



Inside the Minds: Best Practices for Biotechnology Venture Capital

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Investing in Consumer-Directed Health: A New Opportunity for Venture Capital Investment

The Emergence of Consumer-Directed Healthcare

Since its inception, the healthcare industry has been principally focused on treating the sick members of society, rather than preventing the occurrence of disease in the majority of the population who are in generally good health. The biotech industry evolved within this “disease-care” model and has achieved dramatic medical breakthroughs in the treatment of acute diseases ranging from oncology to immunology to neuroscience. These early successes have led to the growth of a complete ecosystem for transferring biotechnology innovation out of research laboratories into biotechnology companies and financing development of these technologies with and variety of capital sources, including venture capital.

In recent years, the industry has begun to move away from this disease-focused treatment paradigm into a health-oriented paradigm that addresses global health from three perspectives: the identification of a predisposition to various conditions; the diagnosis of an individual’s progression down that path; and the identification and development of preventative treatments and individualized approaches to those treatments, in order to fit various lifestyles.

This dramatic shift of the healthcare industry’s focus from disease care to health care is driven by demographic shifts, increased prevalence of chronic disease, and increased availability of consumer-focused healthcare information. Globally, the population is aging, which, in turn, leads to increased health costs. Consequently, all developed and developing economies are facing a

similar challenge of having to supply health care to a population that is transitioning into high health care cost years; and the only way that a nation can maintain health care as a service is to shift into a more preventive mode, and involve the individual patient in the design of and compliance with a particular health care program. As a result, we expect to see increased consumer involvement in developing new health care choices and business models; and new services are likely to emerge that are different from traditional medical models. For example, in the near future an individual might have a real or virtual health care coach just as they would have a financial advisor—someone who is more accessible, real time, and involved in their daily life than the traditional medical practitioner. With the rapid application of IT into healthcare, this coach could work with the consumer in an office setting, or online, or via a mobile device.

Other key aspects of the evolution of the biotech and pharmaceutical industry include the increasing cost of drug development; increasing risk aversion on the part of the FDA; a reduction in the number of in-house development programs at large pharmaceutical companies; and the need to outsource more innovation and development of new technologies. Therefore, the role of venture capital (VC) and entrepreneurship in general with respect to developing, providing, and in-licensing new technologies to large biotech companies is likely to continue and expand. Pfizer, for example, is investing \$10MM per year in a new incubator facility in La Jolla to support life science start-ups that are working on projects related to the company's prime therapeutic areas. Venture capital will be playing a major part in financing these developments, and taking on some of the risks that are involved in bringing forth some of those non-core technologies. We also see an opening of the innovation process within these larger companies where new models of technology development are emerging. Increasingly, we are seeing the development of joint ventures and spin-out/spin-in structures to accelerate development of new technology on a capital efficient basis.

Achieving Success in the Biotech Industry

There are two key factors that are drivers of success in the biotech industry. First, you have to take an innovative approach—do something that is different from what other people are doing. That effort can be driven by a high degree of innovation around a certain area of science, a novel type of drug delivery, or a novel way of approaching the system—i.e., a product or technology that is much cheaper or more convenient than whatever is currently in the marketplace.

Secondly, one needs to consider that the increasing personalization and individualization in this space is increasingly aimed at matching a drug to an individual, and an individual disease type or genomic type. Therefore, one must really understand the ecosystem into which a new therapy will be launched—how the marketplace, including payers, physicians, and patients, will interact around that particular therapy.

Identifying Opportunities in the Consumer-Directed Healthcare Space

Our VC firm is seeing two key changes in the health care paradigm—a move towards more discretionary consumer dollars being spent on health care; and an increase in the amounts of health care dollars being spent on areas such as chronic disease and aging, as opposed to acute

diseases. Therefore, our VC firm looks for investment opportunities that align with these new macro trends, and which fit into a health care paradigm centering on chronic diseases.

Indeed, in addition to the evolution in the medical realm, we are seeing an evolution in the venture investing industry. While some many successful life science venture firms continue to invest in traditional therapeutics, there is a significant increase in the number of VC firms pursuing more consumer-directed portfolio companies and investment opportunities centered on treating the chronic disease paradigms described above. We have adopted this consumer-focused approach to healthcare VC investing because we anticipate that this is a growing trend, likely to yield significant returns in the coming years. In order to choose our investment opportunities we utilize many different sources of information and deal flow including health care providers, consumer products companies, big biotech and pharmaceutical companies, and universities; and the conversations that we have with those sources enable us to develop connections between available technologies and emerging market needs. We aim to identify consumer demand for a particular service, therapeutic, or diagnostic and connect that demand with appropriate emerging technologies, products and companies. By focusing on the consumer demand driving the adoption of products we are better able to understand the market risk associated with commercializing a given technologies and identify business models and development plans that increase the probability of successful development and market launch.

Indeed, our overall focus is on identifying the most potentially successful emerging consumer-health markets. We believe that there are always going to be a number of technologies that will be competing in different markets, and therefore it is important to find other partners who have greater areas of experience around technology assessment. One of our firm's key differentiators is having a better understanding of a company's potential success in the marketplace—a product could be technologically successful in terms of going through a clinical trial and getting approved by the FDA, but if it is not designed to fit a market need, it will not be successful with the ultimate consumer. Simply put, if a product is difficult for patients to use, or difficult for physicians to prescribe, it is not going to be successful in the marketplace, notwithstanding its technical success.

Therefore, we have structured our firm in such a way that we are better able to seek out those opportunities that have the greatest chances of success. For example, we have members on our investment team who are PhD scientists, as well as MDs, executives from health care providers, healthcare consultants, and healthcare marketing experts. Our advisory board includes MDs, and executives from some of the major health care payers, such as insurance companies. Essentially, we try to think about the whole ecosystem of a particular healthcare company, rather than assessing an investment purely from a technological perspective.

Best Practices for Biotechnology Venture Capital

Evaluating the Risk in a Healthcare Investment

When reviewing our portfolio of companies in our current and previous funds, the key determinant of success has been and continues to be good management—having a seasoned management team who are extremely driven is probably the single best determinant of

execution success. Therefore, we always work to get comfortable with our assessment of the management team before we are ready to evaluate the rest of the opportunity.

Any biotech investment has a risk-return profile associated with it and typically the earlier the stage of the technology, the company, and the product, the larger the amount of risk. For example, if a particular investment opportunity is an early stage technology company, then that investment will involve a high degree of technical risk. Alternatively, if a particular opportunity is a later stage investment—i.e., the technology is already in clinical trials or approved—then we are primarily concerned with execution risk. Therefore, we manage our portfolio of investments to balance the risk-return profile of the entire fund by making a mix of investments in early, mid and late stage companies. We also aim to balance technical risk with market and execution risk. This balancing helps to isolate the performance of our portfolio from external macroeconomic factors, such as the stage of the economic cycle. In periods of strong economic growth, those portfolio companies with strong consumer product portfolios are expected to perform well, while those companies still in the technology development phase will face higher costs and competition for research resources and personnel. Conversely, in a recessionary environment, those companies working on technology development will benefit from an improved supply of R&D resources and labor, while those companies launching consumer products will face a more challenging environment.

We also look at risk in terms of stages. For example, if we are looking at an early stage company we will break the product development and market launch development of the company into various discrete segments so that we can finance the company through a particular stage. We always want to understand what happens next; and we try to lay out an overall plan for development—i.e., when do we need to raise new money and bring on new management; and when do we need to make certain strategic connections in order to reduce risk? We try to understand risk at every stage so that we can then work backwards and determine what the company's valuation should be in order to hit some of our return expectations.

Ultimately, the risk in a investment has to be balanced against the potential investment reward. One needs to look at the company in its entirety—the strength of its team and technology; potential market size; and potential for a good exit—we balance all of those factors against the risk we are taking on the investment. If the potential rewards are very high, we may decide to take on higher risk in a particular area, such as IP or technology and then develop strategies to monitor and mitigate this additional risk. We are very mindful of taking on small additional amounts of risk across all of the factors necessary for ultimate success as we find that these risk factors are more multiplicative than additive and not aggressively monitoring your additional risk may dramatically raise the overall risk profile of the investment.

Meeting with the CEO and Management Team

As previously stated, we place top priority on the strength of a biotech company's management team; and while you can learn something about the abilities of those team members by researching their track record, it is also important to meet with them and develop a shared vision of how to successfully develop the company. We always want to know how much of an

understanding the team has with respect to their technology's role in the marketplace; how receptive they are to outside input; and how well they interact with their board members. Essentially, we need to judge the team's abilities, and how easy it will be to work with them.

We also need to understand the CEO's vision for their company. Is the CEO prepared and motivated to lead the kind of rapid growth company required to generate the returns required for a venture capital investment? Or does the CEO want to build a more modestly growing, lifestyle company? We also need to evaluate if the CEO is able to draw other skilled and talented people to their enterprise. As the company develops, its ability to grow its management team is important; therefore, we need to ascertain whether the CEO can articulate a vision for the company that will attract top people from the industry to come and work with them. Perhaps most importantly, we need to get a sense of whether or not we can work with the management team in the years to come, and whether they will be able to execute on the plan they develop. In some cases the CEO will play a critical role in the company for the first two years, but he or she may not have the skills that the company will need going forward; and that kind of assessment can only be made in a face-face meeting.

The Due Diligence Process

We conduct a standard due diligence process for all potential investments. We analyze the company's track record, their technology, Intellectual Property (IP), the potential market, and their customers and suppliers. Our goal is to determine whether a particular therapy is best and/or first in class, and where the company's product is going to sit in the health care ecosystem. We are not interested in investing in therapeutics or other biotech products which are simply great technologies; we also have to understand how and why a consumer is going to be attracted to select that product and benefit from it. Also important is the question of "Who pays?". While this may seem simple in concept, we need to appreciate that the answer to that question may change during the development of the technology depending on how the go-to-market adapts to marketplace changes. We always look for multiple motivated payers to support the successful market introduction of a new product or service. Consequently, any technology that we invest in has to offer an improved consumer experience in terms of drug delivery and efficacy, and that could be something as simple as a pill that is easier to swallow, or a pill that you only have to take once a day as opposed to three times a day. In other instances, it might be a drug that is cheaper, or which has fewer adverse side effects or additional associated benefits, such as a diabetes drug that also helps patients lose weight. In each of these cases the consumer would benefit, increasing compliance and lowering overall treatment cost while delivering a benefit of improved health which are goals strongly supported by their insurer and medical team.

Therefore, we have a few key considerations in the due diligence process—does the company have a good technology, and will a technology person at a potential acquirer be interested in buying it; and when that product goes to the consumer how will you describe it and market it? Why would the consumer go to their physician and say they want that product? Ultimately, we take a holistic approach to the analysis process, by using a broad set of advisors for analyzing a product's market potential along with its technology.

Valuations and Exit Strategies

Three Valuation Strategies for Biotech Companies

We use the three standard approaches to establish valuations for biotech companies—top-down, bottom-up, and sideways. The top-down approach involves looking at the potential size of the markets that the particular technology is going to be selling into, and trying to estimate the share of the market that technology could conservatively achieve, as well as what the potential revenues and margins are likely to be. We then determine what the valuation of the product/technology would be if it were to achieve those goals; and then we discount that valuation back to today using our estimated cost of capital. Based on the exit valuation, we determine what fraction of the valuation company we would need to own to meet our cost of capital.

The bottom-up valuation approach is based on assigning value to what the company has already achieved. For example, if the company has recruited three prestigious scientists, licensed ten patents, and it has two products in clinical trials, we can use experience from our previous investments and those made by other VC firms to assign a value to the company based on these assets. We have a large database of companies that we use to compare valuations at various stages of development and we use this to assess the proper valuation of the company at various stages as it reduces the risk of the technology and creates additional value.

Finally, the sideways approach entails looking at comparable investments that have been made in that class of technology, stage of technology, and market sector—i.e., what are typical B round valuations for metabolic disease companies that have one product in clinical trials?

We typically apply all three valuation approaches to a company or a technology before making an investment—and ideally, we would like to see all three line up in the same way in terms of achieving a similar consensus value that makes sense for us in our investment thesis. In the case of earlier stage companies where there is a lot of technology risk and not a lot has yet been achieved we would probably rely more heavily on a top-down valuation—i.e., what is the potential market that could be achieved?—and we would apply a very conservative probability (ten percent or less) that the company will actually be able to achieve those valuations. For later stage technologies where the company may have revenues or at least be at the clinical trial stage we would rely more on an analysis involving comparables of companies with similar technologies that have recently exited. Frequently, we also consult with Investment Banking firms to understand how the public markets are currently valuing similar companies and technologies.

Achieving Successful Biotech Valuations

One never knows for sure if a valuation was appropriate until the company has reached exit and the investment return on that company is known. Our primary goal is to construct a portfolio of companies at different stages of maturity with different risk profiles so that the overall portfolio rate of return is in excess of 1500 basis points above the risk free rate. Since not all individual investments will be successful, our return projections for an individual investment typically target

returns in excess of this target. However, there are other intangible aspects to the valuation process. For example, we want to create a capitalization structure for the company such that the original founders, scientists, and professional investors have an equitable ownership stake so that we can achieve the type of return we are seeking, and the founders have sufficient ownership so that they are incentivized to succeed.

Generally, an early stage company that is not yet in clinical trials would be valued somewhere between \$5-10 million. However, valuations in this space typically move up and down that valuation range, depending on whatever factors and risks are involved with respect to the management team, market competition, or the pace of clinical trials. A company that is in Phase I clinical trials would typically have a \$10-20 million valuation; a Phase II company would have a \$30-60 million valuation; while a Phase III company's valuation would be based on hard metrics centered around the size of the market, phase of development, regulatory risks, and how much money it will take to achieve commercialization.

Valuation Trends in the Biotech Industry

Valuations change on a regular basis in the biotech area. Valuations of private companies tend to move in step with comparable companies trading on the public markets. However, when valuations are down in the public space there is often a time lag with respect to how long it takes for private companies to accept that the lower valuation is a new permanent level, and not just a temporary adjustment. There is a tendency for private companies to perceive themselves as undervalued; therefore valuations in this space tend to rise up quickly when the public market valuations rise, but drop more slowly when there is a drop in the public market. We are currently seeing a lack of liquidity in the marketplace; therefore we expect valuations in the biotech space will drop a bit reflecting the longer time required for exit and the increased refinancing risk.

Biotech Exit Strategy Options

The three standard exit options for venture backed companies in the biotech industry are merger and acquisition (M&A), Initial Public Offering (IPO), or bankruptcy. An interesting element of differentiation in the biotech space pertains to the fact that the IP that biotech companies accrue during their development almost always has some value. Additionally, Biotechnology companies differ from IT companies in that they often own discrete parcels of IP; for example, they can have several different drugs in clinical trials for different indications, or for completely different molecules. Therefore, one can monetize some of the assets via licensing or sale while keeping another set of assets within the company. Recently, we have seen some interesting exit models where a biotech company will start with two molecules for different indications—one of which is intended to be partnered and sold fairly early in order to provide cash to finance the other molecule, which is then developed in-house in the hopes of being taken to exit. Consequently, there is a great deal of flexibility creatively manage the assets of a biotechnology company to maximize its potential return for investors.

When to Pursue an Exit

The best time to pursue an exit of a biotech company is when there is tremendous excitement around the space. A biotech firm's management and investors should frequently discuss when the company's exit is going to be. It may not be for another five years, but it is important that they always maintain a focus on providing a liquidity opportunity for their investors, and that management design and build the company with that goal in mind, and execute on that plan.

As the company develops one will typically develop a better sense of when it is a good time to exit. For some companies that will be early in their development, because they have technological assets, such as drugs in development that will enable them to show success early on and generate a profitable early stage exit. Other companies, however, will need to go to the end of a Phase II B clinical trial before they exit—historically, the best time to exit is when you have generated enough proof in your technology that a large acquirer would find it to be of value. A smaller company would typically have to raise such a substantial amount of capital to get to a Phase III trial and FDA submission that the original management and investors would be highly diluted; therefore a venture investor would generally wish to exit before that point. Often, the desirability of assets will fluctuate depending on competitive actions and marketplace dynamics. For example, following the Vioxx issue, Merck went on a buying spree to fill to pipeline needs and this raised the price and interest for early stage companies. Interestingly, since many of the companies in the industry were afraid of a repeat of the Cox-2 issues, they migrated away from inflammation and other chronic diseases due to a belief that these conditions had an inherent question about long-term safety. This made assets in this area relatively cheap and only recently have acquirers returned to this area with interest. We typically access the expertise of an investment banking firm to advice on exit negotiations for our target companies. Depending on the transaction type, a management team may have limited experience in identifying who potential acquirers might be and valuing their technology; therefore, it may be useful to utilize the services of investment banks that specialize in all areas of biotechnology in order to create a greater level of interest in the company and to start the negotiating process.

Final Thoughts

Management Team Mistakes to Avoid

Entrepreneurs are optimists by nature, and we like them for that reason, because if you are not optimistic about the future of your technology and company then you are not likely to take the risk of leaving a steady job and invest the time, effort and passion to create that new company. The downside of being optimistic without being realistic about what is needed for successful execution is that a management team may well not plan for the inevitable delays and difficulties that occur in the product development process and that over-optimism leads to the company not raising enough capital to reach an inflection point in their valuation. If the company finds that they cannot exit at the point where they thought they could, they will then be stuck in a very difficult position where they do not have enough capital to de-risk the technology and reach that increased valuation point—and it is very difficult to raise capital in such a scenario. Therefore,

one should always be conservative with respect to how the company is going to achieve its exit plan, and make sure that the company has plenty of financing to make sure you can achieve it—even if things go wrong, and it takes a lot longer to exit than you originally anticipated. There is an old axiom in the industry that no company ever went bankrupt due to dilution.

Indeed, the biggest mistake that management teams make is being so sensitive about dilution that they do not raise as much money as they will actually need; instead, they try to develop an R&D plan that is based upon perfect execution. It almost always takes longer and costs more to develop a technology than you can possibly foresee; and if you do not raise enough money in your first funding round you will have to raise the next round at a lower price.

Another major management team mistake is a reluctance to “sell the baby.” Many companies feel that there is such value in their technology that they are very reluctant to partner and give away any of their future economics, rather than looking at such an opportunity on a holistic basis—i.e., what kind of risk can we reduce by bringing on a development partner, and what is an appropriate share of the economics for that risk reduction? Rather than taking a financial view of the situation, many management teams take an emotional view that will wind up costing them money in the long-run.

A third management team mistake which we see quite often is a general reluctance to switch from what looks to be a failed lead program to something that is earlier stage, but probably offers more long-term upside. For example, if a company raises money to progress a compound from Phase I to the end of Phase II testing, then even if all the red flags and warning signals point to the fact that there is a low probability that the compound will be successful, the management team may still feel that because they raised money on the premise of taking the compound to Phase II they are obligated to do so—rather than making the hard decision to cancel that program, preserve cash, and move to an earlier stage program. Indeed, many times a biotech company will roll the dice and make a single bet that a certain compound will be successful; and when it does not succeed the whole company is gone, because it does not have any cash left, and the team has no back-up plan.

VC Mistakes to Avoid

A common mistake that many VCs make in this area occurs when they fall in love with a technology and invest in it, although the potential returns—once one weighs the risks and market factors—may not make it such a good investment. Indeed, just as entrepreneurs are often reluctant to “kill their babies,” VCs often display a similar mindset. Once we have made an investment and sunk a lot of capital into it, it can be difficult to pull the plug, even when things are going wrong and a cooler head would say that it is not worth investing good money after bad. Another common mistake in VC healthcare investing is to fall into the herd mentality. The VC industry is fairly conservative and we tend to move as a group; if one firm sees that several other firms have had success investing in a particular therapeutic, they will tend to also search for an investment in that area. This increases competition for particular investments, driving up valuations, and therefore reducing the potential financial return to the VC firm.

Another challenge that applies to VCs investing in all areas, including biotech and healthcare, is the tendency to spread oneself too thin by serving on too many boards. This prevents the VC from being able to focus sufficiently on any one company. Therefore, if a problem arises at a particular company it can take too long to recognize that problem and to make the required changes.

Finally, a common mistake that both VCs and management teams make is to believe that our companies are worth more than they actually are; and as a result, we postpone an exit while waiting for a much higher future valuation—which may or may not ever happen.