenues typically at this stage (also called Development); company in business for less than 18 months: 'angel' or accredited individual investors and government research grants.</td>
</tr>
<tr>
<td><strong>Early stage</strong></td>
</tr>
<tr>
<td>Typically first round with venture capitalists, often once service is being delivered; partnerships with pharmaceutical companies formed; some pre-clinical data results, etc.; company in business for less than 3 years: venture capital.</td>
</tr>
<tr>
<td><strong>Expansion</strong></td>
</tr>
<tr>
<td>Needing capital for running trials, expanding to new markets or launching products and services; company in business for more than 3 years: later stage venture capital.</td>
</tr>
<tr>
<td><strong>Later stage</strong></td>
</tr>
<tr>
<td>Product or service may be widely available. Company can be generating on-going revenue; maybe positive cash flow. More likely to be, but not necessarily profitable. Also can include &quot;older&quot; companies that still have products in clinical trials. May include spin-outs of operating divisions of existing private companies and established private companies: later-stage venture capital, private placements of equity and debt by merchant or investment bankers or other late-stage financiers.</td>
</tr>
<tr>
<td><strong>Other later-stage investments</strong></td>
</tr>
<tr>
<td><strong>Mezzanine</strong> is a later-stage financing with an eye towards an IPO. Turnaround focuses on faltering companies, public or private. Buyout looks to acquire controlling interests in firms. Recapitalization reconfigures a company's debt and equity.</td>
</tr>
</tbody>
</table>
Introduction

Citizens of the developing world suffer from a high burden of preventable disease and inadequate access to diagnostics, vaccines, treatments and technologies readily available in developed economies. Lack of interest in health issues unique to the developing world on the part of the health care industry and medical researchers contributes to the growing global health gap between rich and poor countries. This tremendous market failure, evident in the gap between the developing world's health needs and the paltry supply of drugs and related products, is a phenomenon that negatively impacts millions of lives and impedes development. An emerging international agenda for HIV/AIDS, TB and malaria has sparked a flurry of new public-private partnerships (PPP's) and innovative global alliances that seek to eliminate these long-standing scourges. And as a result, the landscape of drug development has changed dramatically in the last several years—with 63 active neglected-disease drug development projects and 18 new products in clinical trials. But despite new organizational models and alliances, capital is all too often the rate-limiting factor—prohibiting faster, more extensive innovation for neglected diseases.

We believe that for-profit enterprise has an important role to play in addressing developing countries' health problems. Entrepreneurial business can be flexible, scalable, efficient, sustainable and focused on user needs to a degree often unequalled by non-profit or government-controlled initiatives. But typically private equity or venture capital funding is unavailable for companies addressing neglected diseases, due to the perception of higher investment risks and lower purchasing power in developing countries; barriers to market entry; and the absence of delivery, training and monitoring infrastructures. The current public-private partnerships dominating the global health scene have paved the way for continued innovation, but social/ double bottom line (DBL) venture capital is one mechanism with enormous potential that has yet to be adequately explored.

This paper was developed as background for the September 2005 Workshop Financing Global Health Ventures. The central purpose of the paper is to review the underpinnings of venture capital (VC) and its potential as a funding mechanism for health care innovation; and to highlight the reasons for the dearth of VC investment in the global health space. In addition, we begin to look at an emerging model of social/DBL venture capital and explore its potential for helping to solve global health problems. Though venture capital is not typically paired with discussions of neglected diseases and the health burden of the poor, we begin to look at the possibility of market opportunities at this intersection. Specifically, we examine whether traditional and social/DBL venture capital may serve to catalyze innovation in some sectors of global health.
Part I: Why Has Venture Capital Failed Global Health?

We had to bring in a heavy from Pfizer to explain to our C.E.O. why he shouldn't pursue the developing world market. He had all kinds of aspirations to bring his drug to the poor, but thankfully, we talked him out of it.

—Anonymous venture capitalist

Despite the fact that venture capital is predicated on a high risk tolerance, it is widely accepted in the VC community that global health investments targeting neglected diseases are simply too risky. Venture capitalists cite myriad reasons for why such investments are outside their risk profile—from political instability to insufficient infrastructure to an inability of the poor to pay for products—but unfortunately, the discussion has largely stopped there. To begin to understand why venture capitalists have not extended their model to finance companies focused on neglected diseases in the developing world, it is first necessary to understand the guiding principles of venture investing.

An Overview of the Venture Capital Model: Market, Momentum and Management

Emmanuel Martinez, managing director of venture firm GreenHills Capital Partners, recently described his criteria for investment as the three M’s: ‘market size, momentum and management.’ Like most venture capitalists, Martinez wants to see that there is a $500 million to $1 billion market for a product; that the company has momentum through product innovation (perhaps protected by intellectual property) and will capture a significant proportion of the market quickly; and that the team that is leading the company has the experience required to achieve the operational goals and financial returns promised. These criteria have led GreenHills recently to work with investors placing $800,000 in a company in the neurological device arena, an area Martinez determined had an annual market of roughly $500 million and was expected to grow in the next few years to $800 million. Investors and founders are striving to sell or take public this new company within five years with sales in the range of $40-to-50 million, driving a firm valuation of $100-to-200 million. The hope is that a modest investment in a company that targets a large and growing market can generate a strong return for investors in a relatively short amount of time.

This type of venture investing—that which promises high returns over short time frames (2 to 5 years)—has blossomed over the past 20 years in health and technology. Last year, the over 100 health care venture funds in the U.S. invested $6.33 billion split between biotechnology (61.1%), medical devices and equipment (28%), and health care services and technology (10.9%). (See Figure 2). Most of the biotech investments focused on chronic diseases in the developed world (e.g., heart disease, cancer and diabetes) whose markets are perceived to be large and growing, while little to no venture money went to fund products aimed at diagnosing or treating neglected diseases.  

There is no question that venture capital has been instrumental in spurring innovation in the health care and biotech sectors by funding the early development of new products. A recent report published by the National Venture Capital Association analyzed contributions to health care—mainly in leading causes of death in the U.S.—by the venture capital industry and concluded: ‘Venture capitalists bridge the significant gap between discovery, development and thorough testing of life sciences innovations by providing both monetary and non-monetary support, thus speeding the time it takes to move a product from the lab to the

Figure 2

Percentages by sector invested in 2004 by U.S. health care venture funds

<table>
<thead>
<tr>
<th>Sector</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotechnology</td>
<td>61%</td>
</tr>
<tr>
<td>Medical devices and equipment</td>
<td>28%</td>
</tr>
<tr>
<td>Health care services and technology</td>
<td>11%</td>
</tr>
</tbody>
</table>
The key benefits of the venture capital model it identified included:

- Acceleration of innovation. Venture-backed medical innovations are developed and made available to patients as much as three times faster compared to a bootstrapping approach to product development.

- Extending lives. More than 70 million Americans have had their lives extended or quality of life improved as a direct result of venture-backed diagnostic and therapeutic innovations (25 million annually).

- Return on investment. Product revenues provide a return of over $50 for every venture dollar invested in recently launched products… and as much as $750 for every venture dollar invested in products launched 10 to 15 years ago.

Clearly the VC model works, but we still have to answer why it has not been applied to global health and neglected diseases. Martinez's three M's-market, momentum and management-can provide important insight into the motivations of venture capitalists and why investments in global health are bypassed.

Market

Economists have concluded that pharmaceutical innovation is directly affected by market size. It is no surprise then that venture capitalists look to fund the development of products that can be sold into large and growing markets. $1 billion is a typical benchmark, and big dollar diseases such as cancer, CNS and diabetes meet or exceed this market size. Many venture capitalists argue that having a large market is the first requirement for a successful investment, because it allows a particular company to capture only a portion of a market and still warrant a strong valuation.

Very little has been done to define and quantify 'global health' markets, but the venture capitalist perception of resource-poor settings is that they do not represent large markets. Moreover, these markets present additional risks—political volatility, corruption and fragmented infrastructures, among others—that are quite unfamiliar and daunting to venture capitalists. Other formidable unknowns include intellectual property rights, validation, regulatory barriers, manufacturing partners and uptake of the technology or innovation by global gatekeepers like the World Health Organization. Lack of understanding of such markets prevents companies from determining how they might profit from a certain health innovation. Because of this, many companies working to develop global health products—such as AVANT Immunotherapeutics, LabNow and Napo Pharmaceuticals—have pursued 'dual-market technologies' (i.e., those products that have a demand in both the developed and developing worlds) that they can depend on for at least one mature marketplace.

While some organizations have attempted to delineate the markets associated with global health, estimates have varied widely. Market estimates of products for the 'big three'—Malaria, Tuberculosis and HIV—exemplify this wide range (See Figure 3).

BIO Ventures for Global Health (BVGH), a new non-profit spun out of the Biotechnology Industry Organization, is making some strides in this area and is working to develop business cases of specific diseases that characterize some promising global health markets. Similarly, some recent work has been done examining the potential for Advanced Purchasing Commitments to create market pull for global health products.

New research into the upsurge in neglected-disease

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>malaria vaccine*</td>
<td>417 to 1,200 (15)</td>
<td>500 to 2,000 (10)</td>
<td>16 to 22% IRR</td>
</tr>
<tr>
<td>new TB drug*</td>
<td>222.5 to 445 (3)</td>
<td>115 to 240 (9.8)</td>
<td>15 to 32% IRR</td>
</tr>
<tr>
<td>HIV microbicide*</td>
<td>20 to 900 (5)</td>
<td>775 (10.5)</td>
<td>7 to 14% IRR</td>
</tr>
</tbody>
</table>


**Returns estimates were variable by scenario. The middle of the range is presented here.
innovation may provide some interesting insights into the types of business models best suited for this work. A report by the London School of Economics reveals some 60 current neglected-disease drug projects are conducted by smaller-scale commercial firms. These small firms operate at a different scale and are motivated by far smaller commercial returns than large multinational pharmaceutical companies. The report details the following three categories of small companies which might make inroads into neglected-disease innovation:

- First, some small companies see neglected-disease markets as sufficiently attractive to warrant investment and will pursue these even without public support—for example, Zentaris, a small company that developed and registered the new anti-leishmaniasis drug, miltefosine.
- Some small firms can use 'add-on' neglected-disease R&D to promote their Western commercial goals (e.g., to expand information on their core commercial compounds, or to help establish proof-of-concept for a technology that can subsequently be transferred to commercial markets).
- Finally, commercial contract research organizations increasingly see neglected-disease R&D as an interesting niche sector.

The report notes that small companies’ potential for neglected-disease product development remains underexplored and underexploited.

And finally, though it is beyond the scope of this paper, we must fully analyze the extent to which venture funds and/or companies located within developing countries would be a more efficient way to cultivate and reach these markets with products for neglected diseases.

Momentum

When VC funds assess 'momentum', they look at market trends driving toward eventual product adoption. By examining market dynamics such as patient and physician demand, regulatory and reimbursement developments and business comparables, they are able to evaluate whether there is sufficient evidence to suggest the ultimate success of their venture. When these criteria are applied to global health ventures, the analysis becomes, at the very least, difficult. While gauging patient need is relatively straightforward, regulatory environments and payer dynamics across the developing world vary significantly (versus the more consistent policies in the U.S., the E.U., Canada and Japan). Pricing is therefore a key consideration, as developing countries may have very high volume markets but require pricing many orders of magnitude below developed countries. There is also much ambiguity surrounding the eventual procurers of health innovations—whether they are central purchasing agents like UNICEF or the Global Fund or the public or private sectors in developing countries. When looking for comparables in a market to help delineate these issues, we again note the lack of existing companies that fit the global health business profile.

Some experts maintain that there is no shortage of appropriate technologies for the developing world, but stress that the rate limiting factor is distribution—delivery mechanisms and service components must be developed in order to serve these markets effectively. Indeed, the severity of this roadblock has spawned new ideas for distribution- and infrastructure-focused venture funds and businesses. This is an area that will ultimately require more collaboration among the various global health constituents in order to stimulate greater interest in the venture capital community.

Despite longstanding lack of momentum for neglected diseases, public-private partnerships (PPP’s) for drug and product development have started to dramatically rewrite this dismal script. The 63 neglected-disease drug projects underway at the end of 2004 include two new drugs in registration stage and 18 new products in clinical trials. Researchers estimate that these efforts have the potential to deliver eight to nine new neglected-disease drugs within the next five years. In addition, increasing international pressure to address the burden of neglected diseases as part of an overall development agenda provides additional momentum on which new models for venture financing might build.

Management

The last M—management—represents the most nebulous category of the three. Venture capitalists generally look to invest in entrepreneurs with proven track records—those who have built and sold companies generating strong financial returns for
venture investors. While there are many 'seasoned' entrepreneurs in the health and biotech sectors, global health ventures require a more complex blend of for-profit business acumen and international health experience that is quite rare given the historic separation of the two fields. This lack of human capital needed to build global health companies has therefore been a major impediment to attracting investment. Moreover, the venture capitalists who pride themselves on industry expertise and value-added investment also lack the necessary experience of getting global health products to market in a commercially sustainable model. The pharmaceutical industry’s creation of new neglected-disease institutes that employ some 200 scientists, as well as the creation of new drug development PPP’s which now conduct three-quarters of all identified neglected-disease drug development, offer a potential new wellspring for such talent.  

Looking ahead, it is clear that the business and global health communities need to work more closely to share institutional know-how, and that opportunities to collaborate on such knowledge sharing should be a major priority.

An Overview of the Venture Capital Model Continued: Fund Structure

Turning to the fundamental structure of the VC fund, we highlight additional limitations to its applicability to global health ventures. Specifically, issues of timelines, exits, return expectations and the desire to syndicate investments pose high hurdles for prospective investments and make investing in global health that much more challenging than biotech innovations targeting the developed world.

Lifecycle of a VC Fund

A typical venture fund has a life of seven to ten years. The first year is spent forming a limited partnership and fund-raising, often with some initial investment out of early committed capital. After the fund’s launch, management invests actively through year seven (of a ten-year fund) and often re-invests in existing portfolio companies during this period. While actual performance across VC funds varies tremendously, most have a stated objective to exit their investments within 2 to 5 years (See Figure 4).

In the biotech industry, which is known for its long development timelines, this can mean that investors often pursue a liquidity event long before a product actually gets to market.

Stages of Company Growth—When Venture Capital Steps In

Although venture capital investment can occur across the entire lifecycle of a company, there are stages of development when VC firms are more active (See Figure 5).

As we discussed in the Preface on Terminology, stages of investment are not well defined in the venture capital industry and are particularly problematic in the health care sector.
Most industry data is self-reported, making common terminology that much more elusive. Recognizing these hurdles, we have tried to create a generalized outline of how a company is financed, citing some specific company examples.

At the seed and start-up stages of an evolving firm, risk is typically borne by those close to the firm—the entrepreneur, 'friends and family' and angel investors. Angels are accredited individual investors who make investments alone or as part of a group of individuals willing to take a calculated risk and perhaps lend their own entrepreneurial experience to aid a new venture. This funding usually occurs before any kind of product is developed and before a company is even formed, when the company is younger than 18 months. While a few specialize in seed and start-up investments, most larger VC funds do not invest quite so early due to the extremely high level of risk and the fact that only very small amounts of capital are needed at this point.

VC funds typically begin to enter the picture once the company is launched (past the seed and start-up stages) and in the 'early stage' of product development. For a biotech company, this can mean that a company has generated significant pre-clinical data or that it has actually entered clinical trials. Examples of early-stage venture capital investments in 2005 include:

**Immune Control Inc.**, a drug development company founded in 2001 on cancer and autoimmune diseases, received $5 million in funding from Domain Associates (a VC fund) in the first quarter of 2005. The company is getting ready to submit an investigational new drug application to the FDA in 2005 and to begin its Phase I and II clinical trials.

**GlucoLight**, a medical device company founded in 2004, received $2 million in funding from LSGPA (a Pennsylvania VC fund) and others. The company, which is developing a low-cost non-invasive blood glucose monitor for diabetics, has generated pre-clinical data from animal studies and plans to move into clinical trials with its recent venture financing.

The largest investments by VC funds occur in the 'later-stage' development of a firm (e.g., expansion and later-stage investments), when a company is running additional clinical trials, launching products and services or expanding into new markets (See Figures 6 and 7). These stages encompass a wide range of activities, and they are often more related to an impending investor exit than to the stage of product development. Expansion and later-stage investments by VC funds in the first quarter of 2005 include:

**Kalobios Inc.**, founded in 2003, received $10.6 million in 'expansion stage' venture funding from 5AM Ventures, GBS Venture partners, MPM Capital and Sofinnova Ventures. The company is developing antibody products for cancer and infectious diseases, and it plans to enter clinical trials in 2005.

**PediaMed Pharmaceuticals Inc.**, founded in 1999, received $15 million in 'later-stage' venture funding from Blue Chip Venture Company, Child Health Investment Company and Essex Woodlands Health Ventures. The company focuses on pediatric products, and it has several products already on the market and some in pre-clinical and clinical development.

As a general rule, venture investment takes place after individuals have seeded and started a company, and continues until a company is sold or until private equity investors take over (assuming product success).
Of the 42 initial public offerings (IPO's) for venture-backed biotech and health care companies in 2004, almost 60% were pre-product, and 40% had not even made it to Phase III clinical trials (Figure 8).  

Moreover, out of the ten venture-backed biotech drug companies that were merged or acquired in 2004, only two of them actually had a product that was either FDA-approved or on the market (Figure 9).  

The VC life cycle is not currently effective at satisfying one fundamental goal of the global health community: getting products into the hands of the patients that need them. The long development cycle inherent in biotech R&D in the U.S. does not discriminate between chronic diseases and neglected diseases, and it takes an average of 10 to 15 years to get most drugs from research to market. Because there is a faster average time to market for devices (5 to 7 years) and diagnostics (3 to 7 years), it is no surprise that almost 65% of the health care IPO's in 2004 with a product on the market were either device or diagnostic companies. Therefore, while the market size for devices and diagnostics may typically be smaller than pharmaceuticals, these segments may present better opportunities for employing venture capital to get products to market.  

Recent venture capital activity may suggest a new opportunity to leverage the venture financing to get global health products to the commercialization stage. In an attempt to lower risk, many health care VC funds have moved to expansion and later-stage investments where products are closer to market (Figure 10).  

As will be discussed below, this may also have implications for venture investment return expectations, as later-stage investments tend to generate lower financial returns.  

Return Expectations  

The need for quick exits is in part driven by the expectation of strong financial returns, where a shorter time to exit often yields a higher internal rate of return (IRR). Since most companies fail, and the VC manager even expects approximately 30% of the portfolio to be worth nothing, the remaining companies must return much higher profits for the whole partnership to make the expected investor return. In other words, the winners must carry the losers and still make high returns for the fund as a whole. This means that every deal a VC considers must have at least the potential of making a very
large return. Loosely, if the fund is to return 30%, then the incoming investments each must promise to return an IRR of 60% or more. This is the high bar, or 'hurdle rate' that confronts companies seeking venture capital. VC funds are willing to take risks, but a big market, visibility on market adoption and clarity on exit are essential.

The issue of 'exit' is not only a matter of when but also how. Exits result from IPO's, management buyouts or acquisitions, and are the only way that an equity investor can realize returns from an investment—that is, by liquidating the investment. Thus, in order to create a company which will be attractive to venture capitalists, it is essential to have companies and public markets interested in the investment. This means that the work of convincing venture capitalists to invest in a company is not merely about a matter of its value (financial or social), but also of convincing the markets at large that there is value that can be bought and sold. The lack of a mature market of larger companies delivering global health innovations means that there are probably only a handful of potential acquirers for any new company. And accordingly, IPO's on the public markets for companies with global health products in their portfolios have been rare.  

Thus, the traditional exit that venture capitalists expect is not readily apparent for most global health companies—a major deterrent to investment.

**Syndication**

The venture capital boom of the late 1990's saw many funds investing in deals on their own. However, syndication or co-investment among venture funds has become much more common in order to mitigate the financing risk that many companies face. Most venture financing is done in stages, and venture investors are well aware that subsequent funding is usually needed as companies progress through the development cycle. To that end, having multiple venture funds invest in a company helps to ensure that future funding will be available. In the second quarter of 2005, 81% of the 167 biotech and health care deals were syndicated with at least two venture funds.  

This desire for syndication among health care VC funds can create a vicious cycle for global health companies; if few to no venture capitalists are investing in global health ventures, then even a progressive-thinking venture capitalist that sees an opportunity may ultimately have to pass because of an inability to attract other investors into a syndicate.

**Conclusion**

Venture capitalist look for management, market and momentum within areas that they know and understand well. At the highest level, they seek a market size of $1 billion, the momentum to capture a reasonable share of the market within five years, management that has delivered value to investors in the past, and a syndicate of partners with which to invest. VC funds are structured around limited partnerships spanning 10 years from formation to liquidation that encourages an exit from investments within the 2 to 5 year timeframe. While historical patterns strongly suggest that traditional VCs will not make forays into global health, an analysis of recent venture activity reveals some potential entry points (e.g., devices and diagnostics, and later-stage investments), assuming some novel market delineation and pull mechanisms that do not currently exist.
Part II: Can Double Bottom Line or Social Venture Capital Offer Any Solutions For Global Health Innovation?

We are beginning to see how angel investors, venture fund managers, foundations and financial institutions can, linked together, become a significant force for social change, supporting entrepreneurial companies that are accelerating the transition to a sustainable economy. There is much to celebrate in this story. And there is much that remains to be done.

—Woody Tasch, chairman & C.E.O. of Investors' Circle

As we have discussed, traditional venture capital as it is currently configured has significant limitations with respect to market size, investment lifecycle, return expectations, exits, experienced entrepreneurs and syndication opportunities when applied to global health ventures. However, a new form of venture capital is emerging that may offer some solutions to the lack of funding available to companies developing global health products. We are just starting to evaluate what is possible when investors add social criteria to the investment equation and whether this new approach may be better suited to address global health innovation than existing models.

What Is 'Double Bottom Line' or 'Social' Venture Capital?

While there is much debate on terminology, 'double bottom line' and 'social' venture capital in this discussion refer to for-profit and non-profit equity financing vehicles with explicit social and financial return expectations (see Preface on Terminology). In 2003, Columbia Business School's Research Initiative on Social Enterprise (RISE) surveyed private equity firms (primarily VC funds) investing in early-stage ventures and found $2.7 billion in assets in 59 funds with approximately $500 million already deployed into social/DBL companies. The 59 funds identified themselves as 'interested in investing to achieve social or environment impact as well as financial return', although these funds vary widely in their emphasis on the mix of social, environmental and financial returns (e.g., screening out 'negative' investments, 'positive' screens, incorporation of planned philanthropy).

While the RISE report notes that all funds looking for an IRR of under 10% were non-profit funds, and that most for-profit funds target a 30 to 50% IRR (although investors in the health sector have historically averaged 15 to 20% IRR), 38 most funds operated according to the traditional venture norms:

By and large, double bottom line funds operate like typical small- to medium-sized venture capital funds. They say they concentrate on identifying great entrepreneurs, building successful business models, aligning with strong co-investors, and actively managing their portfolio companies through participation on their boards. Even the foundations and non-profit hybrids in this group (about 17% of the funds) use VC techniques to actively manage portfolios such as taking seats on boards. Nearly all of the funds report that they measure their success first in financial terms, and then on social or environmental terms. 39

Of the 59 funds, 33 invested in the health care industry. This survey included new, foundation-based funds that blend social and financial returns like Rockefeller Foundation's Program Venture Experiment (ProVenEx) and noted that such funds are often willing to 'accept sub-market financial returns.' It also covered established venture firms like MedVenture Associates, which invests in medical- and health-related fields and seeks to maximize investor returns.

Social/DBL Venture Capital and Global Health

Several social/DBL venture funds have stepped up to experiment with global health venture investing (See Figure 11). The existing and proposed funds are varied in nature—ranging from non-profit to for-profit in structure with differing return expectations—but share a common goal of wanting to invest in global health companies in some capacity.

Provenex, begun in 1998, is the Rockefeller Foundation's financing vehicle for working directly with the private sector. It is an $18 million fund that makes health and other investments to further the foundation's programmatic goals, seeking both a social and financial return on investment. Investments are structured using market principles and include loans, equity investments and loan guarantees to for-profit companies, non-profit agencies and community development investment funds. This fund has already tackled the critical issue of 'exit'. A $3.6 million investment in Biosyn, a
pharmaceutical company with a microbicide product was made through a subsidiary. Biosyn has since been acquired by a publicly traded company and its lead product is in pivotal Phase III clinical trials in West Africa.

Acumen Fund, a non-profit venture fund created in 2001, has invested in several health technologies including bed-nets for malaria prevention, telemedicine and affordable hearing aids. Acumen Fund's model differs from ProVenEx in that it is a non-profit and, while interested in financial returns from the perspective of sustainability, does not seek financial returns as a primary consideration. Nevertheless, direct experience with investing in entrepreneurs in the developing world and a focus on measuring impact make this model an important one for careful study of lessons learned.

ASM Resources Inc., Commons Capital, Foundation Strategy Group and Programs for Appropriate Technologies in Health (PATH) are in various stages of conceptualizing new social/DBL venture capital funds in the field of global health. ASM Resources Inc. (ASMR), the for-profit venture arm of the American Society for Microbiology, has designed a unique fund that enables the participation of multiple foundations in a venture fund. This structure creates the opportunity for foundations to support commercial entities whose goal is to bring treatments and cures to the bedside while ensuring the alignment of investments with foundation missions. This model combines the strengths of existing ASMR investment infrastructure with motivated participants to create a risk-mitigated, early-stage biotechnology venture fund suitable for focused investments in companies working on global health.

Commons Capital, a social/DBL venture fund that has primarily invested in socially responsible health care companies that focus on the domestic market, is exploring a new for-profit venture fund focused on creating sustainable global health businesses. Commons Capital's goal is to attract capital from both foundations and private investors in a for-profit fund that provides financing and a high level of technical assistance to global health entrepreneurs developing products mainly in the areas of diagnostics and devices (with a particular emphasis on women's health).

Foundation Strategy Group's SI Fund for Health Care Delivery would invest private capital to demonstrate the viability of private health sector businesses in developing countries. Specifically, the private capital would target downstream distribution and delivery of health care products and services to be used by the poor in urban and semi-urban areas. Potential investments include hospitals, clinics, pharmacies, diagnostic labs and other health retail operations.
PATH is exploring the possibility of a social venture fund or other financing vehicle to fund global health product companies. This new financing mechanism would be used in conjunction with PATH’s established mechanisms of technical and business collaboration, co-design and development, licensing, policy harmonization and market development to help get high-impact primary health care products through the value chain and into widespread use.

In addition to these specific funds, Investors' Circle (IC) is the nation’s oldest angel network focused on social enterprise. IC has placed over $100 million mostly in equity investments since 1992. These angels not only make direct investments in companies, but also view pooled vehicles as opportunities to make directed investments in growing companies without individual company risk. IC’s showcasing numerous global health companies at its national conferences has led to angel investment in several of them. 41 Internationally, angel networks are in their infancy, but as this model moves into India and China, angel networks may be an important source of support for social entrepreneurs.

While these investor groups have incorporated social impact into their investment strategy and in some cases lowered return expectations accordingly to allow for global health investments, there are still many unknowns: Specifically, issues of market assessment and opportunity recognition, time to market for new products, finding global health and business experienced entrepreneurs, co-investment with other VC funds, staging of investment and opportunities for exit are still big unanswered questions. Because social venture capital is still in its infancy and constantly being redefined, it may offer a more flexible approach to investing than traditional venture capitalism. In addition, new investors such as foundations and socially-conscious individuals are defining ‘return’ in new ways and realize that novel approaches are needed to solve global health problems.

Traditional venture capital has shown the world how to bring medical innovations to the people who need them in the domestic context. What social/DBL venture capital can do is to take those lessons and build on them along with lessons from the global health community. Perhaps longer time horizons are needed for venture funds in order to get products to market. Perhaps new exit opportunities, such as holding companies, need to be created to facilitate the cycle of financial return. Perhaps global health business professionals need to be trained—where they do not already exist—and offered substantial technical assistance as part of any investment. Perhaps social venture capital can cut across the development and commercialization cycles and foster partnerships with investors at all stages. And what is sorely needed to facilitate all of these ideas is a real or virtual marketplace—where investors and entrepreneurs can share ideas and collaborate around investments in for-profit global health companies.

Foundations as Global Health Investors

Foundations have the potential to be important players in social/DBL investing line landscape because of their global health expertise, convening power, interest in building sustainable institutions and flexibility in crafting new financial models. A burgeoning trend toward ‘venture philanthropy’ is shifting grant-making toward market-based principles and focusing on investments in sustainable projects and ventures.

This trend is bolstered by additional dollars made available through program-related investments (PRI’s), the financial vehicle foundations often use for making social/DBL investments. Importantly, PRI’s may play a role in leveraging other funding through a couple of pathways: First, foundations may act as a first investor signaling the ‘worthiness’ of the investment for other investors, for-profit and not-for-profit; second, a foundation’s PRI investment, which typically garners a ‘lower’ return (when structured as debt), can leverage other funding sources with higher return expectations. 42

An analysis of the barriers to development of neglected-disease technologies points to a few key criteria which need to be in place to adequately stimulate donor interest in such investments: 43

1. A clear and well-supported understanding of the need.
2. Well-developed technology performance characteristics to meet the need.
3. A network of qualified partners willing to commit if resources are made available.
4. A realistic view of the hurdles involved.
5. A credible projection of the value in terms of
benefit that could be attributed to the technology once in widespread use.

At present, foundations experimenting with PRI's in global health are not necessarily collaborating with other foundations. However, it is possible to envision a collaborative effort where foundations would pool funds to prioritize key global health innovations. Another possibility is a hybrid fund where foundations, traditional and social/DBL venture capitalists pool their investments and technical assistance in a way that speeds innovation for key global health innovations.

Conclusion

Social/DBL venture capital is an evolving field and may offer some antidotes to the bottlenecks in the traditional venture capital model for global health. The goal will be to leverage what works in venture capital and apply new social criteria and a more flexible approach to serve this emerging global health marketplace. The three M’s can guide the development of these new models, but the realities of health care in the developing world will need to be integrated for any businesses to be truly sustainable. Importantly, other research has also supported the notion that social/DBL equity investing may present a viable funding mechanism for small growing biotech companies that are interested in developing new products for global disease. 44
Part III: Next Steps

While the traditional venture capital industry is quite mature and unlikely to turn its full attention to global health innovation in the near term, the social/DBL venture capital field is still in its infancy and holds some promise. However, the existing social/DBL models present more questions than answers at this point. The Financing Global Health Ventures workshop in September 2005 will focus on refining these inquiries in an attempt to start developing solutions to spur investment in global health innovation. Below are topics of interest to be discussed by workshop participants.

Markets
1. How can we better define and quantify global health markets?
2. What mechanisms might be employed to create more certainty in these markets?
3. Are there specific segments (industry sectors, indications and geographies) that offer more promise for global health venture capital?
4. Would companies or funds geographically closer to these markets be better suited to invest in neglected diseases and health problems in the developing world?
5. Is a dual market strategy viable and preferable to a sole focus on a developing world market?
6. Are there specific market pull strategies that would encourage venture investors?

Momentum
7. What infrastructure needs to be in place to facilitate better distribution of global health products?
8. Are there specific markets that offer more momentum in terms of ease and intelligibility of their regulatory processes?
9. What lessons can be learned from the work of the PPP’s, and how can venture capital build on the momentum they have created over the past few years?

Management
10. What technical assistance could be offered to 'train' entrepreneurs in global health and business?
11. How might we tap into the network of successful entrepreneurs in the biotech community—here and in the developing world—to invite them to start global health companies?
12. What sorts of partnerships with non-profits and others with global health expertise are necessary?

Fund Structure
13. Would a longer timeline for investment vehicles help global health companies get products to market?
14. Are there specific holding companies that should be developed to create exit opportunities for global health investments?
15. What financing gaps should social/DBL venture capital aim to fill?
16. How should financial and social returns be balanced in the context of global health ventures?
17. Should global health venture funds be the sole funders (vs. syndication with traditional venture capital) in an investment seeking to ensure social goals?

Other
18. How can foundations find ways to 'invest' in global health companies and build the marketplace for such companies?
19. What are the major barriers to investing in global health for traditional venture capital, and how might these be overcome?
20. How might we explore social/DBL venture capital in the emerging market setting?
21. What are the lessons learned from the first wave of social VC funds?
22. How can we facilitate a common ‘marketplace’ for investors and entrepreneurs interested in addressing neglected diseases?

We invite participants of the Financing Global Health Ventures workshop to ponder these questions, bring new ones to discuss and help us envision a new future of sustainable investing and enterprise for global health.
## Appendix A: Examples of Equity-Financed Global Health Innovations

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Equity Investor</th>
</tr>
</thead>
<tbody>
<tr>
<td>A to Z Inc</td>
<td>African manufacturer of bed nets</td>
<td>Acumen Fund (Debt)</td>
</tr>
<tr>
<td>AAR Health</td>
<td>East African HMO – (Health services)</td>
<td>Aureos Capital</td>
</tr>
<tr>
<td>Acambis</td>
<td>Vivotif — oral typhoid</td>
<td>Oxford Bioscience</td>
</tr>
<tr>
<td>BioSyn (now Cellegy)</td>
<td>Savvy — HIV Microbicide</td>
<td>ProVenEx and Warburg Pincus</td>
</tr>
<tr>
<td>Celera</td>
<td>ViroSeq — HIV-1 genotyping system</td>
<td>Burrill &amp; Co.</td>
</tr>
<tr>
<td>Chemogen</td>
<td>Rapid urine-based TB diagnostic</td>
<td>CEI Ventures</td>
</tr>
<tr>
<td>LabNow</td>
<td>CD4Now — Remote CD4 diagnostic device for HIV/AIDS</td>
<td>Austin Ventures, Perseus-Soros Biopharmaceutical</td>
</tr>
<tr>
<td>LabNow</td>
<td>CD4Now — Remote CD4 diagnostic device for HIV/AIDS</td>
<td>Austin Ventures, Perseus-Soros Biopharmaceutical</td>
</tr>
<tr>
<td>Napo Pharmaceuticals</td>
<td>Crofelemer — Anti-diarrheal drug</td>
<td>Angel Investors</td>
</tr>
<tr>
<td>PointCare Technologies</td>
<td>CD4 monitoring device for HIV/AIDS</td>
<td>Angel Investors, Strategic Partners</td>
</tr>
<tr>
<td>Sequella</td>
<td>Transdermal Patch — TB Diagnostic</td>
<td>Angel Investors</td>
</tr>
<tr>
<td>Shelys</td>
<td>Antimalarial drug</td>
<td>Aureos Capital</td>
</tr>
<tr>
<td>VaxGen</td>
<td>AIDS vaccine</td>
<td>Burrill &amp; Co.</td>
</tr>
<tr>
<td>VaxInnate</td>
<td>West Nile vaccine</td>
<td>Oxford BioScience</td>
</tr>
<tr>
<td>Voxiva</td>
<td>Alerta — epidemiology surveillance</td>
<td>Angel Investors</td>
</tr>
</tbody>
</table>
Appendix B: A Case Study of Napo Pharmaceuticals

Napo Pharmaceuticals is committed to responsibly developing, manufacturing and distributing life-improving drugs on a global basis, mindful of risk management criteria and investment return.

—Napo Pharmaceuticals mission statement

Napo Pharmaceuticals Inc. is a South San-Francisco, venture-financed company that develops drugs for the world market. The company's first product, Crofelemer, is an anti-diarrheal targeting HIV/AIDS related diarrhea and diarrhea predominant- irritable bowel syndrome (D-IBS). Originally developed by Shaman Pharmaceuticals, the patent and development work (through a Phase III trial) was acquired by Napo in 2001 after Shaman filed bankruptcy that year. Crofelemer is derived from the latex of Croton lecheri, a tree which grows along the Napo River in South America. Shaman Pharmaceuticals was dubbed a 'tree-hugger's dream' by The Economist for its sharing of profits with the community from which the plant was sourced. Napo Pharmaceuticals, the new firm, is now headed by Shaman founder Lisa Conte. Ms. Conte took Shaman public in 1993 at a firm value of $150 million after $15 million in venture investment over 4 years.

Working toward global development and commercialization, Napo Pharmaceuticals recently licensed the US development of the D-IBS indication to Trine Pharmaceuticals and raised funds from strategic partners. Glenmark Pharmaceuticals Ltd. of Mumbai and AsiaPharm Group Ltd. of China have invested in Napo and agreed to develop Crofelemer for global markets. The goal is to reduce cost of goods through increased volume, which will drive profitability in the industrialized markets and accessibility in the developing world. Commenting on the Glenmark deal, C.E.O. Lisa Conte remarked:

This collaboration allows Napo to bring a novel therapy for these debilitating and sometimes deadly diseases to both traditional Western markets and resource constrained areas of the world. With Glenmark and AsiaPharm we secured investment four months after starting partnership talks. All the incentives lined up: We will get through development in India in two years, and reach dozens of countries in the developing world. In our case, we just weren't able to match that scale or speed with non-profit partners, even though we were willing to donate the drug.

Napo Pharmaceuticals aims to generate strong financial returns for investors and founders alike, and to deliver a novel drug to those who need it most. Napo's dual market strategy with domestic and global partnerships holds greater promise, especially when paired with fast-track approval from the FDA for the HIV indication and Trine targeting the new and much larger D-IBS market. However, Napo's predecessor, Shaman Pharmaceuticals, closed its doors in 1999 long after going public—and while it delivered financial returns to early investors, it lost money overall. The firm stalled before bringing Crofelemer to market and consequently never made any direct impact on health—providing some valuable lessons for Napo's investors.

As a company seeking venture financing, Napo Pharmaceuticals appears to have a strong profile. The market for Crofelemer is enormous—the U.S. D-IBS market alone is estimated at $4 billion. Proof of concept for this indication is expected in 2006, which will likely drive up the valuation the company. The momentum generated from the recent FDA fast-track designation for HIV/AIDS-related diarrhea will likely expedite the development process, and the worldwide development partnerships bode well for product commercialization.

Company Financing History

C.E.O. Lisa Conte raised funding for Napo Pharmaceuticals primarily from angel investors, many of whom were investors or partners of Shaman.
Conte cites two reasons for the choice in financing strategy: 1) deal size, as she was looking initially for small amounts of capital (i.e. Series A of $1.7 million) and 2) desire to grow the business for global markets which she felt would put her in direct conflict with investors looking to maximize short-term returns. 'We needed patient investors,' said Conte. 'In the long run our strategy will allow us to squeeze every customer out of the world markets, delivering greater financial return.' The table below presents Napo Pharmaceuticals’ investment history.

### Napo Pharmaceuticals Capitalization

<table>
<thead>
<tr>
<th>Investment Round</th>
<th>Date</th>
<th>Amount Invested</th>
<th>Post-money valuation</th>
<th>Share Price</th>
<th>Investor</th>
<th>Use of Funds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series A</td>
<td>2001</td>
<td>$1.7 million</td>
<td>$2.4 million</td>
<td>$0.30</td>
<td>Angels+2 small VCs</td>
<td>Tech acquisition, Recruit management</td>
</tr>
<tr>
<td>Series B</td>
<td>2003</td>
<td>$3.5 million</td>
<td>$10.0 million</td>
<td>$0.50</td>
<td>Angels</td>
<td>HIV-indication fast-track, TRINE partner</td>
</tr>
<tr>
<td>Series C</td>
<td>2005</td>
<td>$10.0 million</td>
<td>$22.0 million</td>
<td>$0.85</td>
<td>Partners, Angels</td>
<td>Manufacturing deals: AsiaPharm (China) and Glenmark (India)</td>
</tr>
<tr>
<td>Series D</td>
<td>Expected 'Final Round' $8-to-$10 million to be raised late 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase III approval, Pre-IPO preparations</td>
</tr>
</tbody>
</table>


3 ‘Exit’ most often refers to an initial public offering or a merger/acquisition to create liquidity for investors.


10 Ibid.


14 PriceWaterhouseCoopers—2004

15 Ibid.


17 For products referenced in NVCA 2004 (see Endnote 1).

18 Daron Acemaoglu and Joshua Linn ‘Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry,’ University of Toronto.

19 For a full discussion of these barriers see Free 2004.

20 AVANT Immunotherapeutics (Rotavirus and HIV vaccines), LabNow (HIV monitoring device) and Napo Pharmaceuticals (diarrheal drug)—see Appendix.


22 Moran M 2005

23 Moran M 2005

24 Three such VC funds—APIDC (India), Bioveda (China) and Bioventures (South Africa)—are represented at this workshop; Work by Motari et al. South Africa—blazing a trail for Africa biotechnology. Nature Biotechnology. 22: Supplement. http://www.utoronto.ca/jcb/home/news_nature.htm

25 Global Fund for AIDS, TB and Malaria (GFATM)

26 Foundation Strategy Group and Rustom Masalawala (former director of Acumen Fund’s Health Portfolio)

27 The Initiative on Public-Private Partnerships for Health (http://www.ippph.org/) listed 92 PPP’s in its database (this number includes all PPP activity, including the small number of organizations that make drugs, vaccines, and microbicides; and one-off partnerings such as donations and cut-price deals) (Moran M 2005).


29 Moran M 2005. Glaxo SmithKline, Novartis,
Sanofi-Aventis and AstroZeneca are among the large multinationals with neglected-disease institutes, often located in developing or emerging markets.

E.g., Investors' Circle, Band of Angels (India), Angel Health Care Investors and Tenex Medical Investors.

VentureXpert (2005).

Ibid.

Pharmaceutical Research and Manufacturers of America (March 2005)

VentureXpert (2005).

PriceWaterhouseCoopers/Thomson Economics—Database 2005. See also 'Preface on Terminology'.

AVANT Immunotherapeutics (Rotavirus and HIV vaccines) and VaxGen (AIDS/HIV vaccine) are examples.

VentureXpert (2005).

Ibid.


The product is called 'Savvy', a vaginal microbicide that women can apply themselves to prevent the transmission of HIV and other sexually transmitted diseases.

Voxiva, Chemogen, BioVirX, LaGray Pharmaceuticals, et al.


Free 2004

Moran M 2005

www.napopharma.com

VentureXpert (2005).

Conte 2005

Ibid.