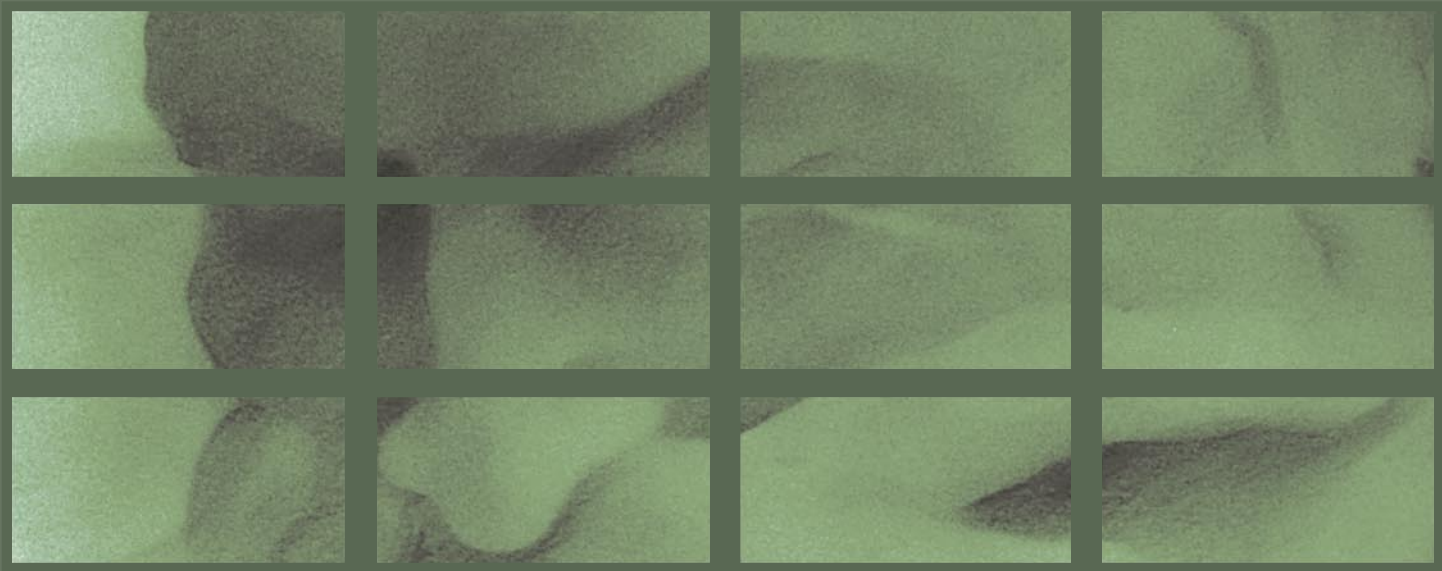


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Contents

<p>ABOUT THE AUTHOR 1</p> <p>ACKNOWLEDGEMENTS..... 2</p> <p>AUTHOR'S NOTE 3</p> <p>THE BIG PICTURE..... 5</p> <p>EVALUATING THE IDEA..... 11</p> <p>THE BUSINESS PLAN..... 15</p> <p>PEOPLE 19</p> <p>PATENTS..... 22</p> <p>ATTORNEYS..... 29</p> <p>LEGAL ISSUES..... 31</p> <p>ACCOUNTING & FINANCE 36</p> <p>REAL ESTATE 42</p> <p>RISK MANAGEMENT & INSURANCE 46</p>	<p>MEDIA & PUBLIC RELATIONS 50</p> <p>PHARMACEUTICAL BUSINESS DEVELOPMENT 52</p> <p>DEVICE, DIAGNOSTIC, & INSTRUMENT MODELS 57</p> <p>DRUG PRICING PRINCIPLES 58</p> <p>CLINICAL DRUG DEVELOPMENT..... 62</p> <p>MEDICAL DEVICE APPROVAL..... 70</p> <p>EQUITY 76</p> <p>RAISING MONEY 82</p> <p>GOVERNMENT GRANTS..... 89</p> <p>IPO: GOING PUBLIC 93</p> <p>NETWORKING..... 95</p>
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In praise of *The Entrepreneur's Guide to a Biotech Startup*:

"I have not seen in one reference all of the topics which the Guide covers; it should be an invaluable aid to biomedical entrepreneurs."

-Michael Lytton, General Partner, Oxford Bioscience Partners

"The Entrepreneur's Guide is also relevant for non-entrepreneurs with industry experience who want to know how a biotech company gets to where it is and where it can possibly go. Well done. "

-David Bancroft, PhD, VP Automation & Head of Intellectual Property, GPC Biotech AG

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ABOUT THE AUTHOR

Dr. Peter Kolchinsky performs due diligence on investment opportunities at RA Capital Associates, a biotech-focused public equity fund. He works closely with Richard Aldrich, a founding employee and former CBO of Vertex Pharmaceuticals.

Peter is the author of *The Entrepreneur's Guide to a Biotech Startup*, a business aid published on www.evelexa.com. Evelexa is an online resource for biotech entrepreneurs and investors, which he launched in 2001 and grew to a membership of 5000 within two years. He also co-founded BiotechTuesday, a popular monthly networking series for the Boston biotechnology community, and the

Harvard Biotech Club, both of which exceeded 2000 members in their first two years and continue to prosper. He has spoken at colleges and graduate schools on biotech entrepreneurship and career development and enjoys helping scientists consider the leap into business.

Peter received a Ph.D. in Virology in 2001 from Harvard. His thesis research in Dr. Joseph Sodroski's laboratory at the Dana-Farber Cancer Institute focused on HIV entry mechanisms. He graduated *cum laude* from Cornell University with a degree in Microbiology. He is also an alumnus of Phillips Academy Andover.

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AUTHOR'S NOTE

ORIGIN OF THE GUIDE

In January 2000, a post-doctoral fellow in my research laboratory approached me to discuss a technology he had developed. He wanted to start a biotech company. I offered to draft an executive summary and help secure financing. Two weeks later, we had an attorney and a three-month option to exclusively license the key patents from our research institution. We met with venture capitalists, who told us that without an experienced management team the company was not ready for funding. A local biotech company offered to incubate our venture but demanded a majority stake. At the time, this seemed unreasonable, and we stalled as we considered our lack of other options. With obstacles looming ahead, our three-month option expired and the university technology licensing office made it clear that it would no longer consider giving an exclusive license to a startup company.

After that failure, I began to systematically study the entrepreneurial process. I supplemented what I learned from business books by interviewing attorneys, investors, entrepreneurs, and other professionals (see Acknowledgements). Subsequently, I wrote *The Entrepreneur's Guide to a Biotech Startup* (the "Guide") and published it on Evelexa.com early in 2001.

Shortly thereafter, I was hired as an investment analyst by Richard Aldrich, a seasoned biotech executive who had just left his post as Chief Business Officer of Vertex Pharmaceuticals to start RA Capital Associates. My job was to evaluate a mostly public and some private companies as potential investments for our fund. The last few years have reinforced our belief that the expensive and protracted development cycles of the typical biotech model would not lead to sustainable businesses in the future. Our investments tended to be in biotech companies that operated efficiently and could achieve profitability in the near-term.

Based on my experience at RA Capital, I have revised the Guide several times. Each new edition featured new chapters, many of which were guest authored by experts. This 4th Edition, in particular, is considerably more pragmatic than earlier versions in addressing the challenges facing emerging companies.

THE PURPOSE OF THE GUIDE

The Guide was designed to present a framework for evaluating a business concept and describes the many steps involved in starting a biotechnology company. The

first three chapters of the Guide ask the reader to consider and explain how a new concept will succeed where old concepts have failed. Subsequent chapters are more of a how-to manual on assembling the various pieces that make up a company (e.g. patents, people, and real estate, and funding). The Guide may help to manage the reader's expectations of the risk, reward, and effort involved in starting a company.

The term *biotechnology* here refers to companies whose products require laboratory or clinical development, including medical devices, diagnostics, and pharmaceuticals. In many ways, all startup companies are alike. However, the biotechnology industry, with its long product development cycles and heavy reliance on science and intellectual property, warrants its own text.

The Guide prompts the reader to ask the right questions. The more one knows about the venture-creation process, the more likely one is to ask the most fundamental question, "Does the idea actually justify starting a new company?" and other questions, for example:

- How much will it cost to develop and commercialize a product?
- How large is the market?
- Will customers buy the products and how much will they pay?
- What's the competition?
- Will patent protection be required and feasible?
- Will it be possible to attract the right professionals to the company?
- Will investors want to invest?
- What else could I be doing with my time?

BUSINESS BEFORE SCIENCE

The common denominator among entrepreneurs is creative initiative; they pursue opportunities that are not obvious to others. While entrepreneurs must possess the ability to tolerate tremendous uncertainty in their decision-making, good science demands precision, creating an internal conflict for business-oriented scientists.

Scientists have a reputation for sometimes failing to appreciate the difference between a science, a technology, a product, and a company. The goal of a company is to develop and sell products that will generate enough profit to justify the effort and capital that goes into building the company. Science and technology are just a means to that end. Therefore, to be true entrepreneurs, scientists must learn to put business ahead of science when developing a

commercial strategy. These precepts underlie much of the advice contained herein.

FOCUS ON DRUGS

Many of the examples in the Guide concern drug development because pharmaceuticals command more attention and capital and offer the greatest potential

rewards of any products in the biotechnology sector. A large chapter is dedicated to clinical drug development. Medical device regulatory issues are also discussed in their own chapter. Readers interested in other businesses, e.g. instrumentation or agricultural biotechnology, will still find the Guide useful but may need to draw their own parallels.

RECOMMENDED READING

The Entrepreneurial Venture, William A. Sahlman, Howard H. Stevenson, Michael J. Roberts, and Amar Bhidé, Second Edition, 1999, Harvard Business School Press. Amazon.com price: \$32

The authors attempt to deconstruct the entrepreneur, construct a business plan, and discuss everything from intellectual property to venture capital. The chapter titled "How to write a great business plan", by William A. Sahlman, provides a good overview of this topic.

Angel Investing, Mark Van Osnabrugge and Robert J. Robinson, 2000, Jossey-Bass Publishers. Amazon.com price: \$26

In addition to explaining angel investing, this book discusses topics that every entrepreneur should consider before starting a company and meeting investors.

The Entrepreneur's Guide to Business Law, Constance E. Bagley and Craig E. Dauchy, 1998, West Educational Publishing Company. Amazon.com price: \$30

You absolutely must read this book from beginning to end to appreciate the many business and legal details involved in starting a company. The text is fast-paced and not nearly as dry as the title might suggest. After you read it, you will understand the need for hiring a highly qualified corporate attorney right from the start.

Additional Resources:

For a glossary of commonly used business terms, refer to: <http://entworld.org/Content/Glossary.cfm>

THE BIG PICTURE

While many investors and entrepreneurs have made considerable money in biotech, as far as creating self-sustaining profitable companies, the old biotech models have failed, for the most part. Biotech companies have inefficiently deployed capital for the last 25 years, learning costly lessons at investors' expense. Long development cycles and underestimation of risk have resulted, essentially, in the destruction of capital. Many companies focused on achieving milestones specific to product development, financing, or strategic partnership, losing sight of what should be the intended end goal of any solid business venture: profits.

Some may assert that we are at an inflection point and just need to wait a little longer to realize that all the spending and entrepreneurship to-date will pay off. However, there is little reason to believe that today's unprofitable majority of biotech companies, many still struggling to raise capital and develop products of value, are well-positioned to make up for their past mistakes anytime soon. The fact is that biotech's reputation as a promising industry is due to the successes of only a few companies.

With 4000 private and 600 public biotechnology companies worldwide, of which over 50% are in the United States, only a few percent have a track record of increasing profitability, including Amgen, Genentech, Biogen Idec, MedImmune, and a few others that belong to the Big Biotech class. All the rest, regardless how profitable they may have been as investments, are not yet successful businesses.

The biotech sector's poor track record does not necessarily suggest a dismal future for emerging companies. The challenge is to learn from the errors of the past before deciding whether to start a company and how to build it into a successful business.

BIOTECH PAST

Biotech's evolution is marked by fits of innovation. What started with a few scientists cloning proteins, transitioned to antibody development, high-throughput screening of small molecules, and, more recently, in-licensing drugs that were partially developed by other companies. At first companies tried to develop drugs on their own, but they would later actively seek larger partners with whom to share the risk and expense. The logic of these transitions is evident from a review of the sector's brief history.

THE EARLY DAYS

In the 1980s, biotech companies plucked what we now know to be relatively low hanging biotech fruit: recombinant secreted proteins such as insulin,

erythropoietin, and interferon that replace what the body lacks. Developing therapeutic antibodies proved more challenging, but these products also started to be approved with some regularity in the late 1990s.

One out of an estimated 5000 discovery-stage drug candidates goes on to become an approved drug and only one-third of those drugs successfully recoup their R&D costs. Hundreds of companies no one ever talks about anymore failed where Amgen and Genentech succeeded, not necessarily because they were less competent but often because the products they pursued were unexpectedly intractable.

The fundamental problem with the make-your-own-drug model was its tolerance of the cost and duration of drug development; setbacks and expenses we now can better anticipate came as surprises back then. With investors and entrepreneurs thinking that each infusion of capital might just be the last before profitability, the difference between success and bankruptcy often depended on how long investors could stay optimistic. Considering how little was known about the perils of biotech product development, many of the companies in Table 1 (see below) may have been just a coin toss from failure.

Throughout the 1980s, big pharmaceutical companies were slow to realize the potential of biotechnology to create value. They had faith in their own R&D capabilities and were reticent to pay biotech companies for their technologies or drug candidates. With little opportunity to share risks and expenses with Big Pharma, biotech companies had to rely on investors. Eventually, Big Pharma began to buy into the biotech revolution through acquisitions and partnerships, giving biotech companies an alternative to commercializing drugs independently.

FROM PRODUCTS TO TOOLS

By the mid-1990s, a number of investors and entrepreneurs focused on developing "faster, better, cheaper" drug discovery tools. Rather than risk their own capital on the success or failure of a few drugs, tool companies offered Big Biotech and Big Pharma technology licenses and services in exchange for milestone and royalty payments.

The switch from drug to tool commercialization was a fundamental business model shift. Tool development cycles were shorter and less costly, suggesting that these companies would turn a profit more quickly. However, the low barriers to entry allowed a flood of competing companies to appear overnight. Some, like Millennium, took a broad approach to genomics-based drug discovery,

Table 1. Top Ten Drugs by 2001 Sales. Based on similar table published by Decision Resources:
http://www.dresources.com/nature/ntr_1102.pdf

Rank	Trade name	Generic Name	Indication	2001 sales (US \$m)	Company (R&D)	Approved
1	Epogen/Procrit/Epex	Epoetin-a	Anaemia	5,588	Amgen	Jun 1989/Dec 1990/ May 1995
2	Intron A/PEG-Intron/Rebetron	Interferon-a2b	Hepatitis C virus	1,447	Biogen/ICN/Enzon	Jun 1986/Jan 2001/ Jun 1998
3	Neupogen	Filgrastim	Neutropaenia	1,300	Kirin/Amgen	Feb 1991
4	Humulin	Human insulin	Diabetes	1,061	Genentech	Oct 1982
5	Avonex	Interferon-b1a	Multiple sclerosis	972	Biogen	May 1996
6	Rituxan	Rituximab	Non-Hodgkin's lymphoma	819	Genentech	Nov 1997
7	Protropin/Nutropin/Genotropin	Somatotropin	Growth disorders	771	Genentech	Oct 1985/Nov 1993/ Aug 1995
8	Enbrel	Etanercept	Rheumatoid arthritis, psoriatic arthritis	762	Amgen	Nov 1998
9	Remicade	Infliximab	Crohn's disease, rheumatoid arthritis	721	J&J/Centocor	Aug 1998
10	Synagis	Palivizumab	Paediatric respiratory disease	516	MedImmune	Jun 1998

while many focused on one approach: yeast 2-hybrid screening, expression profiling, mouse knock-outs, etc. At first, big pharma paid handsomely to secure access to these technologies. For example, the total value of the deals Millennium signed from 1994-1998 with big pharmas such as Roche, Wyeth, Pfizer, Bayer, Lilly, and Pharmacia neared a billion dollars, though much of this value was locked away in long-term milestone payments. The frenzy over genomics and tool companies manifested itself as a surge in biotech stocks towards the end of 1999 and throughout 2000, as well as a dramatic increase in venture capital and public equity financing of biotech.

In 2001, a report by Lehman Brothers and McKinsey suggested that genomics-based drug candidates were more likely to fail in the clinic because they were not as well understood as candidates discovered by traditional means. The report pointed out that, on average, there were over 100 scientific publications discussing each non-genomic drug in clinical development, compared to only 12 publications about each genomic drug and its mechanism. The implication was that, at least in the near-term, genomics would make drug development less efficient, not more. Needless to say, investors were unsettled.

To make matters worse, the proliferation of similar technologies resulted in oversupply of drug discovery tools. Drug targets and preclinical drug candidates, became commodities. Most companies could not command the high prices for their services that they needed to meet financial projections. Unable to offset high expense, they had to raise more money, frustrating investors who had expected tool companies to reach breakeven quickly. It seemed there was no way to build a biotech company efficiently.

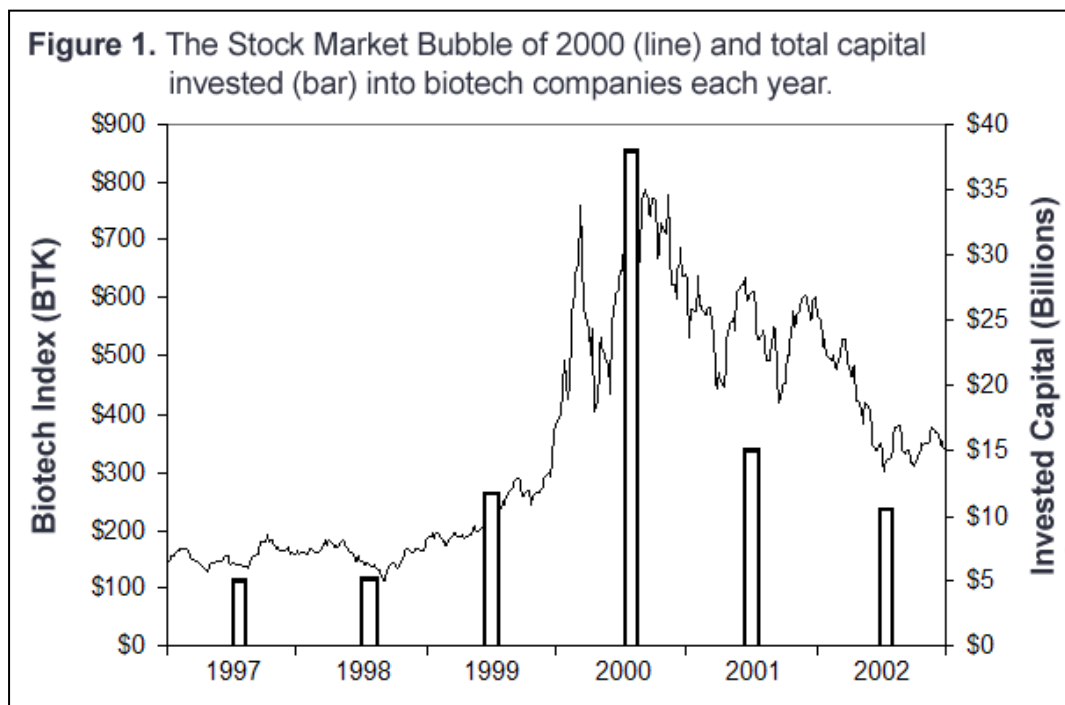
BACK TO PRODUCTS

Enthusiasm for tool companies declined (See Figure 1). Big Pharma stopped doing hundred-million dollar genomics deals and terminated many relationships. Investors cut back funding for tool companies. The collapse of the biotech market, led by the stark devaluation of tool companies, marked the industry's realization that a small company trying to capture the value of a drug had to do most of the development itself. Tired of betting on long-shots in an industry already fraught with risk, drug companies and investors focused their attention on less risky drug candidates closer to FDA approval and sales; in 2003 and 2004, *product repositioning*, finding a new use for an old drug (discussed below), came into fashion.

Many biotech companies in-licensed or acquired drugs, often from Big Pharma. Exelixis, which initially developed animal model systems for functional genomics, licensed the cancer drug Rebeccamycin, already in clinical trials, from Bristol Myers Squibb. Genomics giant Millennium, always a step ahead of the trends, used its stock while it was still highly priced as currency to buy Leukocyte and Cor Therapeutics, acquiring two FDA-approved drugs and a pipeline in the process. Ironically, many of the drug candidates in-licensed by cutting-edge biotech companies had been discovered using old-fashioned methods.

LESSONS LEARNED?

Being successful in biotech, as with any business, is about creating value, and the means are secondary. The biotech product with the highest value is and always has been the successfully marketed drug; profit margins for pharmaceuticals are among the highest of any business. The less a company is involved with actually marketing a drug (for example, by focusing on drug discovery), the



less value it creates. *Science and technology count for little unless they help make a better drug more efficiently, saving time and money.*

DEFINING BUSINESS SUCCESS

Traditional biotech companies consume effort and money for the first 5-10 years or more, offering in return to their shareholders only the promise of downstream profits. Stock is an IOU that entitles the bearer to a portion of a company's assets and profits.

Popular notions of what it means to be a successful entrepreneur are misleading. It's not about building a company and taking it public or increasing a company's valuation day-to-day. It's not about creating jobs or even improving society. Successful entrepreneurship is about building a sustainable, profitable business – everything else is derivative of that simple axiom.

Successful biotech entrepreneurship is less about biotech and more about good entrepreneurship. Whether it is a grocery store or a pharmaceutical company; any business must justify its consumption of resources with profits.

Those of us in the biotech sector who have grown accustomed to measuring success by metrics other than profits, e.g. patent filings, PhDs on the payroll, venture capital financings, may find it worthwhile to review these fundamental principles of business that most everyone outside of biotech finds obvious.

RETURN ON INVESTMENT

When valuing an investment opportunity, consider how much profit one could generate with an alternative investment of capital. If an entrepreneur bought a small store, would a few percent profit (percent of total capital invested) per year be considered a good return? Probably not, seeing as the entrepreneur could buy US Treasury Bonds and earn several percent each year without any effort or risk.

But what if the entrepreneur generates a nice profit each year because he has not hired a staff and is doing all the work himself? He could have kept his savings and found a job that paid equally well managing someone else's store. Therefore, when evaluating a business opportunity, we should also value an alternate investment of the entrepreneur's time.

Opportunity Cost

The merit of an investment should be weighed against how much money you could make by investing elsewhere. An adult earning \$70K annually who then goes to business school full-time incurs not only direct expenses (tuition, room & board, books, etc) but also the opportunity cost of forgoing \$140K in salary during those two years. An investor who puts \$1M into a startup only to receive \$1.6M five years later when the company is acquired may appear to have gained \$600K profit but, in fact, may have lost the opportunity to make an extra \$400K if reasonable investments in the stock market would have conservatively returned \$2M during that period.

THE TIME VALUE OF MONEY

While different businesses have different risk factors, the risk of time is common to all ventures. Time-to-profits is a critical variable in calculating the merits of an investment. What if the entrepreneur needed to spend three years developing the products? A lot can go wrong in that time, and the only sure thing is that the entrepreneur will spend a lot of his money. The opportunity cost of forgoing other investments of money and effort for three years would be high. Only the promise of huge profits down the road would motivate any rational person to take such a risk.

ENTREPRENEURIAL EFFICIENCY

Entrepreneurial efficiency is based on three variables: (1) *invested capital*, (2) *time to profits*, and (3) *profits*. The relationship between all three is graphically represented in Figure 2. The black area between the Expense and Revenue lines is the total amount of capital a company burns before achieving breakeven. If revenue growth outpaces expense growth, the company will rely less and less on investors' capital until it is finally profitable and can theoretically start to give back value to investors. The larger the black area on the graph (accumulated losses), the larger the white area (accumulated profits) must be before you can consider the company a success. Therefore, the company whose performance is described in Figure 2B is more successful than the one in Figure 2C. Unfortunately, most biotech companies resemble Figure 2C and fail before reaching breakeven.

SUCCESSFUL ENTREPRENEURSHIP

To be considered successful, an entrepreneur must start a business that honors its promise of rewarding shareholders for the risks they have taken. These financial rewards are gleaned from the profits a company earns by selling products. Without current or *future profits*,

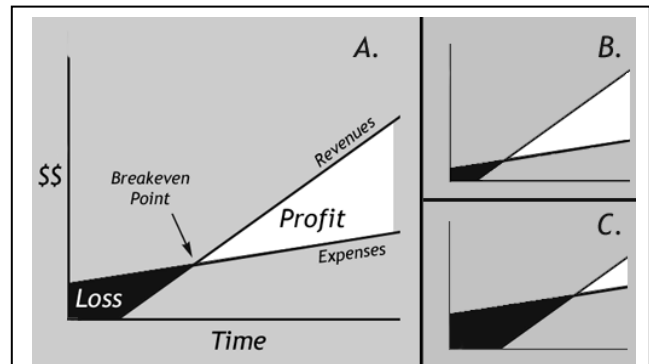


Figure 2. Simple Profit and Loss Model. Keeping expenses low and generating revenue early allows a company to achieve breakeven sooner (shown in B), resulting in lower net consumption of investors' capital (black areas) than if company has higher expenses and takes longer to start generating revenues (shown in C).

companies are akin to Pyramid Schemes, vehicles for moving money from one set of shareholders to another.

Some unprofitable companies with valuations in the billions may appear to be successful businesses considering the handsome returns enjoyed by their founders and early investors. While these companies have indeed been successful investments of effort and money, they are not yet successful *businesses*. At best, you could say that these companies are on their way...

An entrepreneur should not be satisfied that a few early investors profit from the willingness of later investors to pay a higher price for their stock. The company should have a track record of increasing profits, rewarding each new investor with a consistently appreciating share price.

An entrepreneur may profit from selling the stock of a company whose value later plummets when the company

The Ponzi Pyramid Scheme

In 1919, an Italian immigrant named Charles Ponzi discovered that one could purchase a coupon for US postage stamps in Spain for only one-sixth of their value. By buying \$1 coupons in Spain, redeeming them for \$6 worth of stamps in the US, and then selling the stamps to customers, he figured he could make a killing. Ponzi bragged about his get-rich-quick idea, attracting investors who gave Ponzi their money in exchange for IOU notes promising a 100% return in 90 days. People poured into Ponzi's office, arms filled with cash to invest, until the authorities stopped the operation to perform an audit (to which Ponzi submitted willingly for some inexplicable reason). The audit revealed that there wasn't enough money to even pay back current investors' capital let alone give them the profits they expected.

There was no stamp business, and there were no customers. The cost of dealing with various bureaucracies made arbitrage unprofitable. Ponzi so-called business was simply to sell more and more IOUs to new investors to pay off the old ones. It was a classic pyramid scheme. Pyramid schemes are inherently a zero-sum game; money trades hands without any value being created in the process (i.e. no revenues from sale of products). If there were infinite investors, Ponzi could have continued forever. As it were, these promises were destined to be broken because the universe of investors is a closed system and therefore finite; eventually a set of new investors would turn out to be the last, and their tremendous losses would equal all the gains of the preceding investors and Ponzi himself.

is shown to have unrealistic revenue projections. While this can sometimes happen even to the most competent of buyers, if the company's impending failure should have been obvious, then the entrepreneur was fortunate to have sold stock to a "fool". While the often nonsensical gyrations of the stock market may lead one to believe that there are and always will be naïve investors willing to overpay for anything, an entrepreneur should not count on this. The entrepreneur's strategy should assume that investors will know everything about the company and will never pay more for a share than it is worth (e.g. as calculated by discounted cash flow).

BIOTECH FUTURE

As with every innovative sector, the history of biotech is one of unrealistic expectation. Even though each new wave of startups appears to improve on the past, biotech companies seem to consistently overestimate their projected revenues and underestimate time-to-breakeven. Companies seem to require more capital than expected and, no matter how experienced the management team, frequently run into as yet unheard-of challenges. While it may be unreasonable to expect future startups to be any better at anticipating problems than the startups of the past, today's entrepreneurs would be better served being more conservative in their financial projections and estimations of capital markets. For example, with the threat of increasing healthcare regulation, today's biotech startups should assume that they will launch products into a more price sensitive market.

ALTERNATIVES TO DRUG DISCOVERY

As we gain more experience with drugs development, it should be easier to predict how new ones will perform in the clinic. Yet, with more drugs on the market, companies must conduct larger, longer, and more expensive trials to demonstrate a new drug's benefit over standard-of-care. There is no telling whether continued innovation will improve efficiency. In fact, drug development costs have increased over the last twenty years, despite (or perhaps *because of?*) the rapid pace of innovation.

The scenario brings to mind the Red Queen from *Alice in Wonderland*, who has to run as fast as she can just to stay in the same place. To win the cost containment race, a small company might need to change the rules it plays by. Below are several ways that may improve the efficiency with which a company gets a drug to market.

PHARMACOGENOMICS

Using pharmacogenomics to select patients most likely to benefit from treatment may significantly reduce the size and cost of clinical trials since fewer subjects are needed in treatment and control arms to establish statistical significance. Pharmacogenomics can also pre-select

patients likely to tolerate a drug's side-effects, potentially allowing drugs that might be toxic to some patients to still reach the market if accompanied by a diagnostic to weed out those at risk.

BAYESIAN STATISTICS

A Bayesian approach to clinical trial design would allow investigators to modify treatment mid-trial for one set of patients based on how an earlier set responded, as physicians do in practice. Bayesian statisticians insist that, compared to traditional placebo-controlled double-blind trials, one of their trials can test more hypotheses (e.g. dose range and frequency) using fewer patients, and some centers such as the Mayo Clinic have begun evaluating this new approach in earnest. While Bayesian methods are sometimes used in designing Phase I trials, this practice probably won't be further adopted until and unless the FDA starts hiring Bayesian statisticians to evaluate new drug applications.

PRODUCT INCUBATION

With companies increasingly looking for late-stage drug candidates, some academic research institutions left holding hundreds of promising drugs targets are considering doing drug discovery and early clinical development themselves. The goal would be to use public, philanthropic, and possibly corporate funds to generate clinically validated drug candidates that companies would want to license.

PRODUCT REPOSITIONING

Companies willing to forego novelty have commercialized old drugs in new ways for a fraction of the time and cost it takes to get a novel compound to market. Examples of these alternative business models include:

- License a fully or partially developed drug and develop it for a novel indication, for a novel market, or using a novel formulation.
- Reformulate a generic drug to make it substantially better.
- Develop combination products (2 or more co-formulated drugs) for known or novel indications.

Compared to discovering new drugs, reformulating and repositioning old ones involves less risk and expense because the old drugs are often already well understood. The trade-off is that, to ward off generic competition, a repositioned drug may rely on Method-of-Use patents, which may be easier to break or circumvent than Composition-of-Matter patents. This is a compromise worth considering while the cost of developing new drugs continues to grow.

Eventually, companies pursuing this strategy may run out of late-stage drug candidates to reformulate or reposition

Product In-Licensing

Why would one company (Buyer) want to license a drug that another company (Seller) is happy to sell? Unless the Buyer has different capabilities or priorities from the Seller, the drug will meet the same fate. While the licensing strategy is sometimes abused by companies willing to buy a candidate of questionable value out of a desperate need to start touting a pipeline, there are often legitimate reasons for a drug to trade hands. Examples of sensible in-licensing opportunities may include:

1. Big pharmaceutical companies may lose interest in candidates with less than \$500M annual sales potential or will terminate entire divisions for strategic reasons (e.g. lack of sales capability in certain markets). These companies may then out-license partially developed or approved drugs.

2. Seller has terminated development because drug was ineffective in a particular indication. Buyer will test the drug in other indications where it may be more effective.

3. Seller is a non-US company lacking the resources of the Buyer to commercialize a drug in the United States.

4. Seller terminated development because the drug, while effective, was not safe enough or was not easy to administer. The Buyer can reformulate the drug in such a way as to improve its safety or dosing profile.

Note: Big Pharma may not be motivated to devote the business development resources to out-licensing a candidate in which they have lost interest.

and will need either to discover their own drugs or pay others to do it. Hopefully by then, a better understanding of how novel compounds behave in the clinic will make the old discovery-based biotech model viable.

PROFITS, PROFITS, PROFITS

Undoubtedly, biotech entrepreneurship is still a frontier. The only thing you can know for sure is that *no one ever*

went broke making a profit. While using profits as an end goal may seem like common sense to some, many companies become so distracted by the need to develop a new technology, secure a partner, raise money, or arrange an exit for investors that they forget that these objectives are not ends unto themselves.

EVALUATING THE IDEA

Even before writing the business, an entrepreneur should perform a diligent evaluation of the startup concept. The evaluation must answer key questions on the nature of the market, competition, product development path, intellectual property, and related issues. Sometimes, entrepreneurs avoid or forget to ask an important question, the answer to which could have averted or at least foretold failure. More often, all the right questions are posed but the answers themselves are biased.

It is common for people to believe that their instincts are correct, favoring information that supports their conclusions while downplaying evidence to the contrary. However, an entrepreneur must be prepared to convince an audience of cynical investors, who know how to conduct proper due diligence, and expect most business plans to be flawed.

Entrepreneurs must be their own harshest critics and objectively test assumptions. Quite often, an unvarnished answer to a simple question will unveil conceptual flaws. Is it really a billion-dollar market? Is there really no formidable competition? Will product development really only cost \$10M? Before implementing a plan, the management team should seek feedback from people who will challenge their conclusions aggressively.

FIVE BASICS

A strong biotech business concept should cover the following bases:

1. The company must efficiently develop viable products.
2. The company's intellectual property must be defensible and other patents cannot block the path to commercialization.
3. There must be a clear business model/strategy for generating a significant profit.
4. The company should target a large and/or rapidly growing market.
5. Management should have the skills to implement the business plan.

These five elements may seem self-evident, even redundant, but many business plans neglect to address at least one. Common mistakes include:

- The technology concept is "cool science" but not commercially useful.

- The market is so small that the company cannot reach significant profitability.
- The company must convince customers that they need its product rather than selling one that customers already want. Creating demand is more difficult than catering to an existing need.
- Customers claim they want a better product, but are not willing to pay for it.
- The key patents are invalid due to prior art.
- Patents block the company from doing something essential to the process of making and selling the product, thereby restricting its "freedom to operate."
- The business strategy does not take into account regulatory and reimbursement issues. E.g. in the case of a novel type of therapeutic, getting FDA approval may take an unusually long time and insurance plans may not extend coverage until the treatment becomes more commonplace.

THE STARTING LINE

Many seeds of biotech innovation lie in academic basic science supported by government-funded institutions. Whereas investors and corporations cannot afford to do basic research find the rare commercially useful concept amidst thousands of discoveries, academic institutions gladly pursue science to further human knowledge. Academic institutions cannot subsidize the high cost of product development, whereas investors and companies are more than willing to do so in pursuit of profits. Therefore, it makes sense to transfer a technology from a university to a company once there is enough scientific data to support a development plan.

Finding the right time to transfer a project from academia to industry is critical; entrepreneurial scientists and venture capitalists may be tempted to do it too soon. The earlier the transfer, the more of the product's final value the company can retain for itself but the greater the risk that it will fail at the expense of the startup's investors. In particular, with each stage of drug development more expensive than the last, company should identify a drug program's fatal flaws as early and efficiently as possible.

Key Questions

1. What evidence is there suggesting that the product will be viable (e.g. preclinical or clinical data)?
2. What will be required in terms of time, resources, and strategy to develop the product(s)?
3. How will development be staged so as to minimize costly mistakes as early as possible?

INTELLECTUAL PROPERTY

If a startup cannot protect its core technology and product concepts, the company may not be able to fend off competitors and profit from its investments.

Patents are designed to protect the composition or application of novel inventions and expire 20 years from the filing date. A patent prevents others from *legally commercializing* your invention, its derivatives, and downstream products without your permission, but the patent does not guarantee that you will have the *freedom* to sell or use your own invention. For example, you can patent a new type of capillary that accelerates the rate of capillary electrophoresis used in DNA sequencers. No one else will be able to make DNA sequencing equipment using these capillaries without your permission. However, you will never be able to manufacture or sell a complete DNA sequencer with your improvement unless you get permission from those people or companies who own patents for the other machine components. Without a licensing agreement, the owners of those patents may block you from commercializing your technology.

Key Questions

4. Does the company have freedom-to-operate?
5. How will the company prevent others from copying its product(s)?
6. How long will the company enjoy IP protection? Is this long enough to generate adequate profits?
7. If the patent position is weak, what other advantages does the company have over the competition?

BUSINESS MODEL

The way in which a company operates is its business model. The *tool* model involves selling a technology or service that helps other companies develop drugs, whereas the *product* model involves actually developing drugs (or devices). Product companies, in turn, can have a *drug discovery* or *licensing* model, the latter involving licensing partially developed candidates from other companies.

Whether the company will commercialize drugs itself or find a partner is also an element of the business model. Even when a small company can afford to develop a drug on its own, sometimes it makes sense to have a partner if the market is so large and fragmented that only a larger company could provide an adequate-sized sales force.

Another important business model distinction is that between the *one-trick-pony* developing a single product and the *platform* company developing multiple products around a core competency (e.g. expertise in a disease area or formulation technology). A well-diversified company will

have multiple products with few shared risk factors such that no single miscalculation or act-of-god could destroy the company altogether. A small company with its hopes pinned to one program may be tempted to disregard early signs of impending failure, while a diversified company can afford to prudently terminate weak programs.

Other aspects of a business model include product pricing and positioning. Generics companies, for example, offer products that are identical to branded drugs and try to win market share through discount pricing. Other companies position their products as better alternatives to existing drugs to justify premium pricing. It is often a question of being either *better* or *cheaper* but not both.

The business model should also specify whether your company will do its research and manufacturing in-house or outsource everything, thereby remaining 'virtual.' The virtual model is often a good way to start if you do not expect to have enough work to keep employees busy full-time or lack the funds to purchase capital equipment. The downside is that you are subject to the third-party's way of doing things (e.g. speed, quality, expertise).

The FIPCO Model

Large companies that have the ability to discover, develop, manufacture, and market their own drugs are called fully integrated pharmaceutical companies (FIPCOs). All major pharmaceutical companies are examples of FIPCOs, as are Amgen, Biogen Idec, and Genentech. A FIPCO enjoys the ability to market its own drugs, thereby retaining the majority of the profits. However, the price of integration is that a FIPCO's internal R&D operation may not be as efficient and productive as that of a smaller company. To compensate, FIPCOs may outsource the early stages of discovery and development to biotechnology companies by entering into partnership agreements with them.

The nature of one's customers also influences a business model. Companies developing products for the military may be subject to the government's timelines and notions of fair pricing. The conditions of SBIR and DARPA grants can influence a commercialization plan, and not always in a positive way (see *Government Grants* chapter).

Key Questions:

8. Why is the company's business model well suited to its products, markets, and capital resources?
9. Are there comparables out there that suggest your business model is feasible?
10. If the plan calls for partnerships, how will the company maximize the value of partnerships (i.e. increase the payments the partner will make to the company)?

MARKET

Market size is defined by total annual sales of products that address a market's particular need, but one must be specific about what the market's needs are. For example, a company developing a pain drug should assess whether the drug will be used for severe or mild pain; this in turn will determine whether you will be competing in the opioid or NSAID/Cox-2 Inhibitor market respectively.

Factors that influence which market a company will target include the nature and price of the product, the specialization of the sales force, and the nature of the competition. Biopharmaceutical markets are most often broken down by disease and stage of progression. The size and growth rate of a market will give some indication of the potential for profit. Product switching frequency also determines if/when patients on other treatments will try your drug. Patients tend to stick with what already works but may rotate through numerous therapies quickly if no single therapy works perfectly.

For example, 10% penetration into a \$2B market results in annual sales of \$200M. If there is no product switching, then all sales will have to come from newly diagnosed patients using your drug. In this case, if a \$2B market is growing at 10% a year and your product can capture 50% of new patients, then first-year sales would be \$100M, followed by \$210M in the second year, ~\$330M in the third, and so on.

In those cases where no comparable products exist with which to estimate a market's size, look at comparable markets and analogous products. For example, there are essentially no effective therapies approved for ALS (a.k.a. Lou Gehrig's Disease), but the disease is similar enough to Multiple Sclerosis (MS) that effective ALS drugs might command prices comparable to the interferons (Avonex, Rebif, etc), around \$10,000/year. Assuming all 30,000 ALS patients in the US were to take such a drug, the market would have a maximum size of about \$3B/year.

Overestimating market penetration is a common mistake. Projecting 5% penetration into a \$2B market (i.e. \$100M in sales) may be conservative in one scenario but wildly optimistic in another. For example, it is not easy to gain market share in a mature, slow growing market where people rarely switch from their favorite brand, and even 1% of such a market may turn out to be an ambitious goal. Looking at how other products penetrated into the same or a comparable market is an effective way to arrive at a reasonable market share estimate. If the first MS drug achieved 30% market share within 2 years (i.e. 30% of eligible patients went on the drug), then sales of the first approved ALS drug might follow a similar trajectory.

When projecting penetration, there are nuances to consider for every market. For example, physicians who are paid to administer an IV-infused drug to patients during office visits may not want to give up that revenue by switching patients to a self-injectible formulation of the drug. Since physicians are gatekeepers to pharmaceutical markets, it is important to keep the physicians' interests in mind when developing a drug.

Because small biotechnology companies primarily deal with larger companies rather than sell their products directly to healthcare consumers, it is important to define markets according to what the real "customers" (i.e. the potential partners) want. Large companies typically have very good reasons for not addressing particular markets. For example, millions of people around the world suffer from malaria but most are in developing nations where the healthcare system cannot afford to pay for branded drugs. Therefore, large companies probably won't pursue malaria programs and a biotech startup focusing on malaria may find it impossible to attract a partner.

That is not to say that all small markets are unattractive; in the case of drugs, the FDA may grant Orphan Drug status to a drug for a very small market and may assign Fast Track, Priority Review, and/or Accelerated Approval status to a drug that addresses an important unmet medical need. Orphan status offers an extended period of market exclusivity to a drug. The other three qualifications are effective at simplifying and accelerating the process for getting the drug approved in the first place. Depending on the severity of the disease symptoms, a treatment may command very high prices. For example, Genzyme's Cerezyme has generated in excess of \$750M from a global market with only several thousand Gaucher disease patients who pay roughly \$170,000/year for the drug (with the help of insurance).

If the business model calls for licensing a drug candidate to a larger partner company, the partnering "market" becomes another essential consideration. The search should focus on companies that have the sales expertise (e.g. cardiology) to market your particular kind of drug. A study of recent deals will give you a sense of how generous potential partners may be when licensing a product at any given stage of development.

Key Questions:

11. What is the size of the market you are targeting and how fast is that market growing?
12. Are customers/patients loyal to a brand or is there frequent switching between products?
13. How will the product compare with competing products in terms of quality, price, marketing effort, and other factors?

14. How quickly did other products gain market share in this or a comparable market and what sales trajectory is your product likely to follow?

MANAGEMENT

One of the most difficult questions a management team needs to answer is whether they have the capabilities to execute the business plan. The adage goes: a good management may succeed with a bad idea but bad management will ruin a good one.

Key Questions:

15. Who will be responsible for executing each of the steps in the business plan and how are they qualified?
16. Will the management team inspire confidence in investors and employees?
17. Will the management team have the expertise to supervise work that is contracted out?
18. How will the Scientific Advisory Board and Board of Directors be staffed and leveraged?

THE BUSINESS PLAN

The inexperienced entrepreneur faces a dilemma: having a management team, directors, advisors, investors, and employees gives the startup credibility, but it is difficult to convince anyone to be first to join. To short-circuit the Catch 22, an entrepreneur needs:

- A thorough, polished business plan,
- 1-2 page executive summary, and
- A 30 second/~60 word Elevator Pitch (i.e. short enough to say during an elevator ride).

The business plan or summary will be the first thing that most people ask for if they are interested in your pitch and are important to the process of building a startup. Also, the experience of forming and communicating a compelling strategy make the effort of researching and putting the plan together worthwhile.

The questions posed in the preceding chapter provided a general framework for thinking through a business concept. The many similar questions posed in this chapter are intended to guide the composition of a clear and comprehensive business plan that will help convince others to support you.

SECTION 1: SUMMARY/MISSION STATEMENTS

This section concisely states exactly what the company will do and what its product(s) will be. The mission statement must elegantly phrase the company's vision. Do not include unqualified superlatives along the lines of "XYZ is a leading drug discovery company". Readers will just roll their eyes. It is refreshing when a plan conveys useful information without sounding like an infomercial.

SECTION 2: THE OPPORTUNITY

This section discusses the reasons for starting the company and for believing that it can succeed.

- Primary Question: How will the company efficiently generate a significant profit?
- What product are you selling?
- What is the market for the product?
- Who are the customers?
- What is the size and growth rate of this market?
- What criteria do customers use to determine which product to buy?
- Why is competition not a significant barrier?

Do not waste the reader's time with generalizations not immediately relevant to your concept. *If and only if* you will be pitching your plan to investors unfamiliar with the background of biotech, briefly discuss the broader industry (e.g. FDA approval process, healthcare reform, etc), addressing macro forces that may impact your company, business model, and sales projections.

SECTION 3: THE TECHNOLOGY

Describe enough of the technical aspects of your technology so experts will be able to appreciate how it works. Failure to give sufficient detail may cause knowledgeable readers to suspect your credibility. Investors will most likely require that you disclose everything eventually so have a Confidential Disclosure Agreement (CDA) available if you find that discussions are progressing beyond your comfort level.

SECTION 4: THE BUSINESS MODEL

This section describes in detail exactly how you expect to make money selling your particular product. Discuss pricing of the product, the customers/partners, and how much capital the company will need to operate. Break down costs associated with making and selling the product. Taken all together, the information that you provide in this section should allow you to estimate revenues and expenses for the first year or two, which can be detailed in the Financial Section (discussed below). When calculating how much startup capital you need, estimate your expenses for the first year or two and then add a safety margin (50-100%).

- How much will the product be priced and why?
- How and when will the customers or partners pay for the product (up-front, milestones, royalties)?
- How much will development cost?
- What will the company need to operate (cash, etc)?
- How will the company attract customers/partners?
- How will manufacturing be handled?

SECTION 5: THE COMPETITION

There is always competition. If no company offers a product exactly like yours, then, at the very least, the *status quo* is the competition.

Provide a profile of all the significant competing companies, describing their technologies/products, business model, pricing, and current customers. Explain why those companies are successful or not successful, and why you can do better in either case. Do not be too quick to point out only their weaknesses; you will ultimately have to prove that a company like yours can succeed, and demonstrating that a competitor is highly successful, yet will not exclude you from also obtaining a significant share of the market, can be an effective argument in your favor. Pioneers are also guinea pigs, so avoid painting your startup as being too innovative in its business model, technology, or target markets.

- Who are the competitors?
- How is your product better?
- If there are no competitors, why have other companies not pursued your target market?
- Why would a customer purchase your product?
- How will competitors respond to your entering the market and how will you respond in turn?

SECTION 6: INTELLECTUAL PROPERTY

This section should summarize how the company will protect the intellectual property that enables commercialization of its products while keeping competitors at bay. If the company does not yet have the IP it needs, discuss the licensing/filing strategy to make sure that no one else gets it first. If IP is not a critical component of the business, explain why (e.g. sometimes getting to market first with a non-proprietary product is more effective than delaying just to develop a patent-protected version).

- What patents protect the technology, to whom do they belong, when do they expire, and how can they be used to block potential competitors?
- What patents exist that may block you from using your own technology, to whom do they belong, when do they expire, and will you be able to license them?

SECTION 7: EXIT STRATEGY & COMPARABLES

Your investors and other shareholders must be able to sell the stock they own in your company in order to profit from their investment. Shareholders can sell after an Initial Public Offering (IPO), a cash-based acquisition, or after a stock-for-stock acquisition by a public company.

Discuss when the company could be sold or go public and what the expected valuation of the company might be at that time. The best way to demonstrate that your will

create an attractive exit opportunity for investors is to show that comparable companies have done so.

Project what your company will be worth based on the valuations of 5-10 companies that are currently at the stage that your company will advance to in 3-5 years. An effective comparable company should have a similar product and target a similar market (similar in size, type of customer, pricing, degree of competition, etc).

For example, if a startup company has a preclinical candidate for psoriasis and expects that trials will proceed to Phase III within a few years, the company could compare itself to companies today whose value is substantially based on a Phase III psoriasis drug. Other moderate-to-severe dermatologic conditions might stand in for psoriasis, and Phase II or registration-stage programs might substitute for Phase III.

Avoid referring to the exceptional cases. Unless you have good cause to project another stock market bubble during which you expect to raise hundreds of millions in capital, suggesting that your startup could be the next Millennium will cause readers to roll their eyes. Generally speaking, any company with a market capitalization in excess of \$1B should not serve as a comparable for a startup company.

Use the most recent valuation for each company. Financing climates can change quickly and will be immediately reflected in the share price of public companies. Accurately valuing private companies can be difficult as their equity is re-priced only during financings. Therefore, only include as comparables private companies whose valuations have been recently calibrated by a financing, merger, or acquisition.

SECTION 8: PEOPLE

Include short biographies of the management team, scientific advisors, and directors. Clearly state how each will contribute to the company's success. Add the resumes of each of the founders and members of the management team as an appendix to the business plan. Be sure of everyone's commitment to the company; removing a person later can become messy and personal, generating bad publicity at a time when the company can least afford it.

SECTION 9: FINANCIALS

By Jack Malley, Partner, FirstJensenGroup.
See **Accounting & Finance** chapter for information about the author and firm.

The financials are used to document, justify, and convince. They should be prepared in harmony with the rest of the business plan, i.e., conclusions and assumptions detailed in the development, marketing, and manufacturing sections of the business plan should be reflected in the financials. Investors examine these statements to determine if management is realistic in its expectations and to determine if an acceptable rate of return on investment can be achieved.

REVENUE PROJECTIONS

Most business plans include optimistic financial projections while claiming that they are conservative. Investors will have little faith in these revenue projections but will infer from them whether the entrepreneurs are realistic in their expectations. If the so-called conservative projections are not conservative, you will find yourself defending potentially indefensible calculations. Furthermore, your reputation will suffer if you fail to meet your projections down the road. Comparables add credibility; pick several companies that are similar to yours and describe their sales growth and expenses as a means of substantiating your own projections.

STATEMENTS

The financial statement section of the business plan typically appears in two locations within the business plan: summarized data in the executive summary of the plan and in a financials section of the appendix. The summarized data displays annual data, both historical and up to five years of forecast. Line items would include revenues, cost of sales, gross margin, operating expenses, net income, capital expenditures, equity fund raising, and year-end cash balance. Additional references may include gross margin %, net income %, and year-end headcount.

A sample set of financials appropriate for a business plan appendix may be downloaded from:
www.evelexa.com/resources/account_issues.cfm.

The financials section of the business plan should include a listing of assumptions used to prepare the financials, a balance sheet, an income statement, and a statement of cash flows. Historical data should be prepared as annual totals. Forecasted data should be monthly for the first year and quarterly for the second and third years. Annual totals should be provided for the fourth and fifth years.

The list of assumptions may be the most important part of the financials section. Assumptions should identify the timing of the financial event(s) and milestones the company hopes to achieve in the forecasted time period. Specific assumptions should be listed for each revenue type including the method by which revenue is to be recognized and how revenues relate to market size. Specifically, according to GAAP (Generally Accepted Accounting Principles), revenues may not track with the timing of cash receipt. For an early-stage company, the timing of revenue recognition is far less important than the timing of cash receipts. The cost of sales assumptions most often will mirror the revenue assumptions. Major categories of operating expenses, such as compensation, facilities, research and development, and preclinical and clinical expenses, should be identified. Other assumptions that should be included would relate to the company's cash flow activities. For example, the timing of customer/partner cash receipts, vendor payments, payroll, taxes and benefits, and the scope and cost of debt and equity financings would be included. Finally, the assumptions should detail when operating cash breakeven is expected.

The three primary financial statements should have more line items than in the table above but not to the lowest level of detail, which is reserved for a separate operating budget spreadsheet that would not interest most investors. Line items included on the **income statement** should closely match the categories identified in the business plan's assumptions. The income statement should highlight EBITDA (earnings before interest, taxes,

Table 2. Sample Financials for Start-Up Business Plan

\$000s	2001	2002	2003	2004	2005
Revenues	\$0	\$750	\$3,250	\$2,000	\$10,215
Cost of Sales	0	0	150	545	4,659
Gross Margin	0	750	3,100	1,455	5,556
Gross Margin %	0%	100%	95%	73%	54%
Operating Expenses	1,955	4,357	7,380	7,574	9,403
Net Income (Loss)	(\$1,955)	(\$3,607)	(\$4,280)	(\$6,119)	(\$3,847)
Capital Exp.	95	520	1,506	620	405
Equity Raised	1,000	10,000	0	20,000	0
Cash Balance	\$1,059	\$6,932	\$1,146	\$14,407	\$10,155
Science Staff	5	10	17	23	24

depreciation, and amortization), which is used to approximate net earnings from the ongoing operations of the company.

The **balance sheet** should have, at a minimum, line items for cash & cash equivalents, receivables, fixed assets net of depreciation, other assets, trade payables, bank and capital leasing debt, other liabilities, stock, and retained earnings/deficit. There should be no “plug” numbers in the balance sheet. All entries should be formula driven and derived from input data in the other two financial statements. This strategy allows for proofing of the financial statement, i.e., an out-of-balance balance sheet will indicate that a formula is not working properly.

The **statement of cash flows** is usually prepared in a GAAP format, i.e., one that segregates operating, investing, and financing cash activities. The operating activities include the net income of the enterprise, net of non-cash items such as depreciation, and the period-to-period change in most balance sheet accounts. Capital expenditures comprise most of the investing activities

while debt funding/payments and equity funding comprise most of the financing activities.

Since a picture is worth a thousand words, a graphical rendering of key drivers and statement elements, a so-called “dashboard report” that includes four graphs on a page, may be downloaded at:

www.evelexa.com/resources/account_issues.cfm.

**SAVED FOR LAST:
THE EXECUTIVE SUMMARY**

Few people will read the full business plan before first asking to see the executive summary. Therefore, the executive summary must entice the reader to ask for more information. The executive summary must discuss the opportunity, product, technology, market, competition, intellectual property, business model, management team, and exit strategy in 1-2 pages. The process of evaluating a business concept and constructing the plan should identify all the important points for each of these sections, which is why it is best to write the summary at the end.

PEOPLE

People are the primary building blocks of a company and assembling a team is the most difficult part of the entire startup process. Investors and customers will all want to know who has staked their reputation on the success of the company. The management team, advisors, directors, employees, and others dedicated to the startup must inspire confidence, not raise doubts. While VCs may shore up a weak team by recruiting experienced management, it is far more common for VCs to pass on companies who don't already have competent people.

When evaluating people, consider the following:

- What skills and knowledge do they have?
- Where were they educated?
- For whom did they work and in what capacity?
- What professional accomplishments reflect on their ability to contribute to your company?
- Do they have integrity?
- What is their personal and professional reputation?
- How well do they work under pressure?
- Are they motivated, and what are their motivations for joining the company?
- How well connected are they?
- What is their experience with startup companies in this industry?
- What will be their role within your company?
- Will they be dedicated to your company?

Consider whether you would want the person to join as a founder, employee, director, scientific advisor, or member of the management team. It is difficult to draw distinctions between some of these roles. Having the interviewing skills to identify suitable candidates is critical.

FOUNDERS

Before the company is established and any money has been raised, a few key individuals must invest tremendous time, energy, and/or their reputations into the venture. Founders are identified by the risks they take and the contributions they make. Sometimes it is not clear who should be considered a founder until after the company has been financed and launched operations. A founder may join the management team or serve as a director, scientific advisor, or consultant. For example, when a university investigator starts a company and wants to retain his academic post, university policies may forbid him from also holding a management position in the company. A founder may even choose not to remain involved with the company once it is established.

Entrepreneurs riddled with startup anxiety may seek relief by quickly surrounding themselves with people who are interested in the startup but not dedicated enough to truly be considered founders. No matter how much you may like someone or how much you want to consider that person a partner, don't calling them a founder until he or she has actually made a contribution to the venture. You may find it difficult and painful to revoke founder status from someone after you discover he is unable or unwilling to contribute anything of value. Do not sign any contracts or make any binding verbal agreements without first consulting an attorney.

MANAGEMENT TEAM

Members of the management team can have many titles, sometimes more than one, and it is not always clear what title to assign to a particular job description. Do not get carried away with assigning titles. At the earliest stages, a biotech company only needs a qualified head of R&D (e.g. Chief Scientific Officer or Chief Medical Officer) and an experienced business person who can negotiate deals and raise money (Chief Executive Officer or Chief Business Officer). As the company grows, the team may expand to include a Chief Operating Officer (COO) and Chief Financial Officer (CFO). In general, it is best to keep the titles of other employees as humble as possible; having too many Senior Managers or Vice Presidents can appear silly when a company is small.

THE SCIENTIST CEO

Scientists who try to start companies have a reputation for wanting the CEO title, partially out of the conviction that science drives the startup. When venture capitalists decide to finance companies led by scientists with limited business experience, they may install a CEO they consider more qualified. It can be difficult for a scientific founder to give up control to another person, but one of the biggest mistakes an entrepreneur can make is to insist on being CEO just because the company was his or her idea. The CEO should have business experience and enough of an appreciation of science to intelligently describe the product to savvy investors and customers. The CEO must be able to make difficult decisions during times of crisis. Experience running a company is the only real preparation for the duties of running a company. The scientific founder may be better suited to serve as an advisor if he/she lacks the necessary leadership ability to be on the management team.

ALTERNATIVES TO CFO

Many entrepreneurs assume that they need a CFO from the start, but a small company's finances, accounting, and finance activities do not necessitate a full-time person for

such a senior position. You may have an office manager to take care of bills and payroll using common accounting software program. To produce financial statements and budgets, you could contract with an outside CPA. There are many small firms and individual accountants who can provide these services to your company. They can also provide you with valuable information gleaned from their experiences with other startups. Once the company accumulates many customers, employees, and vendors, a full-time bookkeeper or controller may handle accounting internally. Regardless whether you have a CFO, you are obligated by your stock agreements to hire an independent auditor, such as PricewaterhouseCoopers, Ernst & Young, or Deloitte & Touche, to review your records. This same auditor should also assemble high quality financial statements (do not outsource this to a small firm or independent accountant if you ever plan on going public). Depending on whether you can negotiate a discount, auditing and advanced accounting services will cost \$15K - \$30K annually. If your company requires accounting assistance with a complex transaction such as a partnership deal, total annual accounting costs may approach \$40K-\$60K.

Because startup finances are simple and outside accounting services are inexpensive, consider hiring a CFO at a later stage. Your accounting firm may even be able to introduce you to potential candidates without the commission that headhunters charge.

SCIENTIFIC ADVISORY BOARD

Scientific Advisory Board (SAB) members are usually academic scientists who have stellar reputations in their fields, have extensive experience in scientific or clinical areas pertinent to the startup, and may even be well connected in the business community.

Too often, companies recruit scientific and clinical advisors who are either too busy or entirely unqualified to help the company. It may be counterproductive to recruiting an advisor who won the Nobel Prize for work done decades ago but has not accomplished much since.

You may want to ask a scientist to join your SAB if he has key patents that your company will license, being careful that the overlap in interests does not constitute a conflict of interest. An SAB member may help recruit people to the startup from his own laboratory or network. Venture capitalists often rely on their own scientific advisors to screen potential investments; it doesn't hurt if one of them is also on your SAB.

If all you have is a story built on scientific rationale, using that story to recruit an advisor, ideally one who has helped found companies in the past, may be the best first step.

That advisor may then open the door to a good attorney, investors, and possibly management candidates.

Scientists may want to join your SAB because:

- They have the expertise to make a significant contribution.
- They feel their contribution would be appreciated.
- They like the management team.
- They are interested in the startup and want to stay informed of its progress.
- They see licensing opportunities for their own research and technologies.
- They want equity in the company.

If you want a particularly well known scientist on your SAB, odds are that this person is in high demand and may be asked to join a different SAB every week. Some scientists sit on only one or two boards while others sit on a dozen or more. It is hard to imagine that a scientist sitting on more than 6-10 boards could possibly make a significant contribution to each; in a few cases, their name in the business plan and website is that is asked of them. Scientists who want to play active roles on SABs are likely to sit on fewer than six. Like VCs, they may refuse to consider a startup that does not come with a reference from a trusted source. If you want to gain an audience with a high-profile scientist, consider asking one of his or her more accessible colleagues or former students for an introduction.

When approaching a scientist for the first time about joining your SAB, discuss contributions they can make. Even if you only want them for their stellar reputation, focus on how they can be useful. The details of equity should be brought up in the first meeting but should not be the center of discussion. The Equity chapter discusses compensation in more detail.

Scientists will want to know what is expected of them before they decide to join an SAB. Companies may convene their entire SAB several times a month or not even once a year. Some prefer to engage each advisor individually or in small groups for focused discussions about issues relevant to each advisor's area of expertise. A company may go through a period when management interacts with a particular advisor every day.

You may want to sponsor a prospective advisor's laboratory to do research for your company. Because the certain experimental results can impact share price and profit motive may compromise the investigator's objectivity, some universities have strict policies forbidding investigators from doing sponsored research for companies in which they own equity. Be aware of such policies when deciding whom you want on your SAB.

An SAB can have over a dozen individuals, but early-stage companies may start with 3-5 members. The size of the SAB should accommodate productive discussion at meetings even if a few people cannot attend. Having people on the SAB who have worked together in the past, either in the same laboratory or on another SAB, can facilitate discussion.

Having the SAB members join for short terms, such as one to two years at a time, allows you not to renew a contract when an advisor is no longer needed. It is difficult to ask an advisor to step down if the company has set a precedent of allowing inactive advisors to remain on the board for prolonged periods.

BOARD OF DIRECTORS

Directors are elected *by shareholders* to represent the interest *of shareholders*. Ultimately, it is the Board of Directors that is accountable for maximizing shareholder value, and the CEO is employed to that end. All the employees of the company ultimately answer to the CEO, but the CEO must answer directly to the board.

An effective board will consist of the CEO and outside directors (i.e. they don't hold any other position at the company). Anyone on the board may hold the Chairman title and be responsible for running the meetings. Ideally, the outside directors of the company serve as coaches to the CEO, offering an unbiased viewpoint during the decision making process and challenging the soundness of the CEO's plans. Having company insiders on the board can create a conflict; the CEO may not feel comfortable openly discussing certain issues with the outside directors in the presence of insiders.

Visit the website of a number of biotech companies to get an idea of who serves on their boards. Typically, you will find investors, executives from other companies, partners of law or consulting firms, and regulatory or manufacturing experts. You want high profile, experienced individuals on your board with whom you will get along. One entrepreneur offered the following litmus test: would you feel comfortable calling the person in the middle of the night if there were an emergency?

Recruit candidates whose strengths complement the weaknesses of the management team. Well known outside directors can add significant credibility, particularly when the company is trying to raise money. If a director is affiliated with a competitor, exchange of information in both directions may be inevitable. If a director is affiliated with a potential customer, other customers may resent this apparent alliance.

People who are selective about the board seats they take will look at who they would work with on the board and what kind of contribution they will be able to make. Less selective individuals may passively participate on dozens of boards and will not want to get involved with startups that may place great demands on their time.

The Board of active startups that require guidance may convene monthly at first and less frequently later. Ideally, meetings only last a few hours and have a clear agenda. Directors should receive in advance news regarding clinical data, development plans, partnership pipeline, recent new hires, unfilled positions, cash burn, etc.

Keeping in mind that the startup will evolve over time and its needs will change, recruiting too many directors early on may limit your ability to add new individuals later with more relevant experience. Instead, consider bringing certain people on as business advisors on similar terms to those offered directors or simply on an hourly basis.

Circumstance may arise when the best judgment of the board overrides the best judgment of the CEO. For example, a large company may offer to buy an ailing startup with the intention of firing everyone and just keeping the intellectual property and equipment. Management may wish to decline the offer and continue to operate the company. However, the less-biased outside members of the board may feel compelled to approve the transaction on behalf of the shareholders who are eager to liquidate their investments.

The members of the board have the power to replace an underperforming CEO. The CEO may wish to retain control of the company by limiting the number of outside directors on the board, figuring that insiders pose less of a threat. Some entrepreneurs even stock their boards with friends and family. For good reason, investors are wary of companies in which the CEO's decisions go unquestioned. When they invest in such companies, it is often under the condition that they be allowed to elect one or more directors of their choosing to the board.

In the aftermath of the scandals that rocked corporate America in 2001/2002 (Enron, WorldCom, etc), directors of public companies realized that they increasingly would be held accountable for negligence, fraud, or just poor management that resulted in loss of shareholder value. These responsibilities can consume a Director's time, making the position feel like a full-time job if the company is executing a complex partnership, financing, or merger. Furthermore, constraints on the compensation that corporations may legally offer directors have made it more difficult to recruit qualified candidates.

PATENTS

Biotech innovation relies heavily on patents and trade secrets, and less so on trademarks and copyrights.

The Entrepreneur's Guide to Business Law (see Recommended Reading) describes a US patent as "an exclusive right granted by the federal government that entitles the inventor to prevent anyone else from making, using, or selling the patented process or invention in the United States". The purpose of the patent is to encourage inventors to publicly disclose their inventions in exchange for 20 years of protection of their idea from the application filing dating. Once the patent expires, the knowledge it contains becomes public domain.

According to US law, anyone who "invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent". *Machine* refers to any physical device or instrument and *manufacturing* refers to novel ways of making something. In biotech, *composition of matter* often refers to the chemical structures and formulations of drugs, genes, and proteins. *Process* patents, also known as *Use* or *Utility* patents cover novel applications of a product, which may itself be covered by a separate Machine or Composition patent.

PATENTS IN ACTION

The most useful patents in the pharmaceutical arena are those that cover the composition of an effective drug and its application to treating particular diseases. No other company may manufacture that drug using any methods and sell that drug for any indications without first obtaining a license from the owner of the composition patent.

A utility patent, on the other hand, claims the use of a drug for treating a particular disease. For example, if the composition patent for a particular anti-inflammatory drug fails to claim its utility in treating leukemia, you may obtain a patent for this indication if you are the first to conceive of and provide evidence for this novel use. The company selling the drug for its anti-inflammatory indications would only need your license if it wanted to officially label the drug as a treatment for leukemia; practically speaking, physicians still could prescribe the drug off-label for leukemia without fear of being sued for patent infringement.

When pursuing a market for which there is already a patented product, it may be possible to engineer a new product that functions similarly enough to the existing product to address the same market without infringe on the original product's patents. In the case of drugs, the

cost of such a project is sometimes so high that pharmaceutical companies would sooner in-license patents for the original drug than try to engineer around them. The value of these patents will depend in part on how much time is left before their expiration.

Patents covering manufacturing methods may also be commercially useful. Depending on the complexity of a manufacturing process, the high cost of making a drug may preclude its profitable sale. Therefore, a company that invents a cost-effective manufacturing process may be able to use its intellectual property to ensure that its product is the only affordable version on the market.

GENE PATENTS

In pharmaceutical development, though drug composition patents are considered most valuable, gene patents theoretically also have value since gene expression is frequently used in drug discovery and development. Any company that commercializes a drug discovered using a gene for which you have a patent would be infringing your intellectual property, assuming you can prove that the company physically used the gene (or its protein product) after your patent issued. In some cases, a gene patent may take so long to issue that, by the time it issues, other companies have progressed to a point in drug development (e.g. clinical trials) where they no longer need to use the gene itself. Even if it means infringing on a newly issued patent, companies may continue using the gene in their discovery effort until they decide that a particular gene corresponds to a valid drug target and only then seek a license to the key patent. Indeed, it does not seem prudent to pay for gene patents sooner since most of them won't lead to drugs and few companies will go so far as to sue.

Since patents are only valid and valuable if they can hold up in court, it should be noted that gene patents have not fared well under scrutiny. In *University of Rochester vs. GD Searle*, Rochester lost its claim that discovery of the Cox-2 gene and characterization of the Cox-2 receptor entitled it to royalties from sales of the Cox-2 inhibitor Celebrex.

Companies developing gene or even protein arrays for research or diagnostic use run into *freedom-to-operate* problems when they try to put content (i.e. gene probes or protein ligands) on their arrays. A single array with dozens of different spots may require dozens of licenses for specific probes from the patent holders. Consequently, many companies sell instruments and reagents for making arrays and leave it up to the end-user to spot their own content.

CRITERIA FOR PATENT ISSUANCE

For an invention to be patentable, it must be useful, novel, and non-obvious. Each of these criteria has a strict legal definition. Furthermore, there is an *enablement requirement* that the patent must actually teach the reader how to make or use the invention properly. If a reasonably trained professional cannot follow the instructions in the patent and get it to work, the patent may not hold up in court if challenged. It is estimated that over 50% of patents can be invalidated on the basis of prior art or other technicalities. It is no trivial matter to obtain a defensible patent.

USEFUL

The usefulness of an invention is demonstrated by describing its applications. However, one cannot just claim that the invention could be used as cattle feed, as some unsuccessful gene patent applications supposedly have in the absence of function data.

NOVEL

Novelty is established relative to *prior art*, information pertaining to your invention that has been publicly disclosed prior to the filing date of your patent. Novelty is established by searching all patents and publications for evidence that the claimed invention was not described previously. Public disclosure also includes presentations at conferences and non-confidential distribution of business plans. If there has previously been public disclosure of a similar idea, your invention may not be considered novel. Even if a patent is allowed on the claimed invention, your competitors may be able to invalidate the patent if they can demonstrate that prior art existed and was not taken into account during examination of the application.

NON-OBVIOUS

Even if technically novel, your invention must not be an obvious extension of another technology. However, just because something may seem obvious does not mean it is by the legal definition of *obvious*. If an old patent claims that a drug should have anti-cancer activity yet studies fail to show this, you may be able to patent your own subtle derivation of the drug by showing that it actually does have anti-cancer activity. The logic is that if it were obvious, people who tried before you would have been successful by following the instructions in the old patent.

ENABLEMENT

Enabling an invention is not the same as proving that it works; enablement is actually a much lower hurdle. For example, showing that a molecule has activity in an *in vitro* inflammation assay may be adequate for a composition of matter patent that may block others from commercializing that compound. To secure a Use patent claiming the use

of an anti-depressant to treat irritable bowel syndrome (IBS), you would only need to show that the drug improved the IBS symptoms of a single patient. Unlike the FDA, the US Patent and Trademark Office (USPTO) does not require double-blinded controlled clinical trials.

CLAIMS

The patent application's list of *claims* defines the composition and utility of the invention. The claims also describe obvious variations on the invention to prevent others from easily engineering around the patent. For example, for a method of immobilizing proteins on a surface, the first claim may describe the invention in detail and specify the use of a biotin tag on the protein that will bind streptavidin attached to the surface. The second claim may assert that the method in the first claim can also be modified to use a histidine-tag and nickel coating in place of biotin and streptavidin. Other claims may mention other binding-reagent pairs. Without supporting evidence, claims worded too broadly may be challenged and invalidated (e.g. you cannot simply claim "any method of attaching a protein to a surface").

Patent litigation has been compared to cards... a full house of claims beats three of a kind. The stronger your claims, the less likely someone will challenge you in court.

The claims made in the patent cannot be purely theoretical. To patent a particular molecule, you must have successfully synthesized it and provided evidence that the molecule actually has the uses for which you seek patent protection. For example, there is much confusion over the patenting of genes. Like any other chemical entity, a gene may be considered for patenting. The gene must be cloned and its composition (sequence) described. However, because the patent must also describe a use, such as synthesis of the protein that the gene encodes, the inventor must demonstrate that a specific protein can actually be produced from the cloned gene and that this protein is likely to have further application, such as protein replacement therapy for a disease or screening of small-molecular inhibitors. The patent can also be worded to cover gene variants so that one could not change the sequence slightly to get around the patent.

PRIOR ART

When preparing a patent application, you must investigate relevant prior art, most of which can be identified by searching scientific publications and patents. Not all prior art is accessible, even to a patent attorney or search agency; you will not be able to access patent applications filed during the previous 18 months because they have not yet been published. Nor can you know about scientific manuscripts submitted for publication that have

not yet been published. Poster presentations also count as public disclosure but can be very difficult to dig up.

What you can do without money:

- Search relevant scientific literature.
- Identify related patents using online databases.
- Identify companies and academic research groups that are working in this field and read their publications and patents.
- Predict whether these groups are likely to have filed patents or publications before your priority date to which you may not yet have access. Talk to people discretely to gather more information.

What you can do if you have money:

- Hire a patent attorney and/or IP search firm.
- Hire a retired patent examiner to do a prior art search. Your patent attorney can arrange this, likely passing the cost (\$500 - \$1000) directly to you without additional charges. This search may not be thorough and will likely be limited to US publications.

LOSING PATENT RIGHTS

Researchers are capable of rendering their own inventions unpatentable by disclosing information prior to filing the patent application. Even submitting a manuscript to a journal for review may qualify as public disclosure if that manuscript is circulated to others prior to publication. Starting a clinical trial before filing could also count against you. The United States has a one-year grace period that allows filing for patent protection within one year after the invention has been publicly disclosed. However, no other country is so generous, and disclosing an invention even one day before filing will nullify your international patent rights.

If you patent a technology and list five applications, someone can still patent a sixth application that you had not thought to claim, potentially blocking you from using your technology for this sixth application. However, the other person will also not be able to use your technology for that application without your permission because your patent describes the composition of the technology.

It is a tragedy that many investigators are not aware of the damage that can result from failing to patent. Some investigators, who have no interest in profiting from patent licensing, believe that they are doing society a service by publishing their unpatented discoveries. Others are so focused on the abstract implications of their discoveries that they overlook patentable applications. If significant investment is required to commercialize a novel technology, companies will only want to invest in those opportunities that can be protected from competition. Companies are often apathetic to non-

patented innovation. Consequently, these discoveries may never leave the academic laboratory and may never benefit society. Therefore, a truly generous scientist should file patents and donate them to a company.

RETAINING PATENT RIGHTS

Do not publish or publicly discuss any aspects of a potential invention until you have first spoken with your institution's Technology Licensing Office (TLO). If you do discuss an invention with people outside your laboratory before filing a patent application, have them sign a Confidential Disclosure Agreement (CDA). A template is available at:

www.evelexa.com/resources/legal_issues.cfm.

If you have prepared a manuscript for publication and realize at the last minute that some aspect of the discovery may be patentable, contact your TLO immediately. They can file a provisional patent application on very short notice (within hours, even), setting the *priority date* for your invention. A standard patent application must then be filed within one year of the provisional filing or else the priority date expires.

A provisional application can consist of as little as a cover page attached to a copy of the scientific manuscript describing the invention. Information that enters the public domain after the priority date, including the information contained in your manuscript, will not count as prior art and will not invalidate your patent rights. Once the provisional patent is filed, you will be able to submit your manuscript and present at conferences while putting together a more complete patent application. However, because the priority date only applies to those claims that you state in the provisional application, it is important to make sure that the provisional application mentions all the composition and utility claims that you hope to protect.

COSTS AND TIMING

Universities own the rights to inventions that arise out of the research activities of its investigators and selectively invest in patenting promising inventions. Filing a US patent application costs \$400 upfront and another \$600 when the patent issues. Attorney fees may amount to ~\$6,000 or more per filing. There is also about \$3000 in maintenance fees over the lifetime of the patent, which a university will likely pass on to the patent's licensees.

Once a patent application is filed with the USPTO, a patent examiner will review each claim, often challenging their novelty and non-obviousness on the basis of prior art. The patent attorney will defend the claims, possibly amend or delete some of them, until the patent examiner is satisfied that the claimed invention is patentable.

It may take several years of review before a patent is issued (i.e. is approved). With some exceptions, patent applications are disclosed to the public 18 months after filing, regardless of how long it takes for the patent to issue. Between the dates of disclosure and issuance, anyone may read the patent and use the invention. However, the day the patent issues, everyone in the United States must either stop using the invention, license it from the patent owner, or run the risk of being sued by the owner for patent infringement.

INTERNATIONAL PATENTS

Though European and US market are typically the most lucrative, increasing globalization is making the rest of the world worthy of attention. For example, if you fail to patent your drug or manufacturing methods in Brazil, a Brazilian company can cheaply duplicate your work and legally sell the drug in Brazil and any other country where you have not filed for patent protection (actually, Brazil may disregard your patents anyway, as might other countries that don't play by global patent rules). Furthermore, if your patent protects pre-manufacturing steps involved in development of a product (e.g. an early-stage drug discovery technology), companies in foreign countries where you do not have protection may use your invention and *legally* export downstream products to countries where you do have patent protection.

Conveniently, most of the industrialized countries where you would want to have patent protection have signed a Patent Cooperation Treaty (PCT), allowing inventors to file a single PCT application to get a priority date in all of those countries at once. Filing the PCT within one year after filing for patent protection in the US gives your US priority date international recognition.

The cost of preparing and filing the PCT is approximately \$5,000. Within 30 months of the priority date, you must decide whether to file complete patent applications in individual countries at a cost of about \$5,000 or more per country. International patent filing costs can accumulate rapidly, often exceeding \$100K. Translating an application into Japanese alone can cost \$10,000. Not all inventions are worth this expense. Universities, for example, may just file a US patent application and only proceed with international filings if potential licensors request additional protection and agree to cover all costs.

FREEDOM-TO-OPERATE

The ability of a company to actually use and commercialize its own technology is referred to as Freedom-to-Operate. Rarely does a single company own all the patents related to developing and manufacturing a product.

A patent may describe a new way to manufacture DNA microarrays. If you want to start a company that will make and sell these microarrays together with compatible scanners, the following obstacles may block your freedom-to-operate:

- Large competing companies such as Motorola and Affymetrix may sue your startup, claiming that you are infringing on their patents. You may not even find out if your patent holds up in court because the cost of legal defense might bankrupt your company.
- Even if your microarray chip technology does not infringe anyone's patents, scanner technologies may be heavily patented. You could alter your business model by:
 - Licensing scanner patents and commercializing a dual microarray/scanner platform.
 - Engineering around current scanner patents by inventing a new scanner and commercializing a dual microarray/scanner platform.
 - Forget about scanners and only sell the microarrays, making sure they are compatible with other companies' scanners.

BLOCKING PATENTS

To understand if other patents may obstruct you from operating, consider what it will take for your company to use its technology and make its product. For example, though you may have a patent on an asthma drug, the final product may be a sustained-release formulation of the drug administered using an inhaler. MIT and Alkermes may have patents that protect the sustained-release method you intended to use. Other companies, such as 3M, could have patents covering the inhaler. You need to determine what patents cover every step of product development including:

- Patents held by direct competitors.
- Companies who will not license to you.
- Unlicensed patents held by universities or other non-profit institutes that competitors may license and enforce against you.

Once you are certain you have identified all relevant patents, the next step is to figure out whether your startup should license, circumvent, or ignore them.

Your options are:

1. Infringe on the patents and hope their owners don't sue. This is not a strong plan as your company will surely be sued once it becomes successful.
2. Engineer around the patents so that you don't infringe on them. No company enjoys having its

patents circumvented and your competitor(s) may sue you anyway, even if they have no real case.

3. License the necessary patents from their owners. This is the most reliable method for avoiding trouble. Sometimes, several companies with similar technologies may be engaged in litigation, and it is unclear whose patents you need to license. Licensing from them all may be the most prudent but expensive course of action.

FREEDOM-TO-OPERATE STUDIES

Patent law firms and some consulting firms offer Freedom-to-Operate studies, which can be quite expensive (\$10K - \$150K), though a few people have quoted estimates under \$5K. These studies vary in their comprehensiveness. As your company approaches the end of product development and larger investments are on the line, the costs of doing an extensive freedom-to-operate study may be justified and affordable.

Even if you had the resources to do a full study early on, knowing too much about the patent landscape may be dangerous for a startup. The entrepreneur and potential investors may become disheartened to learn about all the patents potentially blocking the company from making and selling its product. One investor pointed out that patent uncertainty should rarely be the reason to abort a startup as patent issues can often be solved one way or another. While this philosophy is not without basis, an entrepreneur probably should not embrace it too openly lest others take IP issues more seriously.

LICENSING BLOCKING PATENTS

If your company must license other technologies to have freedom-to-operate, figure out whether you can get a license and on what terms. Though *exclusive* licenses are valuable, they may be prohibitively expensive. Exclusivity is only useful when you want to exclude others from using a technology; *non-exclusive* licenses are sufficient for having freedom-to-operate. For example, all Microsoft software (which your computer most likely uses) comes with a non-exclusive license agreement. Does it matter that other companies can also use Microsoft's software? No, your only concern is that you be allowed to use it, too.

A company can investigate on its own the availabilities of blocking patents for license, getting attorneys involved for the negotiation of terms. However, if you are concerned about alerting a competing company to your activities, your attorney may discretely make the preliminary inquiry.

IF ACCUSED OF INFRINGEMENT

In an industry as saturated with patents as biotechnology, most CEOs will eventually receive a Cease and Desist (C&D) letter from a competitor accusing the company of infringing their patent(s). Some would consider it a badge

of honor - a sign that the company is worth threatening. The letter may insist that you *cease and desist* from further infringement, agree to license the competitor's patents, or risk litigation.

Patent litigation is a sport of kings - very few can afford to sue or be sued. Typical patent infringement cases in biotech can cost upwards of \$1M to prosecute and 50% of verdicts are overturned on appeal. Unless truly threatened, a larger company usually won't bother to sue a startup. A lawsuit would probably bankrupt the small company, leaving little for the victor. However, once the startup has something to lose or has partnered the technology with a larger company, litigation against the startup and/or its partner may be a legitimate threat.

By sending you a C&D letter, the competitor may be specifically targeting your company believing that you are infringing. However, if there are only general similarities between the patents, odds are that your company was just one of many targets. Some companies regularly send out letters, like shots across the bow, as a means of scaring up licensing revenues from the easily intimidated.

Although the chances of a startup being sued are small, the consequences of ignoring a Cease & Desist letter can be significant as it serves as official notification of possible infringement. If you are infringing, then the letter offers a chance to fix the problem amicably, e.g. by signing a licensing agreement or not using the competitor's invention. However, if you ignore the letter, you become liable for 'willful infringement'. Should your company lose subsequent challenge in court, your company will likely pay the competitor's legal fees and treble damages (a penalty equal to triple the actual damages incurred from the time of notification, as determined by a judge or jury).

A company receiving a C&D letter may feel compelled to contact the competitor to deny infringement. If you really want to be aggressive, you could exercise your right, upon receipt of a C&D letter, to file a Declaratory Judgment (DJ) lawsuit against your competitor (at the location/time of your choice, no matter how inconvenient for your competitor) asking a judge to decide whether infringement has occurred. To avoid the risks of being slapped with a DJ lawsuit, the competitor may word the C&D letter such that it does not actually threaten you with a lawsuit or accuse you of infringement; it may simply mention the possibility of an overlap. Such a delicately worded letter (which is not technically a C&D letter anymore) may still start the treble damages clock because it informs you of possible infringement.

Engaging the competition in a debate in or out of court will lead to huge legal bills as the attorneys go back and forth. Therefore, don't ignore a C&D letter (not even a

very polite one), but also don't be too quick to start up a dialogue with your competition. Consider taking the middle ground: ignore the letter with a patent attorney's blessing. A well-written opinion from an independent patent attorney asserting the case for non-infringement can serve as a strong defense against an accusation of willful infringement. On the off chance that your company ends up in court and loses (and then again loses on appeal) your losses will most likely be limited to simple damages and your own attorney's fees.

TRADE SECRETS, TRADEMARKS, & COPYRIGHTS

Though investors do not place much faith in trade secrets when evaluating startups, mature companies may elect to protect technologies as trade secrets rather than deal with the hassle and expense of patents. For example, instead of patenting components of its technology platform, Millennium Pharmaceuticals patents drug targets and compounds which may eventually become products. Like patents, trade secrets can also be licensed and treated as intellectual property, but the legal methods used to define trade secret status are complex and less reliable.

Trademarks are used to protect company names, product names, logos, and mottos. Before incorporating your company, consult your attorney and commission a \$300 a trademark search on your company's name. Changing the name later may be disruptive.

Copyrights are used to protect publishable works such as books, articles, and almost anything else that has an author, including software code. Copyrights are generally not relevant to your company's technology unless it involves proprietary software; even then you may consider trade secret or patent protection.

LICENSING FROM UNIVERSITIES

This section focuses on licensing IP from a university technology licensing office (TLO). The chapter on Business Development addresses licensing arrangements between companies.

Universities are obligated by the Bayh-Dole Act to transfer technology to industry through patent licensing to permit development and commercialization of government-funded discoveries that may eventually benefit the public. However, the universities' TLOs decide who gets the right to commercialize a particular technology. The right to use a patented invention may be transferred either to a single company through an exclusive license or to multiple companies via non-exclusive licenses. When a technology has more than one application (e.g. an antibiotic with human and veterinary

use), a company may acquire exclusive rights to one or multiple markets through a field-limited license.

Companies bid for licenses and, when demand is low, universities may ask for a license fee that merely recovers the cost of filing the patent. When patents are valuable, the TLO may negotiate complex and expensive agreements involving up-front cash payments, milestone payments contingent upon additional development of the licensed technology, and royalties as a percentage of product sales. TLOs may be flexible in allowing a company to pay more up-front and less in royalties (front-loaded license) or less up-front with some milestones and larger royalties (back-loaded license). The TLO may even accept or demand equity in the company. The university considers both the value of the license agreement and the likelihood that the company will be able to meet all the milestones and generate sales. If only the inventor is qualified to shepherd the invention through development, then doing a deal with the inventor's startup may be a better option than doing a deal with an established company with which the inventor will not be involved.

LICENSING TO STARTUPS:

UNIVERSITY ATTITUDES AND POLICIES

TLOs have different policies and attitudes on licensing technology to startups versus established companies. Not all TLOs have the experience or desire to work with a startup. A licensing office which has mostly worked with established companies in exchange for up-front payments may not feel comfortable structuring a back-loaded license with milestones and equity. An inexperienced TLO may over-value a technology and try to extract an unreasonable price, possibly making the venture unattractive to the entrepreneur and investors. In such cases, talk to people at other institutions or companies to assess licensing terms for comparable technologies and try to convince your TLO to agree to similar terms.

Some TLOs do not mind startup deals or are even proactive in helping their research investigators with the startup process. Boston University, for example, has worked with investigators to write a business plan, put together a management team, and secure financing. Some universities even have their own venture funds (e.g. BU and Vanderbilt) and/or may incubate startups in university-run facilities that offer access to shared equipment.

Before you invest time and energy into forming a company, figure out what your TLO's attitude is regarding startups and whether it will even consider exclusively licensing the technology to a startup. The TLO will most likely tell you that they are open to the idea but first want to see a written proposal or business plan. Harvard University, for example, has a policy that requires the TLO to shop a technology around to establish its fair

market value before giving an *option* (see below) to a startup.

With few exceptions, you will not be able to attract investors without exclusive rights or an option to develop the technology into a product addressing with a significant market. If the TLO will not consider such an arrangement, your chances of success are slim.

GETTING AN OPTION

If the technology licensing office is open-minded about granting an exclusive license to a startup, the next step is to obtain an *option* to exclusively license the patent from the university. If you have a 6-month option to license the technology for \$50,000 and 4% royalty, then you have 6 months to decide whether you actually want to sign a contract on these terms. During these 6 months, you can try to form the company, raise money, find laboratory space, and recruit a management team. Having the option allows you to assure potential investors that the university will actually grant the startup an exclusive license on the specified terms. It also assures you that the university will not license the technology to another company while you are trying to form the startup and raise money. Conveniently, there is no obligation to exercise the option in case you fail to start the company or chose to focus on a different technology. Because the university risks wasting time if you do not exercise the option, you may be asked to pay for the option as a token of your seriousness. This payment may only be a few thousand dollars. Not all universities grant options with pre-specified terms and not all of them charge for options, so you should get to know your TLO's way of handling such matters.

A university TLO may consider it a conflict of interest to discuss option or license terms with an employee of the university and may insist on speaking with another member of the management team or an attorney representing the startup. Unless there is experienced management, a good corporate attorney is probably the

most qualified to formally discuss option and license terms with the TLO. Even if the TLO is willing to negotiate with the scientific founders directly, be aware that mistakes in license agreements have legal implications best appreciated by an attorney.

BALLPARK LICENSING TERMS

Licenses are very case-specific and terms may vary substantially from the numbers mentioned here. A typical licensing agreement may involve <5% equity with anti-dilution protection through a reasonable level of funding. For example, the TLO may stipulate that it must own 5% of the company at the point when the company has \$2M of financing, following which the TLO's stake will be subject to dilution by additional financing (see Equity section for an explanation of dilution). Furthermore, the TLO may demand up-front payment, possibly deferrable, of \$25K-\$100K (exceptional technologies can command far more) in addition to incurred patent fees (usually \$3K - \$15K), and annual maintenance fees of \$25K - \$50K.

Royalties tend to vary according to the type of product the startup will be commercializing. If the licensed patent is only peripheral to the product, the royalty may be ~0.5% of sales. If the patent covers the product itself, chemical composition of a drug candidate, the royalty may be ~5%. If the company will sell a medical diagnostic, the royalty will usually be <5%. A common rule-of-thumb TLOs try to use to estimate royalties is that the university should receive about 25% of the profits. In the simplest of cases, if the profit margin for a product is 20% of sales, then the TLO will demand 5% of sales.

A company will often have to license multiple patents before it can market a product, resulting in stacking of royalty obligations that can significantly cut into a company's profit margin. To offset the effects of royalty stacking, a university license may allow up to a 50% reduction of its royalty if the company negotiates additional royalty-bearing licenses.

ATTORNEYS

CORPORATE ATTORNEY

An entrepreneur should secure a good corporate attorney in the early stages of venture creation. Corporate law covers contracts and agreements, including licenses and options, confidentiality agreements, employment contracts, equity distributions, leases, etc. Experienced corporate attorneys are also qualified to assist with business plans, assembling management teams, intellectual property issues, product development strategies, and business models. Because corporate attorneys are involved in the process of corporate financing, most are well connected to venture capitalists and angel investors. Introducing entrepreneurs to investors is an unofficial service that most corporate attorneys will gladly provide, though they are not obligated to do so.

Those unfamiliar with the legal and business world often assume that lawyers merely serve a bureaucratic function, intentionally complicating matters to justify charging their clients for the extra work. In fact, good attorneys have more work than they can handle and do their best to be efficient. Attorneys generally try to keep complexity to a minimum.

Firms vary in size, location, expertise, and industry focus. Partners at larger firms are typically more expensive per hour than their counterparts at smaller firms. You may have heard that smaller firms give their clients more personal attention than larger firms, but this is not always the case. When comparing firms against each other, consider factors such as partner/intern ratio, client/partner ratio, and whether you are a client of the firm or just a client of whichever partner you first sign with. Some firms encourage partners to sign on more clients by paying them more for doing work for their own clients than for working with clients recruited by other partners. Partners at such firms are less likely to fill in for each other when one of them is momentarily over-committed. Other firms have policies that foster greater cooperation among partners; the signing partner serves as primary contact and handles most of the work while other partners are likely to help out when necessary.

Having a respected counsel gives your company credibility and facilitates not only fundraising but also recruiting of management and directors. These individuals have large networks and can open doors that others may not know exist. Not surprisingly, the best attorneys are extremely busy and their time is very expensive. They are selective about the companies they take on as clients, and passing their screening process may be a challenge. Some will only look at a startup that comes to them through a trusted source or has a credible reference. They may want

to look at an executive summary or a full business plan and will meet with you before deciding to take you on. They are interested in establishing long-term relationships with clients and are not as eager to get involved with companies they feel are likely to fail in the short-term, even those able to pay up-front. Attorney may also decline to take on a client if they are already working with a competing company.

An estimated \$10K - \$25K in corporate legal fees will get most startups through their first financing. Almost all corporate law firms with experience working with startups will consider deferring collection of fees until the company has secured financing. Because the law firm bills the startup, not the entrepreneur, it risks not being paid if the startup fails to secure financing. Consequently, the law firm and the attorney take on startup clients cautiously and may ask the startup to pay an up-front retainer of a few thousand dollars as a sign of commitment. Law firms may also ask for a small equity stake to compensate them for the risks inherent in deferring fees. The equity percentage is rarely more than 1% of the company's shares, though a few of the most prominent corporate law firms may request 2%-5%. This kind of deal is likely to be done with common shares (see Equity section).

Smaller firms may lack a large firm's prestige but may have other strengths to offer. Partners at smaller firms may have the flexibility to work with startups that larger firms consider too risky and may be more willing to defer fees without a retainer. The partners may give each client more personal attention and do more of the actual legal work themselves rather than assign it to a less-experienced junior attorney or intern.

A large firm is not necessarily more expensive than a smaller firm if the larger firm works more efficiently. All legal work is costly and most attorneys will recommend that their cash-conscious clients do a considerably amount of background research before picking up the phone to ask them a question.

PATENT ATTORNEY

In the earliest stages of forming a company, the entrepreneur should turn to a patent attorney for an assessment of the patents protecting the startup's technology and of other patents that will affect the ability of the company to use its own technology. There are several factors to consider when selecting a patent attorney:

- Is the attorney familiar with your field?
- Does the attorney have experience with intellectual property strategy as well as filing and litigation?
- Is the attorney willing to state opinions and make recommendations rather than just list options?
- Will the patent attorney be able to work effectively with the corporate attorney?

Take the time to meet with partners at several firms, including at least one boutique (small/specialized) firm and one larger firm. Your first meeting with an attorney is free of charge to allow for mutual evaluation.

A university TLO will hire a patent attorney to write and prosecute its patent applications, which includes extensive prior art searching of online databases and libraries and possibly manual searching of the patent stacks in Washington D.C. The TLO may arrange for you to meet with the attorney to discuss the patent and prior art, but the TLO will not invest in having the patent attorney do further research on the startup's behalf. It is essential that you hire your own patent attorney before licensing technology from the university, even if it happens to be the same attorney hired by the TLO. Hiring the same attorney that the TLO used can save time and money since the attorney is already up to speed. However, the TLO may not have selected the most experienced attorney or the right firm for you.

Some patent attorneys have the business expertise to advise on the strategic management of a patent portfolio. When a company has a focused IP strategy, it can redirect its research program to generate new patents that will strengthen the company's patent position or block competitors. Your company may elect to use a single IP law firm for both patent prosecution and IP strategy or may use two separate firms.

An experienced attorney willing to actually recommend a course of action can be a valuable partner. Ask the attorney, for example, whether the value of a particular patent to the company's business model warrants the expense of filing for international protection of the technology. These kinds of questions will help you

determine how comfortable the attorney is thinking about IP in a business context and offering advice.

If you know that your startup might want to sub-license your intellectual property to a particular company, consider retaining that company's patent law firm (patents list the law firm that prosecuted the application). The firm may introduce you to the company and would ensure that your patents are constructed according to the company's standards. This tactic is only feasible if the attorney is not conflicted by overlap of your IP with the other company.

Patent law firms rarely defer their fees. Most patent attorneys are overworked and can afford to insist that clients pay promptly. Because patent fees can accumulate rapidly, the law firm would take on significant risk by deferring collection from an unfinanced startup. Preferring to keep things simple, most patent firms will not take equity in lieu of fees or in exchange for fee deferment.

It is quite common for a company to have one or more patent law firms handling its IP and to have a corporate law firm doing other legal work. Some corporate law firms have recently started patent practices, a few of which are well respected for their biotechnology expertise. There are advantages to working with a firm that has corporate and patent law practices. During financing or negotiation of alliances, corporate and patent attorneys may need to confer with each other to resolve issues at the interface between business and intellectual property (e.g. IP-related milestones). Attorneys in the same firm can easily confer with each other and may be more productive than attorneys at separate firms.

Another advantage of working with a firm that does both corporate and patent work is that it may defer all fees, including those that are patent-related. However, some multi-practice law firms will still only allow deferment of corporate legal fees, refusing to defer collection of patent-related fees for the same reasons that patent firms don't do this. In all cases, law firms do not defer collection of third-party disbursements such as incorporation fees and patent filing fees.

LEGAL ISSUES

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This chapter outlines the appropriate legal framework for an entity seeking venture capital. A legal structure that is biased towards the company's founders, fails to protect the core intellectual property, or creates an unworkable capitalization structure is just as likely to cause the loss of a financing opportunity as a company that has a poor business model or an inexperienced management team. As with the rest of this book, this chapter is less a self-help manual than a prep-tool for discussions with a qualified lawyer. Where it is noted, templates for certain legal documents are available for download from Evelexa at www.evelexa.com/resources/legal_issues.cfm. These documents are not "deal specific" and must be analyzed in the context of a particular transaction.

INCORPORATION

Many companies start by incorporating in the state where the founders live or the company is doing business. "Local" states are preferred because counsel is more familiar with the corporation statute and incorporation process, and it is assumed that professional and filing fees can be saved. However, venture capitalists, almost without exception, favor Delaware as the state of incorporation. Thus, many investors will require a company to re-incorporate in Delaware or merge with a Delaware corporation and then qualify as a foreign corporation in the state(s) in which business is going to be conducted before an investment is made. In addition to the delay and expense of reincorporation, there is the risk of having another entity reserve the proposed name.

Incorporation in Delaware is favored because its General Corporation Law (Title 8) is easy to comply with and offers management speed and ease of operation. Title 8 is supported by extensive case law and a business court that brings predictability and multiple precedents to almost every issue of corporate governance. Thus, when negotiating and drafting the language of a term sheet or transactional document, the venture capitalist is guided by multiple precedents and an appreciation of how a court would rule on many issues.

Deciding what entity form is best for your company when incorporating requires an understanding of how each entity is taxed, as well as other liabilities. LLP, LLC, C Corporation, and Subchapter S entities are all discussed in more detail in the **Accounting & Finance** chapter.

INTELLECTUAL PROPERTY

Intellectual property is the core of every biotechnology company. It is essential that the nature and source of the intellectual property including patents, know-how, and trade secrets be understood and protected through appropriate documentation and agreements. Since founders bring their expertise and prior work experiences to a new organization, it is rare that a start-up organization will begin without significant intellectual property. The ownership of that intellectual property must, therefore, be understood.

To address the intellectual property issues, the following questions must be answered:

- 1) Who are the Company's founders and are all of the inventors part of the Company? If not, the entity will require an assignment and/or license to acquire the rights and inventions from a holder who is not going to be part of the new entity.
- 2) What agreements have the founders, in any capacity, signed with prior companies that impact on the ownership of the intellectual property?
- 3) Has the intellectual property been developed or enhanced through university research and/or government sponsored research, and, if so, what ownership claims can be made by those institutions to the intellectual property?

The due diligence required to understand the issues and possible conflicting contractual claims is significant. The best practice is to research and develop an intellectual property due diligence report.

The second level of intellectual property protection relates to the documentation and agreements that should be put in place at the time of incorporation including:

- 1) Founder's agreements that provide for the ownership of the intellectual property to be transferred to the company with the attendant filings made with the Patent and Trademark Office ("PTO");
- 2) Waivers or disclaimers of conflicting rights;
- 3) Invention assignment and non-disclosure agreements for each service provider including, consultants,

independent contractors, scientific advisors, consultants and members of the Scientific Advisory Board. Forms are available for download from Evelexa.

- 4) Confidentiality and non-disclosure agreements that include provisions controlling publications.

All of this work and analysis is preliminary to a venture capital financing. Each investment transaction will include a Securities Purchase Agreement that will contain standard representations and warranties to be made by the company and occasionally the founders regarding the ownership, lack of infringement and control of the intellectual property. The company must anticipate these issues. The following are typical provisions:

- 1) "The Company owns or possesses sufficient legal rights, free and clear of any lien, encumbrance or other restriction, to its intellectual property necessary to conduct its business as it is currently being conducted and as proposed to be conducted without any conflict with, or infringement of, the rights of others. There are no outstanding options, licenses, or agreements of any kind relating to the foregoing..."
- 2) "The Company has done nothing to compromise the secrecy, confidentiality or value of any of its intellectual property required to conduct its business as it is currently being conducted or as proposed to be conducted. The Company is not aware that any of its employees, consultants or advisors are obligated under any contract (including licenses, covenants or commitments of any nature) or other agreement, or subject to any judgment, decree or order of any court or administrative agency, that would interfere with the use of his or her best efforts to promote the interests of the Company or that would conflict with the Company's business as proposed to be conducted."

To avoid ownership and control problems, a company should initiate an Intellectual Property Ownership Program that helps it build, maintain and protect the intellectual property portfolio. The components of an Intellectual Property Ownership Program would include:

- 1) A centralization of information that limits access to the company's patents, know-how, confidential information, and trade secrets;
- 2) The right to review, delay and possibly edit the publication of any article to provide the company an opportunity to file patent applications; and
- 3) The development of a checklist identifying each agreement that an employee, advisor, consultant and other service provider has to execute that would include the assignment of all of his or her rights to

the intellectual property to the company. It is essential that these agreements be signed when the employment, consulting or other form of relationship commences to insure that there is adequate consideration for the assignment of the rights.

TRANSACTIONAL DOCUMENTS

From inception, the founders and the company will need to consider a variety of agreements including, Founders' Agreements, Employment Agreements, Stock Option Grants, Non-Disclosure and Confidentiality Agreements, and Scientific Advisory Board Agreements among others. Each of these agreements must be carefully drafted in order to balance the individual's interests while appropriately protecting the company. Each agreement is important, and will be reviewed by the venture capitalist during the due diligence process.

FOUNDER'S AGREEMENT

The Founder's Agreement takes many forms and is often referred to as a "Stock Restriction" or "Shareholders' Agreement". The document will focus on multiple issues including restrictions on transferability, the commitment that each individual is making to the venture in terms of time and money, and assignment of intellectual property. Additional provisions will relate to rights of first or last refusal, co-sale rights, tag-along, and drag-along rights. The purpose of this document is that it ensures that all of the founders are in agreement with each other, with their respective obligations to the company and with the focus and scientific direction of the Company.

Another area of concern relates to stock ownership and vesting. Many (if not all) founders will consider their shares vested when the entity is created. This issue (which also arises in the context of negotiating an employment agreement) creates significant concerns for the remaining founders and the venture capitalists. If a founder, for whatever reason, prematurely leaves, is terminated with cause, suffers a disability, or dies, the company must have the right to "claw back" some or all of these shares, thus making them available to the founder's successor. Generally, the venture capitalist will require the founder and other significant officers and employees to make a 3-4 year commitment to the company, with a small portion of their shares vesting up front and the rest thereafter vesting monthly or quarterly.

Tax planning also plays a role in the drafting of these documents. From a tax perspective, the best approach is not to use options but to issue restricted shares at a nominal price (i.e. before the intellectual property or rights or contracts are transferred to the company), with the company having the right to claw them back on a decreasing monthly, quarterly or other negotiated basis.

In this structure, the parties will articulate the exact circumstances under which there will be a divestiture of the shares and the purchase price to be paid by the company in the event of a repurchase. If the repurchase occurs at a time when the company has not made significant scientific progress, then a repurchase at the same purchase price paid by the founder or other grantee may be appropriate. However, if the termination occurs near the end of the vesting period and/or after scientific or other due diligence milestones have been achieved, then a formula approach to determining the purchase price that recognizes the founder's contribution is the better method. A form of a repurchase right that arises in an employment context may be downloaded from Evelexa.

CONFIDENTIALITY AND NON-DISCLOSURE AGREEMENTS

The confidentiality and non-disclosure agreement is central to a company's ability to protect its confidential information, trade secrets, know-how, and intellectual property rights. These agreements should be signed by everyone having access to the non-public information including, employees, founders, directors, advisors, collaborators and consultants to the company. As recommended, one individual should be responsible for coordinating this effort and ensuring that originals are maintained in a secure, central file. They will be examined by the venture capitalist during the due diligence process.

While there are many templates for confidentiality agreements depending upon whether they are one way or mutual and whether the companies are private or public, such agreements should contain the following:

- 1) A clear definition of what constitutes confidential information and whether oral information must be reduced to writing and submitted to the other party within a specified period of time;
- 2) A stated purpose for entering into the agreement;
- 3) The agreed upon exceptions to confidentiality;
- 4) The period of confidentiality; and
- 5) The right of a party to seek injunctive relief to prevent a breach of the agreement without the need to prove actual damages.

A form of a mutual confidentiality agreement is available for download from Evelexa.

EMPLOYMENT AGREEMENTS

It is rare that a start-up entity takes the time to negotiate employment agreements; but they serve the same critical function in the employment area that Shareholder Agreements serve in the equity ownership area.

From the company's perspective, an employment agreement confirms the individuals' commitment to the

company and covers important subjects including, duties and responsibilities, confidentiality, assignment of inventions, publication rights and non-competition. These issues are interwoven with the protection of the intellectual property and work together to form a fence around the disclosure of the company's technology.

A well-drafted non-compete provision will prohibit the employee from competing, directly or indirectly, with the company for an agreed upon period of time after the employee leaves or is terminated. Critical to this document is the definition of the company's "business". If the language is too narrow it may miss key elements and not anticipate a change in the company's focus; and if the definition is overly broad (i.e. "the development of therapeutics for the treatment of autoimmune diseases"), it may not be reasonable in terms of time and space rendering it unenforceable. Each sentence must be thought through since a request to renegotiate the language is certain to be rejected. A form of a non-compete provision may be downloaded from Evelexa.

In *EMC Corp. vs. Kenneth Todd Greshem, et al.* (Suffolk Superior Court, NO. 01-2084 BLS), the Court permitted a former employee to consult with a competitor because the negotiated clause, while broad, did not actually prohibit consulting. Attention to detail is crucial when drafting these provisions; the agreement must contain a prohibition against the disclosure of confidential, proprietary information and be broad enough to capture what the employee learns either alone or in conjunction with others while employed by the Company.

In the initial stages of development, a start-up company is likely to enter into a number of agreements with individuals such as consulting agreements, fee-for-service agreements, master service agreements and scientific advisory board agreements. These agreements must contain provisions relating to confidentiality, assignment of inventions, publication and non-competition.

A form of a consulting agreement and a form of a Scientific Advisory Board Agreement are available for download from Evelexa.

STOCK OPTION PLAN

A well-drafted stock option plan ("Plan") is essential to attracting and retaining key employees, directors, consultants and scientific advisors. The Plan should provide the Board of Directors with as much latitude as the Internal Revenue Code allows and specifically, permit the Board to accelerate vesting in the event of a merger, consolidation or initial public offering. A cashless exercise provision is also essential. In addition, it is important that the qualified and non-qualified grant

agreements contain the customary investment representations to insure that the exercise of the options and purchase of the shares does not constitute a distribution in violation of the Securities Act of 1933, as amended (the "Act"). 15 U.S.C. § 77a *et seq.* A form of a Plan, an Incentive Stock Option Agreement, and a Non-Statutory Stock Option Agreement are available for download from Evelexa.

The Plan should be adopted when the founder's shares are granted. Generally, 15%-20% percent (depending on whether the key executives are already incentivized) of the shares then issued and outstanding are allocated to the Plan. The parties will also need to agree on a number of key issues including: 1) the length of the vesting period; 2) the strike price for the granting of non-qualified options; and 3) the approximate number of options that will be granted to employees at each level of employment.

It is also important that the company work closely with the firm's accountants to ensure that the accountants treat the options issued, for both tax and accounting purposes, in the manner expected by the company. The tax and accounting rules governing the treatment of options are complex and fact specific; as such, careful planning and coordination are essential.

COMPLIANCE WITH FEDERAL AND STATE SECURITIES LAWS

In any private offering, it is critical that the founders consider and comply with state and federal securities laws and regulations. Founders often believe – incorrectly – that an offering to "friends and family" is exempt from compliance with securities laws and regulations. In fact, friends and family are still investors and must be evaluated and treated as such. Although several exemptions from registration exist under the Act, the law and regulations still require that the founders pay close attention to the status of their investors and how they are solicited.

The private offering exemption under section 4(2) of the Act exempts from registration "transactions by an issuer not involving any public offering." 15 U.S.C. § 77d(2). To qualify for this exemption, the purchaser of the securities must:

- 1) Qualify as a sophisticated investor or be able to bear the investment's economic risk;
- 2) Have access to the type of information normally provided in a prospectus; and
- 3) Agree not to resell or distribute the securities to the public.

In addition, the company may not use any form of public solicitation or general advertising in connection with an offering under Section 4(2) of the Act. The larger the

investor pool, the more difficult it will be to show that the transaction is exempt. If one person does not meet the requirements, the exemption may be destroyed, potentially putting the offering in violation of the Act.

Regulation D of the Act provides important exemptions from registration for private offerings. A key feature of each exemption is the prohibition against general solicitation and advertising. Additionally, investors who purchase subject to a Regulation D exemption are buying "restricted" securities and may not resell them without registration or an applicable exemption. Two of the Regulation D exemptions are:

Rule 505 provides an exemption for offers and sales of securities totaling up to \$5 million in any twelve (12) month period. Under this exemption, a company may sell to an unlimited number of "accredited investors" and up to thirty five (35) other persons who do not need to satisfy the sophistication or wealth standards associated with other exemptions. Purchasers must be purchasing for investment only and not for resale, and the issued securities must be "restricted." Consequently, the company must inform investors that they may not sell for at least one (1) year without the shares being registered.

Rule 506 is a "safe harbor" for the private offering exemption under Section 4(2) of the Act. If the company satisfies the following standards, the company will be assured of satisfying the Section 4(2) exemption:

- 1) An unlimited amount of capital may be raised;
- 2) No general solicitation or advertising to market the securities;
- 3) An unlimited number of accredited investors and up to thirty five (35) other purchasers; and
- 4) All non-accredited investors, either alone or with a purchaser representative, must be sophisticated - that is, they must have sufficient knowledge and experience in financial and business matters to make them capable of evaluating the merits and risks of the prospective investment.

The definition of an "accredited investor" is the same for each of the above exemptions:

1. A director or executive officer of the company;
2. A person with a net worth, together with a spouse, of more than \$1.0 million; or
3. A person who has had income greater than \$200,000 for the past two years or joint income with a spouse greater than \$300,000 for the past two years.

When dealing with accredited investors, a company is not required to provide a Confidential Private Placement Memorandum ("PPM"). The company must, however, provide adequate financial statements prior to beginning

the offering. What is essential is that there be full and fair disclosure of all relevant information regarding the company. This can be achieved through a PPM, a Business Plan, an executive summary, or Powerpoint presentation. The more written information that the company provides the less chance there is for misunderstandings by the investors.

To ensure that the sale will only be to accredited high-net worth individuals, appropriate Subscription Agreements and Investor Questionnaires should be used. An investment should be accepted only after those documents have been completed, reviewed and accepted by the company. A form of a Subscription Agreement and Investor Questionnaire is available for download from Evelexa.

It is important to consider state securities laws or "Blue Sky" regulations. While exemptions vary from state to state, there is some degree of coordination. Typically, if the offering is exempt from registration under federal securities laws, the offering will often require only a notice filing in the states where the offering is done – sometimes accompanied by payment of a fee. The company must evaluate the impact of the state securities laws in each state in which an investor resides.

Finally, when dealing with restricted securities, Rule 144 is important. Rule 144 provides for the public sale of restricted and control securities in limited quantities without the requirement that such securities become registered. As discussed above, restricted securities are securities acquired in unregistered, private sales from a company or from an affiliate of the company. Control securities are those held by an affiliate of the company. When an individual purchases securities from an affiliate there are resale restrictions even if the securities were not restricted in the affiliate's hands. As a general matter, under Rule 144, restricted securities may be sold to the public if the following conditions have been met:

- 1) The securities have been owned and fully paid for at least one year. The holding period only applies to restricted securities. Because securities acquired in the public market are not restricted, there is no holding period for an affiliate who purchases securities of the issuer in the marketplace. But an affiliate's resale is subject to the other conditions of the rule.
- 2) Current financial information is made available to the purchaser.
- 3) The seller files a Form 144, "Notice of Proposed Sale of Securities," with the SEC no later than the first day of the sale. If the sale involves more than 500 shares or the aggregate dollar amount is greater than \$10,000 in any three-month period. The sale must take place

within three months of filing the Form and, if the securities have not been sold, the seller must file an amended notice.

- 4) If the securities were held for between one and two years, the volume of securities sold is limited to the greater of 1% of all outstanding shares, or the average weekly trading volume for the preceding four weeks. If the shares have been held for two years or more, no volume restrictions apply to non-insiders. Insiders must always abide by volume restrictions.
- 5) The sales must be handled in all respects as routine trading transactions, and brokers may not receive more than a normal commission. Neither the seller nor the broker can solicit orders to buy the securities.

The last step in selling restricted securities under the Rule 144 safe harbor is to be certain that the restricted legend is removed from the stock certificate(s). Only a transfer agent can remove the legend, but a transfer agent must first obtain approval from the company – usually in the form of an opinion letter from the company's counsel.

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ABOUT RUBIN AND RUDMAN, LLP.

Rubin and Rudman LLP is a business oriented firm with seventy five (75) attorneys. The areas of concentration include, business and corporate finance, regulatory and environmental, litigation, and general real estate matters. For more information about the firm, visit www.rubinrudman.com.

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ACCOUNTING & FINANCE

Jack Malley

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This chapter will cover some of the more financially-oriented aspects of starting and growing a company, including the finer points of debt financing, selecting a form of entity (heavily tied to taxation issues), financial software, and insurance. A discussion of business plan financials is included in **The Business Plan** chapter.

FORMS OF ENTITIES

In general, there are five types of entities from which an entrepreneur may choose when setting up his (her) company. They are (1) a sole proprietorship, (2) a partnership, (3) a limited liability company "LLC", (4) an "S" corporation, and (5) a "C" corporation. Each has its distinct advantages and disadvantages.

SOLE PROPRIETORSHIP

This is the simplest of all entities. Here are the highlights:

- There is one owner and the profit or loss of the business is reported on the owner's personal tax return on schedule C.
- Legal registration is not absolutely necessary except to file a DBA with the city or town where the business is located (presuming the owner's name does not appear in the company name).
- However, there can be many disadvantages:
 - The owner is fully liable for all actions and inactions taken by the company. This is a substantial risk for a biotechnology company.
 - Succession is an issue.
 - Your health insurance and group term life insurance up to \$50,000 of coverage are not deductible.
 - Once your company is profitable, you may not avail yourself of lower corporate tax rates.
 - Employees may not be compensated with forms of equity; you are the owner and there can be no others.

PARTNERSHIP

A partnership is very similar to a sole proprietorship except that there is more than one owner. Other differences include:

- While certainly advisable, a legal agreement is not necessary.
- The company's profit or loss is reported on a partnership tax return (Form 1065) and your share is

reported on your personal tax return via a schedule K-1.

- You may compensate your employees with equity and, in certain situations, you can transfer assets "tax free".

LLC

For the first time, the entity begins to bear some of the legal liability burden, though the amount will vary from state to state. In certain cases, ownership interests may be freely transferred. In most every other way, the LLC looks and feels like a partnership, including the manner of tax reporting.

S CORPORATION

This form of entity is truly a hybrid of the partnership and the C corporation. There can be between one and seventy-five owners. However, there can be only one class of stock, i.e., no "special" owners except by the number of shares controlled. The tax return is a Form 1120S (corporate-like) but the owners' share is reported on a schedule K-1 (partnership-like) and, therefore, the owners' share of the profit and loss is still subject to individual income tax rates. That's good when you are losing money but terrible when you are making money. There is limited liability but you still can't deduct owners' health insurance and <\$50,000 group term life insurance.

C CORPORATION

With a C corporation, you may have an unlimited number of owners with as many classes of stock as you desire. Personal legal liability is limited though, certainly, there are many fiduciary responsibilities. You are working in the best interest for all of the shareholders, not just you. The company's income is subject to more favorable corporate tax rates though any dividends paid to you get taxed twice; once at the corporate level and once at the personal level. All insurances are deductible.

The C corporation is the entity of choice if you will be seeking venture capital financing because more than one class of stock may exist. VCs will be issued "preferred" stock, preferable in distributions to owners of common stock, generally the management team. You don't have to choose this type of entity on day one. You can elect to do it on any given day prior to the VC financing or have the financing automatically convert the company on the day of the financing through the issuance of a second class of stock. Some entrepreneurs have elected to have an S corporation until their financing so that they might claim the losses on their personal tax returns. In any case, seek

the guidance of your CFO, tax accountant, and attorney in these matters.

FINANCIAL SOFTWARE

There are several different types of financial software that will become necessary as you grow your company. The first will be accounting software that will help track cash and the expenses that you will incur, automate the payment of vendors and employees, and provide various managerial and financial reports required to monitor your business. The second is fixed asset software, which performs double duty as a better depreciation calculator than a tedious spreadsheet and as an asset tracking and identification tool. The third is equity tracking software that will not only aid in equity record keeping but also with the complex calculations required for audited financial statements.

ACCOUNTING SOFTWARE

As noted above, accounting software provides the means to track cash and expenses, automate certain redundant tasks, such as writing checks, and provide various financial reports. While it is not necessary for the entrepreneur to be able to analyze the various product offerings, it is important for the entrepreneur to be able to communicate to their accountant what types of financial information will be required from the software in order to manage the business.

Some points to consider are:

- **The target audience(s) for your reports.** The investors will want to see the three common financials (balance sheet, income statement, and statement of cash flows) but in a summarized form. However, the software should be able to easily provide more detailed information for each financial statement line item to better provide explanations to the investors and to aid company management in their monitoring of expense activities.
- **The need for departmental reporting.** At a minimum, you will need to segregate your company into a Research & Development department and a General & Administrative department. This will allow your tax accountant to be able to easily calculate amounts in order to claim research and development tax credits on your federal and state tax returns. As your company and management team grow, the need for departmental reporting will become more necessary.
- **The need for reporting against budget and the ease with which to make changes.** The more budget revisions, the greater the need for a transfer

utility to/from the budget source. While most all software programs provide a utility to input budget data and provide relevant reporting, the number of versions that can be tracked and the ability to upload/download budget data from a spreadsheet or budget software varies widely.

- **Your budget for accounting software.** Don't overspend early on but don't skimp as your company grows. The first software you buy won't be your last. Your reporting requirements will change as you evolve, particularly when you consummate partnering or joint venture deals or expand into foreign countries and establish new entities. Your rate of growth will also have an impact. Beyond your initial stages, you'll want software that can grow with you. You don't want to have to retool with new accounting software at every stage of your company's growth. Properly fitted accounting software will save you administrative expense.
- **The need for security.** In a very small operation, minimal amounts of password security will be required. As the company grows and more people become involved in the various accounting facets, a more complex security structure will be required. Restricting access to certain reports, data, software modules, input windows, and even input fields may be necessary. Another security measure should include the *inability* to delete or alter previously recorded transactions. You don't want to find out your historical data has changed in the software from previously published reports without an audit trail as you are about to go public!

In turn, with this information and a budget, the accountant will be able to acquire the proper software. Following is capsule summary of categories of accounting software and their relevant price points. We will defer the discussion of the enterprise class of software (for large companies); when you're at that stage, your company's needs will far exceed those discussed above and the price points are in the six and seven figure range, with implementation costs approaching 2 to 3 times software costs.

- **Low End.** This category includes the two leading products in their field: QuickBooks and Peachtree. Each comes in several flavors, come in single-user and multi-user configurations, and can be purchased at retail outlets such as Staples and OfficeMax. Costs will range from \$300 to \$3,000. Implementation costs will be ½ to 1 times the software cost. Other competitors in this area include BusinessWorks and Cougar Mountain. Watch for Microsoft's answer in this field, The Small Business Manager.

- **Mid-Range.** This category includes several tried and true packages such as Great Plains, Solomon, MAS90, and Macola, which come in LAN and client server offerings. Their cost is not only dependent upon the number of modules required but also the number of concurrent users needed. Costs will range \$20,000 - \$80,000. Implementation costs will generally be 1 to 1½ times the software cost.
- **ASP.** One attractive alternative to the significant cash outlay for a more sophisticated software package is to outsource its residence to a managed data center (**ASP – Application Service Provider**) through the software reseller. You'll still have to pay for some implementation costs, though the cost should be less than with an implementation on your office server. You'll also need to have a high-speed data line to ensure reduced latency for your accounting staff as they enter transactions and run reports. Advantages include:
 - More rapid implementation;
 - Capable IT management of related hardware;
 - Regular software upgrades;
 - Remote backup;
 - No requirement for internal IT support;
 - Predictable monthly service fee;
 - A far smaller upfront cash outlay;
 - Flexibility to change your mind later on if you chose to bring the application in-house or switch applications;
 - Laptop users who have Citrix server software loaded can access the application wherever they can use a high-speed internet link.

FIXED ASSET SOFTWARE

During the early stages, companies typically maintain their capital expenditure information on a spreadsheet. For each asset purchased, the information would include the date purchased, the cost, the economic life, and a depreciation calculation for the required timeframe. The spreadsheet's maintenance can be a chore especially when a new depreciation method is required, such as for tax returns. A fixed asset software program is organized as a database and, with the better packages, can:

- Calculate multiple depreciation methods, including proscribed federal tax methods;
- Track non-accounting data such as location, serial number, component of, warranty dates, vendor, and several user-defined fields;
- Provide a variety of standard reports such as a monthly depreciation calculation sorted by asset class;
- Provide a report writer to generate a warranty expiration date report sorted chronologically, for example;

- Provide the ability to easily provide necessary insurance reports.

EQUITY SOFTWARE

Like fixed asset tracking, stock and stock option tracking in the early stages of a company is usually done on a spreadsheet, which lists stock issuances sorted by type of stock, identifying percentage of company ownership, and a detail of stock option pool comings and goings.

However, since the early 1990s, required footnote disclosures in audited financial statements and the calculation of charges incurred by certain option and stock issuances posted to the income statement have become more complex. Unlike fixed asset tracking, which requires the use of relatively simple functions in a spreadsheet, stock option valuations require the use of complex mathematical models incorporating natural logarithms (remember them?) and normal distributions. Stock and option vesting schedules, in order to be foolproof, should make use of complex date arithmetic functions. Add to these "simple" issues, changes in employment status, multiple plans with varying parameters, option exercises, and tax issues, and you quickly realize how difficult an animal this is to control and maintain.

Inevitably, these needs have given rise to software programs that can provide reports for both the benefits manager and the CFO incorporating these complex formulas. Likewise, data entry of stock and option data is relatively easy. Two leading software programs that help manage this function are Express Options™/Express Share Tracking™ by Transcentive and Equity Edge™ by eTrade. Costs are rather inexpensive while you are a private company (\$3,000-5,000/year) but rise significantly when you go public (\$xx,000).

INSURANCE

There are two types of insurance coverage you will need to consider: one for the operation of your company and one for your employee benefits. The process of determining appropriate company operations' risk coverage requires the identification of possible exposures. Industry surveys are helpful in determining an appropriate employee benefits plan. Some insurance coverages are readily apparent, such as property damage, general liability, health insurance, and workers' compensation. Others are not and require the expertise of an insurance agent, ideally one who has working knowledge of your industry.

Depending on coverage amounts and deductibles, a 10-person company would expect to pay approximately \$4-\$7k annually, exclusive of D&O insurance. A 100-person

company would expect to pay \$50-\$75k annually, exclusive of D&O and clinical trial insurances. Read the *Risk Management and Insurance* chapter for details.

DEBT FUNDING

In addition to selling equity to investors, a company may also have the option of borrowing money, either from an angel investor or an institutional investor specializing in debt financing.

PROMISSORY NOTES

As will be discussed in the Equity Issues chapter, angel investors oftentimes fund a startup with a promissory note (i.e. loan) rather than with stock. The angel may not wish to protract the funding negotiations with discussions of how much money your company is worth; not enough science, people, and money have passed to allow one to determine a proper value.

One form of a note is a simple cash note. The repayment term is either “payable upon demand”, on a schedule, or at a specific date, preferably beyond the time when additional financing is expected. If the note is due beyond 12 months, then a rate must be provided; otherwise one will be implied by the IRS or be re-characterized as dividend income. A cash note has several disadvantages to the prospective investor. Upon its repayment, the investor would realize a simple 1x return. Future investors may be discouraged by the knowledge that a portion of their investment will be used solely to pay back the loan and accrued interest owed to a previous investor.

Usually the note will have some form of an equity kicker. In one method, the note is convertible to the next round of equity at the next round price discounted by a factor of 10-30% from the financing round's price. A second method attaches a warrant that allows the note holder to purchase stock in the company at a future date, with limitations, at a pre-determined price. The amount of the warrant will usually be expressed as a percentage of the loan amount. For example, if the principal amount of the convertible note is \$100,000 and it has 10% warrant coverage with an exercise price of \$0.50, then this would allow the note holder to purchase 20,000 shares of stock ($\$100,000 \times 10\% / \0.50) at a future date.

BRIDGE LOANS

Sometimes the best-laid plans for equity funding do not materialize at their designated time. When cash starts to run low, certain current investors, banks, or other hybrid institutions may agree to advance the company funds until the latter of the closing of the next equity round or a fixed date in the future. Lenders will perform due diligence to ensure that the advancement of funds is indeed a “bridge” to the next round of financing, not a permanent issuance.

As with a promissory note, the bridge loan will carry an interest charge, a conversion rate based upon the share price of the next round of funding, a fixed repayment date if the equity event has not yet occurred, and an attached warrant. The amount of the warrant will be expressed as a percentage of the loan amount. In these cases, the warrant coverage may be as high as 50% of the loan amount. Some loans will have a tranche effect on the level of warrants. For example, the warrant conversion rate might increase if a particular milestone were not achieved, such as raising the next round by a certain date or the successful completion of a clinical trial.

The loan may be advanced in increments rather than as a lump sum. Entrepreneurs should seek terms that include multiple advances. Should the entire amount of the note not be advanced (e.g. in the event that the company closes a round of financing sooner than expected), there would be proportionately less dilution in the next round.

You should discuss these transactions with your tax advisor before their execution. Further, while these types of notes avoid the valuation discussion, negotiations are still necessary to determine the amount, conversion rate, maturity date, whether the note automatically converts upon financing or if conversion is at the note holder's option, the equity kicker, and the consequences of no liquidity event.

SECURED EQUIPMENT FINANCING

One might ask: if I have raised enough equity to carry the company beyond a key milestone, why would I want to also receive debt financing. The answer is twofold: debt financing is cheaper than equity financing and it is most always better to have more cash today than to count on receiving more tomorrow. To determine the cost of equity financing, one needs to examine the “cost of capital”. Investors, VCs in particular, are seeking a 30-50% annual rate of return on their investment in your company. On the other hand, banks, leasing companies, and others who offer debt financing are seeking a 10-20% annual return, including all payments and fees.

Some of the terms in a debt deal would include the following:

A. Loan Terms

1. **Loan/Lease Amount** – usually expressed as a commitment amount that would be drawn over a fixed period of time
2. **Soft Costs Allowance %** - soft costs include leasehold improvements, software, installation, sales tax, and shipping. Soft costs generally are regarded as being more risky and, therefore, carry a more expensive debt cost

3. **Takedown period** – the period over which the commitment amount is available for advance to fund the assets
 4. **Documentation requirements for takedowns** – invoice copies, purchase orders, cancelled checks (try to avoid this one; it extends the time which the company would be required to fund the asset)
 5. **Depreciation schedule** for older items to be financed – with equipment financing, items with an invoice date of as young as 31 days old may not be funded in its entirety
 6. **Items not fundable** – sometimes certain soft costs, used equipment, items purchased with a credit card or on an employee expense report item are not funded
 7. **Loan Term/Maturity** – the period of time over which the borrowed funds must be repaid. There may be an initial period where there are only interest payments followed by a fixed term for payment of principal and interest or a separate loan amortization may be defined at each month or quarter in which advances were made.
 8. **Balloon/Backend payments** – this is a payment that may be required as the final payment of a loan, typically expressed as a percentage of the amounts advanced
 9. **Interest Rate** – may be expressed as a fixed rate, as a percentage over the lender's prime rate, or as a hybrid of the two (e.g., the rate would be Prime + 1% but no lower than 6%)
- B. Advance payments or deposits required** – upon acceptance of the lender's term sheet, the borrower is required to make a good faith deposit. The lender will deduct from this deposit any out-of-pocket processing and legal fees and will then return the remaining balance to the borrower once the loan has been approved.
- C. Commitment Fees and/or Loan/Lease Fees** – any number of other fees could be assessed; caveat emptor.
- D. Collateral and Lien(s) required as security** – the lender has the right to take and hold or sell the specified collateral property of a borrower as security or payment for a debt. The specified property may range from just the assets being funded (e.g. equipment) to all the assets of the company, including intangible assets such as intellectual property. *Guard your IP with your life*; at a minimum, obtain a negative pledge on IP with exceptions permitting licensing, partnerships, or joint ventures entered into in the ordinary course of business. An all asset lien may hinder your ability to seek future debt financing with other institutions or even vendors offering attractive lease terms. The workout is to have your lending institution provide a subrogation agreement, which may be difficult to obtain. A compromise position would be to negotiate a specific dollar value carve-out for use in securing future debt.
- E. Prepayment Penalties or Similar Payments required** – should you decide to repay the loan early, for example, because of a merger, the lending institution will typically ask for all future amounts to be repaid, principal *and* interest, less a discount factor.
- F. Financial or Operating Covenants** – may be as simple as a requirement to submit monthly financial statements and a copy of the annual budget, putting adequate insurance in place, or agreeing to deposit substantially all funds with the lending institution and maintaining stringent financial ratio requirements. In the latter case, you should determine what the lender's return on invested funds has been and how that compares to other deposit sources.
- G. Restrictions on or Allowances for additional debt being taken on by the Company** – the inclusion of this term generally depends on the financial condition of your company.
- H. Legal Work and Fees** – addresses whether lender legal fees are to be paid by the Lender or the Borrower and if there will be a cap on such fees.
- I. Warrants:**
1. Coverage % (as % of loan amount)
 2. Life of warrant
 3. All other terms
 4. Have your attorney review a draft of the warrant agreement prior to signing a final term sheet.
- J. Investment rights** – the lender may request an option to invest in your next round of financing. A cap should be determined, and the lender, if it chooses to take advantage of this option, should be required to pay the same price as all other investors in that round.
- K. Material Adverse Change (MAC clause)** – this is the lender's wild card. Put simply, in the lender's sole discretion, if it feels uncomfortable with the general affairs or financial direction of your company, or if you have deviated sharply from your business plan, they may cease to advance any further amounts to you and, in the most extreme circumstance, transfer the remaining unpaid principal from your bank accounts without notice. This is a difficult clause to avoid. The lender's record on this matter should be well understood.

LETTERS OF CREDIT

A letter of credit (LC), long popular in international trade, is frequently used as an alternative to cash security deposit for an office lease. An LC is an instrument issued by a bank guaranteeing the payment of a customer's obligation for a stated amount for a stated period of time. In effect, the LC substitutes the bank's credit for the buyer's. The LC would be drawn in favor of the landlord, meaning that if the company defaults on its lease, upon written notice, the bank would pay the landlord his security deposit.

Often, as equipment financing is being negotiated, the rate the lender would charge for providing an LC and the maximum amount to be provided could be included in the negotiations.

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ABOUT FIRSTJENSENGROUP

FirstJensenGroup is a partnership of skilled senior managers and advisors that provide a comprehensive range of interim management, consulting and tax services to the technology and life science sectors. Clients include entrepreneurial start-ups, established private and public companies, private equity investors, banks and specialty lenders.

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REAL ESTATE

Alfred Vaz

Vice President, Vertex Pharmaceuticals

This chapter will focus on the basics of real estate, factors to consider when choosing a location, planning and implementing construction, facilities costs, and whether the virtual model is an alternative to leasing laboratory space. Rent is noted in \$/square foot (sf) on an annual basis. Construction is noted in \$/sf on a one-time basis.

REAL ESTATE CYCLES

There have been two major real estate cycles in the history of biotechnology. In the late 1970's, Genentech and Biogen left the universities to found their own homes in South San Francisco, CA and Cambridge, MA respectively. As these companies and their peers grew, they created demand for new research facilities. This growth phase eventually reached a plateau and subsequently declined as venture capital for new start-ups grew scarce towards the late 1980's. In the declining phase, construction of new facilities slowed down and older buildings were re-used as supply exceeded demand.

Over the past 10-15 years, this cycle has been repeated, beginning all over again with strong growth throughout the 1990's. At the beginning of 2001, Cambridge alone had about five million square feet of industrial laboratory space, all occupied, and had just passed a moratorium on the construction of new space. This was done, much like in the early 1980's, so that regulators could re-assess the development priorities of the community. Regulators wanted to ensure that the community was not over-built and that there were not many empty buildings detracting from the economic vitality of the area.

However, there was an unplanned effect from that building moratorium. At the time, all available space was leased and there were no options for companies looking for space. It created a "landlord's market" and rents reached an all time high, some higher than \$70/sf. Soon thereafter, the moratorium was lifted, new development regulations were enacted, and building began once again. The space was built in anticipation that demand would continue to exceed supply. Instead, the economy entered a downturn and demand for space declined as many companies downsized and the industry consolidated, leaving many spaces empty or underutilized. In 2003, real estate became a buyers market as dozens of vacant facilities, some with hundreds of thousands of square feet of beautifully built-out lab and office space, stood empty. In two short years, the rules changed as rents dropped to

as low as the mid-\$20's/sf. To fill their buildings, landlords often had to agree to fund tenant construction.

ROLE OF LANDLORDS

In any environment, landlords seem poised to provide the real estate and laboratory space biotech companies required. However, very few would ever consider building a new facility until they have a leasing commitment from a company. By pre-leasing the space, the landlord stays slightly ahead of the game, anticipating downturns so they are not left owning unoccupied buildings during periods of low demand. Consequently, landlords generally demand the kind of rental prices and long-term commitments to large spaces that only established companies can afford.

Constructing a building as a laboratory-ready shell (more about "shell space" below) costs \$80-\$120/sf. To then build out this shell space into a typical laboratory facility would cost an additional \$100-\$125/sf. Therefore, a finished 150,000 sf building would around \$30M.

A landlord will often take out a short-term high-interest construction loan to build a new facility, but will refinance to a long-term low-interest loan once the building is completed *and* a tenant is occupying the space. If a large company that has committed to a space decides not to use it, there is an increased risk that the company may break the lease (i.e. refuse to make its payments), and this risk is unacceptable to the institution offering the landlord the long-term loan. Therefore, the landlord will need to find tenants who actually will use the facility at a rate comparable to the original lease to meet the conditions of the long-term loan. If no other large companies want the space, the landlord might consider splitting the space into units that multiple smaller companies can lease to ensure that the building is occupied.

The landlord's prime concern is the financial stability of the tenant. Most leases require a 10-year commitment, giving the landlord a stable return over a long time as long as the company can afford to make its payments. To provide some comfort to the landlord, a tenant will be required to place a security deposit in escrow typically equal to one year of rent and associated operating costs. In the event a tenant goes out of business and defaults on the lease, the security deposit buys the landlord time to re-lease the facility (sometimes at a higher rate than the previous tenant paid since now the facility is finished).

LOCATION

A startup may be highly dependent on consultants, scientific advisors, investors, and part-time employees and should consider locations where these resources may be easily accessed. Just as the high tech companies in the 1980's preferred to be along the Route 128 belt in Massachusetts or in California's Silicon Valley, the biotech industry has similar epicenters in Massachusetts, Southern California, and North Carolina. What makes these epicenters ideal for emerging technology-oriented companies is that they offer close proximity to exceptional universities, venture capital firms, and numerous businesses that provide services every company needs (e.g. law and accounting firms,), along with public transportation, hotels, and access to major airports.

In Massachusetts, biotech startups want to be in Cambridge, near Harvard, MIT, other biotech companies, and Boston's financial center. California companies may choose San Francisco or San Diego for the same reasons. As companies mature and become more self-sufficient, they may relocate operations from the epicenters to regions where real estate is considerably less expensive.

REGULATION

A biotechnology company with plans to conduct typical biomedical research on its premises must obtain 10-15 different permits before it can begin operating. Many of these include authorization from the city or town to use hazardous chemicals and radioactive materials, perform animal research studies, and operate critical equipment such as fume hoods, emergency generators, and waste treatment systems. Not all towns are familiar or comfortable with the health & safety aspects of biotechnology research. Some may entrust its regulation to the local Board of Health, which, unfamiliar with how biotech companies operate, may not be prepared to efficiently handle this responsibility. However, once one company has successfully located in a community, it becomes easier for other companies to follow suit.

Established biotech epicenters have already developed well-defined workable regulations, and some even have full-time local agencies focused on ensuring that permits and licenses are issued efficiently. Cities and towns with a well defined regulatory framework will allow companies to flourish while protecting the public health of the community. Therefore, a town's level of comfort and experience with biotech should factor into a company's choice of location.

BROKERS

A biotech company should secure the services of a real estate broker to assist in evaluating real estate options and even negotiating a lease. In the Cambridge / Boston area

for example, only a handful of real estate brokers specialize in biotechnology and have the resources to locate all available space. The landlord pays the broker's fee so companies are free to use the services of as many brokers as they like. Before representing a company, a good broker may want proof that the company is well financed or is, at least, backed by credible investors.

NEXT GENERATION SPACE

Next generation space includes facilities that have already been leased at least once before (e.g. 3rd generation space will have been gone through 2 lease cycles). A company may build-out space but never use it or have excess space after downsizing. By sub-leasing, the primary tenant hopes to cover most if not all of its rental obligations to the landlord. A company 6 years into a 10 year lease paying \$40/sf may be willing to charge only \$30/sf for a 4 year sub-lease, covering 75% of its obligation to the landlord, rather than let the space sit empty. Leasing the same space directly from the landlord at current rates (not those set 6 years ago) may cost considerably more and may require a longer-term lease commitment. Therefore, sub-leasing next generation space is often a good option for a startup company.

Next generation space may also become available when a primary tenant goes out of business or an expired lease is not renewed because the company relocates. Depending on your company's needs, the space may already be ready to use or may require some renovation to meet your specific R&D requirements.

FINISHED VS. SHELL SPACE

Some facilities are ready for use with everything from chemical fume hoods to laboratory benches and thus are considered finished spaces. Others exist as just empty shell space that have all the necessary infrastructure but still need to be built out into laboratory and offices.

Leasing a fully built-out facility will cost less up-front since little construction will be required. However, rent will be higher because the landlord will capitalize on the intrinsic value of the built-out space. Therefore, you could expect to pay twice as much per square foot for finished vs. shell space, which becomes significant over the course of the lease.

Conversely, leasing empty shell space costs much less and allows you to customize the facility to your exact specifications. However, construction costs may be variable and difficult to control. For a 20,000 sf facility, a company may expect to spend as much as \$3 million on build-out (\$150/sf). For a startup with \$20 million in venture capital, committing 15% of its working capital

upfront to build-out is onerous. Furthermore, because most leases do not allow the tenant to remove these improvements during or at the end of the lease, the company loses its investment if it ever moves out.

Smaller companies may not be able to afford \$150/sf to convert a building into an R&D facility. The landlord may finance the build-out to attract the tenant, but the landlord will then recoup the expense by charging a higher rent. A general rule of thumb is that for every \$25/sf of tenant improvements a landlord finances upfront, the tenant will pay an extra \$3-5/sf each year over the course of a 10-year lease. If the lease period is shorter, the additional cost/year is higher.

ESTIMATING COSTS

Rent Costs

Rent is determined by many factors, none more critical than location. The rent for a building in a biotech epicenter may be double the rent for a similar one located in the suburbs. Construction and cost of operation also contribute to the total cost of leasing biotech real estate. In a normal market, a biotech startup outside an epicenter may spend \$15-20/sf for shell or \$30-40/sf for finished space. Comparable spaces in an epicenter might go for \$25-35/sf for shell and \$40-\$55/sf for finished space. However, during peaks in the commercial real estate market, these rates were as much as 30% higher.

COST OF BUILD-OUT

The cost of building out shell space ranges from \$60-\$150/sf, depending on the mix of office space (less expensive) and laboratory space (more expensive). For a typical drug discovery company with 65% lab and 35% office space, costs may run \$100-125/sf.

OPERATING COSTS

The operating costs of standard office space are steady and predictable, allowing the landlord to comfortably include them in one simple rent rate per square foot. Costs for biotech facilities, particularly the utilities, are less predictable and the landlord will quote a "triple net" price (i.e. net of taxes, utilities, and insurance), which consists only of the base rent. The tenant will be solely responsible for paying all associated operating costs.

Operating costs include real estate taxes, property insurance, utilities, management fees, certain maintenance & repair activities, landscaping and grounds upkeep, security, and other measures needed to "operate" the building. These are very difficult to estimate until you have 12-18 months experience with the facility. For example, the costs in Southern California are more predictable than in the Northeast, where the cold of winter and heat of summer can be taxing on a building's

environmental controls. Until you have a track record on which to base a better estimate, assume that annual operating costs will add \$7-15/sf to the base rent.

BUILD-OUT

It can take anywhere from several months to a couple of years from the time you sign a lease until R&D operations can commence in a new facility. Each project is different, be it moving into a finished facility, renovating an existing space, or developing a new facility from the ground up. Misconceptions regarding timing can lead to unfulfilled expectations and cost overruns. Taking the time upfront to plan properly can result in greater time savings later.

Project Manager & Contractor

Once you have found a space to build out, consider hiring a qualified project manager (PM) to oversee construction with your interests in mind; there are issues involving, permits, budgeting, and coordination etc. that must be managed with experience to avoid disaster. Sometimes the real estate agency through which you found a location will offer to provide project management services. You may also consider asking a local industry trade association such as the Mass Biotech Council (www.massbio.org) for a referral to an independent PM. A PM may charge an hourly rate or a fixed percentage of the value of the construction project.

The PM will help you find an architect and engineer who will develop blueprints based on your specifications. Based on the blueprints, the PM will collect bids from several contractors qualified to do the build-out. The contractor will hire a number of sub-contractors to complete tasks such as wiring, plumbing, carpeting, painting, seeing to it that each step is done in the proper order. Periodically, the PM and architect will do a walk-through to make sure that everything is done according to the company's specifications. The company should assign one of its own people to work closely with the PM, participating in these walk-throughs.

The contractor will bill the company monthly as the work progresses, withholding 5-10% of each invoice (known as "retainage") until the client is satisfied that the entire project has been completed properly. In case of poor workmanship, the contractors will be required to fix any problems to the satisfaction of the PM and the company before the retainage is released for final payment.

STAGES OF BUILD-OUT

The various stages of project development include programming, design, budgeting, permitting, and finally construction. Once constructed, there is a period of testing and validation known as commissioning, which is one of the most critical stages and most commonly

overlooked. Why? Because the facility is complete at this time and looks ready for scientists to move in, but if commissioning is not done, one can never be certain that the facility systems work as designed and have all the necessary operational and safety features.

Typical build-out timeline for empty shell space:

Programming	1 month
Design	3 months
Budgeting & Pricing	2 months
Construction Permitting	1 month
Construction	9 months
Commissioning	1 month
Move-in and Occupancy	2 months
TOTAL TIME TO OCCUPY	19 months

Regardless of complexity, any project will require 3-6 months of programming, design, budgeting, and pricing to provide the company enough information to making an appropriate commitment to construction. Duration of construction can vary from 3 months for moderate renovations to an existing facility to 9 months for constructing a lab out of shell space. Being as prepared as possible for all the pitfalls and curveballs of construction will greatly enhance the success of meeting timelines and delivering a lab facility on time and on budget.

Because some tasks can be done in parallel, the timeline above does not specifically mention operating permits, which are different from construction permits. However, even when sub-leasing a finished facility, a company must obtain operating permits. This process typically requires 2-3 months, though the rate limiting step is often obtaining permits such as the Sewer Discharge Permit which allows you to discharge building effluent into the sanitary sewer system. These permits can take up to 5 months from when you start to write the lengthy application until it issues. Therefore, even if you find a facility that you are reading to move into, the permitting process alone will delay start of operations by several months unless this time is built into the planning phase for getting a new lab operational.

OTHER STARTUP OPTIONS

OPERATING VIRTUALLY

Rather than leasing laboratory space of your own from the start, you may be able to outsource research to an

academic laboratory or contract research organization (CRO). The company will only need to lease office space for management, thereby spending less money on rent. The downside of operating virtually is that the company pays a premium for research services (since the university or CRO wants to make a profit), may have to share intellectual property rights, and allows other people to dictate how quickly and how well the work is done. Therefore, the virtual model is usually a temporary solution; a company that relies on drug discovery will eventually need to have its own R&D facilities.

INCUBATOR SPACE

In an incubator facility, a tenant can lease finished space that is already built-out to suit the needs of the average biotechnology companies, including biology, chemistry, and instrumentation support. The tenant could also lease access to operating infrastructure, including support space and staff. Services would include facilities management, laboratory operations, administrative functions, property management, regulatory compliance, and purchasing & procurement. This incubator space then allows a group of scientists with precious venture capital to avoid the large up-front capital investment that comes with leasing and building a facility. Instead, the startup would pay the landlord with equity and monthly rent. Such an arrangement might work for several years before the company outgrows the model and needs to bring equipment and personnel in-house. See the chapter on Raising Money for further discussion of Incubators.

ABOUT THE AUTHOR

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Alfred Vaz, Jr. is a member of the management planning team for Vertex Operations, which includes corporate real estate, facilities, space planning, engineering, materials management, health & safety, and general operations. He also manages Vertex's facilities in California and the UK. Mr. Vaz has 21 years of experience in the biotech industry. Prior to joining Vertex in 1989, Mr. Vaz worked at Millipore and for 5 years in Biogen's Safety & Laboratory/Facilities Services Group. Mr. Vaz holds a BS in Biology from Providence College and an MS in Public Health from University of Massachusetts Amherst. He has served on various boards and membership committees representing the biotech and pharmaceutical sectors.

RISK MANAGEMENT & INSURANCE

Ty Howe, ARM,
Vice President, Marsh USA Inc.

To protect the assets of a corporation, it is recommended that management follow a basic protocol. The first step in the process is to analyze the risk by asking the question, "What could possibly happen that will cause financial harm to my company?" Typically, life science companies face risks in the following areas:

- Property (buildings, lab equipment, computers, and compounds or products in development),
- Workers Compensation,
- Liability from products in clinical trial,
- Liability from premises liability,
- Directors & Officers liability,
- Auto,
- Crime (also known as Fidelity),
- Fiduciary liability (for assets in a 401k plan)
- Intellectual Property (for claims either brought by others for infringement or for claims brought by you against others that infringe against you).

For each of these areas of risk, there is a process of analysis for identifying, analyzing, and mitigating risk. Periodically each of these risks must then be reanalyzed to make certain the management of the risk is appropriate. Once the analysis is complete, insurance should be purchased to protect the company from the claims that cannot be avoided in any other fashion. In all cases, the mantra to be followed is, "Manage the risk first, then buy the insurance."

Take, for example, the risk posed by a product entering clinical trial. On occasion, a subject may be injured in a trial. When this happens, the sponsor organization will be liable for the injury, right? Maybe, but then again, maybe not. Under this scenario, how can one "manage the risk first?" First, the agreement with the trial site should clearly spell out the responsibilities of the parties. It is only reasonable that the trial site be responsible for injuries arising out of the negligence of its staff. If the study drug did not cause the injury, but instead it was caused by a dosing error, a well-constructed contract will put the liability in the hands of the responsible party, that is, the trial site. Further, if injuries to subjects arise out of failure to follow the protocol, failure to gain proper informed consent, or failure to conserve the drug under the proper storage conditions, the trial site should hold the responsibility. Good risk management practices in this case therefore, start with a tightly written contract and a quality informed consent document.

What follows here is a discussion of each of the areas of risk noted above, with suggestions for how the risk might be managed and then how to insure those risks that cannot be comfortably controlled.

PROPERTY

Property will typically consist of Real Property (buildings), Personal Property (lab equipment), Electronic Data Processing equipment (computers), and compounds or products in development. Most entrepreneurs are not obligated to insure a building, unless the terms of the lease are "triple net." Personal Property and EDP equipment is insured at replacement cost (not depreciated or cash value!). Commonly, start-up companies will lease equipment and the lessee should beware – the lessors will charge a monthly insurance premium if proof of insurance is not provided to the lessor with a Certificate of Insurance issued by your insurance agent or broker. When you buy insurance for the leased equipment, be sure to tell the leasing company so that you do not pay two premiums for the same type of coverage.

The possibility for managing this risk is limited, but insurance is cheaper if your premises are better protected. For example, a sprinklered building is better than non-sprinklered, a non-combustible building better than wood frame, and property located away from a flood zone better than being right on the waterfront.

Software and valuable papers can also be insured, but attention should be devoted to managing the risk first. In both cases, a good records retention policy will give a company access to duplicate records, if original records are destroyed. If full duplication exists and duplicate records are stored off site, the need to buy insurance coverage is far less. A number of biotechs purchase only enough software and valuable papers insurance to replace and restore that which is not in duplicate form. The valuation of these items can be tricky, as the policy can be designed to pay for the cost of restoring damaged records. The insuring value therefore, must be set at a level to reflect the estimated restoration costs.

The risk of insuring compounds can vary widely, depending on the nature of the compound. The key questions are whether the compounds are climate sensitive and whether they can be replaced. Climate sensitive products require diligent risk management by examining the storage site to determine if the facility has redundant features that limit the possibility for loss of the climate control conditions. Many cold storage companies have inadequate controls in place to make sure

temperature alarms will sound if the freezer gets too warm and that back up power will be produced during a power outage. If the climate controls are inadequate, many insurers will refuse to insure the compounds for spoilage.

It is very common for companies to outsource the production of compounds and this third party dependency creates one of the most critical risks for a start-up company. Simply put, it is nearly impossible to minimize the risk of third party dependency. First, the lack of available production capacity puts the buyer of production services at a negotiating disadvantage. A start-up cannot hope to negotiate a production contract that guarantees instant replacement of clinical supply. Second, as of 2003, the market for this service is a seller's market for the foreseeable future. Since the risk cannot be reduced through a guaranteed supply contract, insurance of this material is critical. The goods should be insured on a replacement cost basis, and business income insurance must be purchased to reimburse the following costs:

- The cost of continuing expenses while the company waits for replacement supply. These expenses may include continuing rent, equipment lease costs, payroll costs, and health insurance.
- Extra expenses incurred following the loss. The biggest extra expense may be the surcharge a start-up may have to pay to speed up the production of your critical compound. It is easy to imagine your chief scientist saying, "I will pay anything to get my producer to make me more product for clinical use." The extra cost paid above the actual replacement cost of the product is insured as an extra expense.

WORKERS COMPENSATION

For all companies that have employees, state laws require Workers Compensation insurance coverage. The limits of coverage and basic rates are determined by each state. Rates are determined through a formula that measures the cost of worker injury based on the actual cost of injuries for each industry. Fortunately, biotech has proven to be a relatively safe work environment, due in part to the highly educated work force and the high level of regulation of the industry. Consequently, the cost of Workers Compensation is lower than for almost all other industry classifications. Risk management practices start with good OSHA compliance.

LIABILITY FROM PRODUCTS IN CLINICAL TRIAL

As discussed in the example above, the liability to a drug sponsor can be managed to reduce liability risk to actual injury caused by the study drug. An inherent problem with clinical trials is that it is difficult (if not impossible) to separate injury caused by the study drug from the symptoms of the ailment that brought the subjects into the study in the first place. Given this, how can an

argument separate liability of the sponsor from the rest of the medical costs produced by the disease? A sponsor will incur considerable cost defending its position before incurring any liability costs.

Since the liability cannot be avoided or contractually transferred, the sponsor will be required to purchase clinical trials liability insurance and provide proof of the same to any Institutional Review Board that is reviewing a proposed study. Though U.S. law does not require the coverage, from a practical standpoint, all IRBs will demand it. Limits typically start at \$1,000,000/occurrence, and many IRBs require no less than \$5,000,000/occurrence. Although litigation arising out of clinical trials is uncommon, recent news reports speculate that clinical trial liability claims are on the rise. Since injury or death of a subject is very serious, most development stage companies are well advised to buy no less than \$5,000,000 in limits. Deductibles are no less than \$5,000/claim and are more often \$25,000. To limit the cost for multiple claims, an Annual Aggregate Deductible should be part of the insurance policy. For example, for an insurance program with a per claim deductible of \$25,000, a company should seek an Annual Aggregate Deductible of \$125,000. While this may seem like a staggeringly high amount, the commercial insurance market will not offer aggregate deductibles of less than five times the per-claim limit.

If your company intends to run clinical trials overseas, the rules are different and country specific. Some countries will require clinical trial liability as a matter of law, while others will have standards that must be met. Still others will require "no fault" insurance that will pay all medical costs of the subjects, without regard to the cause or liability. The rules of the road change frequently, and an insurance broker with international capability should be consulted to make certain that the insurance is correctly structured. Finally, unlike many other insurances, it is not possible to effectively bid clinical trial liability insurance. The cost of the insurance will vary little from insurer to insurer and the choice of insurer should instead be dictated their financial security and ability to issue certificates of insurance quickly. Many companies have seen their clinical trials delayed due to the insurer's inability to efficiently provide the required proof of insurance to the IRB of a hospital in a foreign country.

LIABILITY FROM PREMISES AND OPERATIONS

All tenants are required by their landlords to carry Commercial General Liability as a condition of the lease. This requirement is expressed in the following way:

\$1,000,000 per occurrence
 \$2,000,000 General Aggregate
 \$1,000,000 Personal/Advertising Injury
 \$10,000 Premises Medical Payments

Further, the landlord will require a Certificate of Insurance to give evidence of such coverage and may require that the policy name the landlord as an Additional Insured. All of these requirements are normal, but should be reviewed by your legal counsel. There is no standard wording of insurance requirements in a lease, and some leases are notoriously weighted in favor of the landlord. Fortunately, insurers issue policies that combine these coverages into a single policy and provide a rating discount if Property insurance is purchased in a "package" format.

When negotiating the lease, take care to limit your responsibilities as a tenant. Specifically, a tenant should accept liability for care of the occupied premises but may want to specifically confirm that it will have no liability for public areas and tasks such as snow removal. Once a tenant takes occupancy, it should reduce risk by using common sense. Some of the simplest measures apply here. If the carpet is torn, if the entryway is slippery, if power cords are in high traffic areas, consider the risk they create for visitors unfamiliar with your premises.

DIRECTORS & OFFICERS LIABILITY

With the corporate governance scandals at Enron and WorldCom, many articles have been published on the subject of D&O. For a new company, the most important point to consider is that almost all of the shareholder litigation has been brought against publicly traded companies. The cost of D&O insurance for a public company is much higher than for a private company. For a \$5,000,000 policy, if the premium for a private company is \$30,000, the cost for a public company would be \$350,000!

Claims data indicate that actions against private company D's and O's are primarily based on employment related acts such as discrimination or wrongful termination. Shareholder litigation against private company D's and O's is less common. Risk management practices should focus on instituting and following procedures for hiring and firing employees. Also, a private company should follow the SEC rules established for public companies in the area of Audit Committee responsibilities.

Outside directors will usually require corporate by-laws indemnification and D&O coverage before joining the board and recommended limits are at least \$5,000,000. For private companies, the most common deductible is \$25,000.

AUTO INSURANCE

This coverage is self-explanatory if a company has an auto. However, even if a company does not have an auto, it should purchase Non Owned and Hired Automobile Liability. This coverage protects your organization from liability claims arising out of accidents involving employees' own cars when engaged in company related

activity. It is a risk that should not be trivialized, as plaintiffs counsel will seek out the deep pocket in the event of an accident. The insurance is inexpensive and limits of \$1,000,000 usually cost less than \$1,000/year. It may be worthwhile to run a check on the motor vehicle record of any employee who drives on behalf of the company.

CRIME (ALSO KNOWN AS FIDELITY)

Although this policy features coverage for theft of cash from the premises and theft of cash in transit, the most important feature of the policy is coverage for employee dishonesty. Good risk management controls include strict second signature requirements for issuing checks and requiring that account reconciliation be done by someone other than the keeper of the checking account! The insurance is inexpensive and limits for start-ups are usually \$100,000. In the event your company establishes a 401k plan, this coverage is required by ERISA and is sometimes referred to as a Fidelity Bond.

FIDUCIARY LIABILITY

(for assets in a 401k plan)

The Fidelity Bond should not be confused with Fiduciary Liability, which is insurance for the mismanagement of a retirement plan or any other health and welfare plan offered by the company. This coverage pays for defense costs as well as compensatory damages owed by plan administrators to a claimant. Liability claims are not common, and they usually involve complaints concerning the lack of investment choices in a 401k plan or poor communication by plan administrators. Coverage limits are \$500,000 or \$1,000,000 and the premium under \$5,000/year.

INTELLECTUAL PROPERTY

As with some of the other critical risks described above, good risk management practices can reduce IP risk for a company. When assessing the risk, a company should examine its documentation first. How clear is the title to the IP? How well documented is the research that led up to the filing of the patent application? Are duplicate records kept of critical documents? If the IP is in-licensed, does the agreement carry a strong indemnity of the IP by the licensor? In 2003, it is expected that the number of new IP litigation cases will exceed 2,500, if litigation trends continue.

The implications of a claim are obvious – for example, a large drug company last year lost its patent on a major blockbuster drug. The company lost its royalty stream and the investment community fled from the stock, driving the share price down by one third in a single day. With this magnitude of risk some VC's are looking at IP insurance as a backstop to protect their investment.

Intellectual Property insurance can be purchased in two ways - the first to pay for the legal expenses and damages incurred in defending one's position against a claimant and the second to pay for the costs of enforcing your position by attacking the infringer. Few markets will insure these risks and Lloyd's of London is the preeminent insurer. The largest of IP awards far outstrip the available insuring limits (over the past two years, the aggregate value of the five largest damage awards exceeded \$2,000,000,000!). For smaller companies, where IP represents the major asset, purchasing limits of \$2,000,000 or \$5,000,000 will be expensive and deductibles will be no less than \$250,000. Premiums start at \$100,000. Premiums reflect the number of patents being insured and the effectiveness of risk management practices.

Intellectual Property insurance is expensive and companies that consider it should go to some length to outline the risk management practices in place to reduce the risk of an infringement claim. It is an area that requires the services of a broker that specializes in the analysis of the risk and the placement of the coverage.

FINAL THOUGHTS

To the uninitiated, insurance can appear to be a thicket of incomprehensible jargon overlaid by illogical practices. The risks of life science companies are many, and some of these risks can be devastating. Not all can be managed, but many can be reduced with some forethought and action. Because the world of life sciences is complicated and dynamic, any start-up should seek the services of a broker that knows the risks of the life science industry. This knowledge will lead to more effective advice and efficient purchasing of insurance.

ABOUT THE AUTHOR

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Mr. Howe manages Risk Management and Insurance Brokerage services for the Life Science practice of the New England Operations for Marsh. He has counseled life science companies on matters of property and liability risk for 15 years. He currently serves as Vice President of the Board of Trustees for the Boston Biomedical Research Institute and is a member of its Executive, Patent & Tech Transfer, and Stewardship committees.

ABOUT MARSH USA

Marsh, the risk management and insurance broking arm of the Marsh McLennan Companies (MMC), is the largest subsidiary of MMC, a global professional services firm with revenues in excess of \$19 billion. With 410 owned-and-operated offices and 38,000 colleagues, it serves clients in more than 100 countries. Marsh's annual revenues are \$5.9 billion.

MEDIA & PUBLIC RELATIONS

A well run Public Relations (PR) effort will earn a company recognition and build credibility in the eyes of those whose opinions matter, including potential employees, customers, investors, thought leaders (e.g. physicians), and the media. The communications strategy should focus on conveying the company's position statement clearly and consistently to the proper audiences and to point out when the company has progressed in its mission. Towards this end, management must first decide on the position and mission statements for the company and its products. A position statement explains the nature of the company, while the mission statement explains the company's objectives. Here are examples:

A position statement: XYZ develops and sells molecular research reagents to academic and industry laboratories.

A mission statement: Leveraging both internal development and an M&A strategy, XYZ is dedicated to becoming a leading reagent provider to the drug discovery industry.

Develop a timeline of milestones and figure out which represent newsworthy business progress. Not all milestones are newsworthy. For example, merely announcing an IND filing sets the expectation that clinical trials will commence in a month; the company risks embarrassment if the FDA rejects the IND. Therefore, it would be best to wait until the FDA has approved the IND before issuing a press release. Credible milestones often involve third-party validation of the company's position and mission, such as publication in a peer reviewed journal, issuance of patents, initiation of clinical trials, financings, and getting partnerships or notable customers. Seek opportunities to do joint announcements with other respected organizations in lieu of separate announcements. Mark medical, scientific, and investor conferences worth attending or presenting at over the upcoming year (plan to submit an abstract as much as 8 months in advance for some).

To present your company in a professional manner, put together a Media Kit with a company overview, recent press releases, relevant publications, and management bios. Have camera-ready photos of top executives ready to send electronically. A corporate website that communicates your messages clearly and allows visitors to sign up to receive future announcements is also an important tool. For details on building a website go to: www.evelexa.com/resources/web_dev.cfm.

Reporters are increasingly skeptical and cynical of unproven technologies that have yet to be

commercialized. Mainstream business publications may focus on biotech companies that have already been recognized by key trade publications (e.g. BioWorld, BioCentury, Nature Biotech, The Pink Sheet, Scrip) and local business publications. Therefore, when seeking mainstream exposure, lay the groundwork through local and trade press coverage beforehand. However, overexposure in the media is not always a good thing. The cover of Newsweek sets expectations that may be hard to live up to. Consider saving the 5 minutes of fame for when it is truly justified.

The company's PR strategy should manage the company's image in the local community and the public's perception of the company's position on issues, particularly if there is local opposition to animal testing or biotechnology in general. Depending on the company's focus and stage of development, it may also be useful to develop a relationship with disease-specific associations, foundations, or lobby groups, as they can be both vocal proponents and opponents of your agenda.

PRESS RELEASES

A press release is a basic PR tool. To issue these, one only needs an account with PRNewswire, BusinessWire, or another similar organization. You may select distribution by industry, region, and type of media. Depending on word count and whether you want to send the release only to local print media or to print/radio/television all over the country, the cost ranges from \$100-\$600 or more per release. Usually the least-expensive biotech distribution channel will still include major online media such as Yahoo and BioSpace.

TALKING TO REPORTERS

The best way to get the media's attention is to pitch the story directly to reporters. Keep in mind that the reporter is not always the final decision maker. He or she may need to justify to the editor why the news belongs in the publication. Be familiar with each reporter's topics and audience and the general nature of the publication. The pitch has to get you in the door. Most reporters prefer to receive a preliminary pitch by email, followed by a well-timed phone call (it is best to know each reporter's preferences in advance). The email should be short enough to fit on a single screen and have a captivating subject line. If the reporter is interested, you can send 2-3 pages with a detailed description of the key news event, an overview of the company, and contact info for people inside and outside the company whom the reporter might interview. Keep the technology explanation relatively simple and define the market you are targeting.

You have the option of contacting the reporter in advance of a news event and offering the story under embargo, i.e. asking the reporter to wait until a designated time before issuing a story relating to the company's news. Whether the reporter breaks or doesn't break an embargo sometimes depends on their relationship with you. Also, if a reporter agrees to abide by the terms of the embargo but then sees another publication running with the story early, the reporter may decide to also break the embargo or, worse yet, not write your story and never cover your company again.

Publication deadlines will determine the best time to reach a reporter live on the phone. Always ask, "Is this a good time?" after introducing yourself but before explaining the reason for your call. Daily papers typically begin to file stories after 2:30-3:00 p.m., so those reporters should be contacted during the morning or early afternoon. Weeklies file the stories by Thursday evening or first thing Friday morning. The best times to reach weekly reporters may be Monday, Tuesday, or Friday afternoon. Monthlies typically work 2-4 months in advance and pitches (specifically regarding planned news announcements) must be timed accordingly. Following editorial calendars allows you to pitch relevant news for an upcoming article.

Do not leave long-winded voice messages or call/email repeatedly unless there is something new to say. If a story is not well received, have a second one to pitch instead.

When speaking with a reporter, do not reveal anything you wouldn't want to see in print. Unless you specify that certain information is for background only, anything you say is quotable as the reporter heard it not as you said it. Nothing is ever "off the record". Stick to the company line whenever possible and try to deliver the key messages, including the position and mission statements. If you are asked a difficult question, either offer to get back to the reporter on it later or stick to the key message (even if it does not exactly answer the question). When discussing sensitive information, you must trust the reporter with whom you are working. Not every journalist will respect an embargo or your wish not to be quoted on something.

Do not take the accuracy of the reporter's final article for granted. It is highly unlikely that a reporter will agree to submit a draft of the article to the company in advance of publication. However, during your conversation with a reporter, you might ask the reporter to repeat back important points from the interview. At the very least, send the reporter a summary of your statements, biography, company history, references, and industry

contacts that may serve as additional sources etc. The goal is to make it as easy as possible for the reporter to write the piece accurately, cutting and pasting statements directly when appropriate.

HIRING PROFESSIONALS

Management that is serious about implementing a communications strategy should work with a professional, either through an internal hire, an independent consultant, or a PR firm. For a small company, a consultant can serve as an on-call or in-house PR and Communications executive, handling media relations, issuing press releases, pitching stories, securing speaking engagements at conferences, and coaching management on how to talk to the press and public. Even at a rate as high as \$250/hour, a consultant's services can be a bargain compared to a full-time hire.

However, a consultant may not have access to all the resources or media databases that larger agencies use. Going with a full-service firm makes sense if the company needs help refining its business and marketing strategies, prerequisites for an effective communications program. For example, some firms do extensive market research to focus a client's presentations on issues that will further the client's mission. An early-stage client may pay \$50K - \$100K per year to a firm for services that could include strategic positioning, development of key materials, and media relations activities. A major PR effort designed to secure general and trade media coverage of a key event, such as the publication of important clinical results together with presence at a medical meeting, might run \$20K/project. Though expensive, creating and executing an effective PR strategy is worth doing right, especially if millions of dollars of startup capital are on the line.

INVESTOR RELATIONS

The goal of investor relations (IR), at a minimum, is to address the questions and concerns of prospective and current investors, as well as to get the company on the agenda of investor conferences, many of which are held by investment banks. In some respects, IR is PR focused on the investment community. However, investors can ask very probing questions, more so than the media. Therefore, the person handling IR should be someone who is well-versed in the company's business strategy and technology and can go beyond reiterating mission statements and other sound bytes. While the CEO or CFO can often perform IR duties when the company is small, the large investor base a company often amasses after a few rounds of financing deserves the attention of a dedicated IR or IR/PR person.

PHARMACEUTICAL BUSINESS DEVELOPMENT

The key to building a biotech company successfully is finding the right balance between managing the cost and realizing the value of product development. Unless development is short and inexpensive, rarely the case with pharmaceuticals, a small company will have to share costs with a partner, which also means giving up some value. A company's business development (BD) team must define partnerable programs, identify potential partners, and successfully negotiate the terms of agreements.

DEFINING A PROGRAM

To maximize perceived value, it is generally useful for the seller to partition programs into as many discrete but justifiable units as possible. Having many chips with which to negotiate gives you options if negotiations reach an impasse. If you have three anti-cancer compounds at different stages of development, present each as a different R&D program with its own unique name. Developing each compound for a different cancer, even if they could all be developed for the same cancers, makes it easier to justify why they are separate development programs. A buyer may try to license them together, treating one compound as a lead and the other two as backups, but your goal is for buyer to pay for three separate programs, each valuable in its own right.

The same compound may be formulated in several different ways to address disparate markets with multiple unique products. Furthermore, it is possible to partition market rights by region, partnering each individually. The US market is the largest and most profitable single market, estimated at 50%-80% of the total global market for various indications. Europe and Japan are also notable, though other countries do not factor significantly into high level marketing strategy.

TELLING THE STORY

A biotech company should talk to prospective partners on a regular basis. Partnership discussions come out of ongoing relationship-building.

Some companies feel that they must develop a product to a certain stage *before* shopping it around. Their assertion is that they do not want to do a deal too early; they would rather let the program mature and appreciate in value. However, if someone offers to license a program earlier than you expected for less than you would like, you can always say NO. As long as you feel you do not want to part with a specific program, the burden is on the buyer to make an offer you can't refuse.

Management should strive to insulate the company's mission from the agenda of outside parties by negotiating from a position of strength; pursue partners before you absolutely need them just as you would raise capital from investors before you run short of funds.

A company presenting itself confidently might say, "*Here are our mission and pipeline. We look forward to hearing about your goals and discussing appropriate opportunities, if any, for collaboration between our companies.*"

At any given time, a biotech company should have a development timeline plotted out of how each of its programs will progress to an NDA filing. As far as each prospective partner is concerned, the biotech company will meet its objectives with or without their involvement. However, confidence should be more than cosmetic; the company should always have enough cash in its coffers to fund further development of a product if attractive deal terms cannot be reached with a prospective partner.

SHAPING THE STORY

Science must serve the company's business agenda, not the other way around. Through BD discussions, management will learn what other companies are looking for. By appropriately redirecting R&D, management can arm itself with the data and assets that will convince other companies to sign deals. For example, if Pfizer wants to see how your compound performs in a particular animal model before continuing discussions, getting that experiment done should be high on the CSO's list of priorities.

DEAL STRUCTURES

Partnerships may be described as front-loaded (the partner will pay more upfront and in near-term milestones) or back-loaded (less upfront but higher royalties down the road).

On one end of the spectrum, there are small companies trying to out-license preclinical candidates. A partner might pay, for example, \$100K upfront upon signing such a deal, \$500K in preclinical milestones, and then \$500K, \$1M, and \$3M in milestones upon initiation of Phase I, initiation of Phase II, and FDA approval, respectively, with a 4% royalty on net sales. The tangible value to the struggling startup is small, little more than the sum of the first few payments (\$1.1M). In exchange for shouldering much of the risk, the partner keeps most of the profits.

From the small company's perspective, engaging in the early-stage front-loaded deal described above is similar to doing contract research with little or no upside if the drug is ever successful. Most of the value of drug development

is realized near the end of the process, when the risk of clinical failure has been mitigated with positive data. Therefore, if a biotech company wants to be more than a contract research organization (CRO), it must take on more risk than a CRO. It must develop its drug candidate into the later stages of human trials. With positive Phase III data, for example, the company may be able to negotiate a deal with generous upfront payments and a large share of the downstream profits.

On the other end of the spectrum, Millennium's 2003 Velcade deal with J&J is an example of a heavily back-loaded arrangement. The deal was announced in June 2003, when the drug had just been approved in the US for treatment of multiple myeloma and was awaiting approval in Europe. Millennium gave up rights to Velcade outside of the US, keeping US marketing rights for itself. J&J only paid \$15M upfront to Millennium but shouldered 40% of Velcade's further development costs in cancers and agreed to pay up to \$500M in sales and development-based milestones as well as an estimated 20% royalty. Millennium kept all the revenues from US sales. With about \$1.5B in the bank, Millennium could afford to forego upfront payments in exchange for retaining the lion's share of Velcade's economics.

The following sections describe in more detail some of the components and devices employed by companies to

share expenses, revenues, and risk. Each may be incorporated in some fashion as a term or option in a corporate partnership.

UPFRONT FEES AND MILESTONE PAYMENTS

The company buying into the partnership will often make an initial cash payment and agree to make several additional payments contingent upon:

1. Successful completion of development milestones such as
 - i. Initiation of Phase III trial
 - ii. Submission of NDA
 - iii. FDA Approval of NDA
2. Achievement of sales thresholds (e.g. first \$100M of sales, \$250M sales)

Depending on the product and stage of development, both the amount and timing of upfront and milestone payments may vary. A Phase I drug may only justify a \$2M upfront and \$20M in milestones, whereas the same program that already has Phase II data demonstrating the drug's efficacy might command five times more. The total value of the deal will depend on whether the partner will pay for future development costs, buy equity, and pay a royalty.

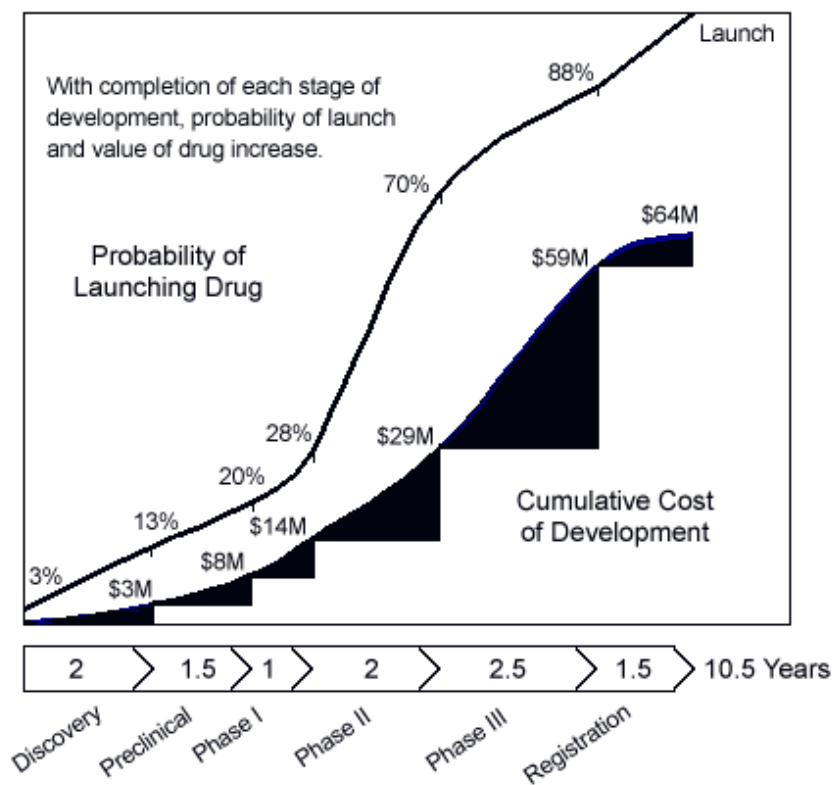


Figure 3. Drug Development. Probabilities are based on industry averages. Costs are typical of what small biotech company incur developing a single product.

R&D SPONSORSHIP

The costs of running an R&D program can be significant, and it helps to have a partner cover all or part of the expenses, which include the cost of in-house labor (measured in Full-Time-Equivalents or “FTEs” such that 2 half-time employees add up to 1 FTE) and out-sourcing expenses such as those associated with process and clinical development.

Some companies, eager for validation of their technology and a source of revenue, may too quickly agree to work for their “partners” in exchange for little more than having their expenses reimbursed – such arrangements are profit neutral, not hurting but also not helping the bottom line. Companies that neglect to partake in the significant upside of drug sales may become little more than contract research organizations, covering their costs but not generating the levels of profit that justify a high valuation. It is important to consider that management’s bandwidth (the number of tasks that can be managed at one time) is a limited and precious resource. Partnerships mostly involving research sponsorship, while profit neutral, may distract management from more ambitious goals.

A research sponsorship gives the company doing R&D little incentive to be more efficient since any cost savings are enjoyed by the paying partner. An alternative to counting FTEs is to negotiate for success-based milestones, which reward efficiency.

EQUITY INVESTMENTS AND LOANS

A new partner may make an equity investment in a smaller company as a form of payment. Usually, the valuation of the stock is inflated relative to what ordinary investors would pay for it since the new partner is getting more than just stock out of the deal.

Equity purchases are reported as investment on the balance sheet transaction instead of as cash expense on the income statement, which lower reported earnings. The partner usually will not acquire more than 19.9% of the total stock. If Company X owns 20% or more of loss-generating Company Y, an equal percentage of Y’s losses would have to be included on X’s income statement, thereby lowering X’s reported earnings and hurting its stock price.

Loans are also a form of payment, particularly when they are interest-free, convertible to stock, or potentially forgivable (e.g. the partner will not require repayment of the loan if a particular milestone is met on time).

ROYALTIES

A royalty is a payment based on product sales. Royalties may be a flat percentage of sales or tiered, like US federal tax brackets. A tiered royalty, for example, might be structured as 10% on annual sales up to \$100M, 12% on

sales >\$100M, and 14% on sales >\$300M. Compared to marketing your own drug, one advantage of receiving sales-based royalties from a partner is that you get paid even when the drug is not yet generating profits. While royalty payments may be too far off to provide a startup with the cash flow it needs to grow, royalties are an effective means of generating significant value in the long-term and each percentage point is worth negotiating for.

Royalties are also larger than they seem. For example, a typical Phase II-stage deal may include a 10% royalty on worldwide sales, with the pharmaceutical company covering all future expenses. Therefore, when the drug is generating \$500M/year, the pharmaceutical company will keep \$450M and give \$50M to its biotech partner. However, after manufacturing, sales, and other expenses, the pharmaceutical company may be left with only \$250M, which would mean that the biotech company’s 10% sales-based royalty represented 17% of profits (\$50M out of \$300M). To go a step further, a 30% royalty may have the same effect on a company’s bottom line as a co-development profit-sharing deal in which both partners split revenues and expenses 50/50.

One rarely sees licensing arrangements in which the marketing company pays the developer a royalty in excess of 30%. This is because a royalty that is 30% of sales is roughly equal to half of the profits. Considering the huge effort and expense of marketing a drug, it would require very unusual circumstances for a pharmaceutical company to part with more than 50% of its profits from a drug. Theoretically, if clinical data suggested the product will be a blockbuster, a pharmaceutical company might still pay generously for less than 50% of the profits. Consider the BMS-Imclone deal for the cancer drug Erbitux.

In 2001, presumably after reviewing Phase III results, BMS agreed to pay for half of Erbitux’s future development costs, bought \$1B in Imclone stock at a 40% premium to its price on the open market, agreed to pay upfront and milestone payments totaling \$1B and a 39% royalty on sales in N. America, and agreed to split profits 50/50 in Japan. With all these expenses, BMS is giving to Imclone more than half of the total profits from US and Japanese sales. Had Imclone partnered Erbitux at an earlier stage in development, the terms of the deal would have been far less generous to Imclone.

PROFIT-SHARING

A company developing a drug may agree to share in the ongoing development and commercialization costs of the drug, including the high costs associating with first launching a new product, in exchange for also proportionately sharing in the drug’s profits. This means that both partners accept the risk that the drug might never be approved or become profitable. However, just because two companies enter into a profit-sharing

arrangement does not mean that the company that discovered and partially developed the drug will not be paid upfront fees and milestones. In fact, these payments from the partner may be what allow the company to shoulder its share of the ongoing commercialization costs.

MANUFACTURING

FDA regulations concerning Good Manufacturing Practices of drugs are very strict and a factory that fails an inspection may be promptly shut down, possibly resulting in product recall and millions of dollars in lost sales. Therefore, big pharmaceutical companies are generally hesitant to trust inexperienced biotech companies with manufacturing and will negotiate for this right during partnership discussions. Since manufacturing a drug is a step towards maturity and full integration, young company may try to retain the right to manufacture the drug and sell it at a slight markup to the marketing partner. For example, the Erbitux deal mentioned above had Imclone selling the bulk material to BMS at a 10% premium to Imclone's cost of manufacturing it.

CO-PROMOTION VS. CO-MARKETING

While often used interchangeably, there is a fundamental difference between *co-promotion* and *co-marketing*. If two companies agree to co-promote a drug, this usually means that both will deploy their sales forces collaboratively to sell a drug under a single brand name. When co-marketing, each will sell the drug under a different brand name, as if they were two entirely different drugs, and may avoid competing with each other by targeting different markets.

Co-marketing arrangements are rare, though a notable example concerns erythropoietin. Amgen sells this compound as Epogen in the US for the renal market. Amgen also licensed erythropoietin to J&J for sale as Procrit for all other indications (most notably cancer) in the US and for all indications outside the US. The drugs are identical; in fact, J&J buys its recombinant erythropoietin from Amgen. Squabbles arise whenever one appears to encroach on the other's territory, demonstrating how difficult co-marketing can be.

Co-promotion arrangements, on the other hand, are not uncommon and make sense if one company lacks the sales force to penetrate a market to which another company could sell effectively. For example, while a biotech company developing a drug for overactive bladder might build its own 100-person sales force to target the 12,000 urologists in the US who write 30% of the scripts, the same company would be hard-pressed to build a 3,000-person sales force to market this drug to the hundreds of thousands of primary care physicians (PCPs)

who write the majority of OAB scripts. Therefore, the biotech company might partner with a pharmaceutical giant that could target PCPs while allowing the biotech company to co-promoting the drug to the smaller and more tractable urology market. Most importantly, the bigger partner will usually cover the costs of the smaller company hiring and maintaining its sales force.

A biotech company will often prefer a co-promotion agreement that involves sharing of sales revenue and expenses, essentially profit-sharing, rather than a royalty-paying deal. The contributions to the biotech company's bottom line may be the same in either case, but a co-promotion deal lets the biotech company report substantially more in top-line revenues. Booking top line sales of a drug product is considered more prestigious than merely collecting royalties- the former is indicative of a more mature company with sales/marketing capabilities.

However, not all co-promotion arrangements allow both partners to book sales to their respective top lines. In many cases, all sales are credited to the big partner, who then pays royalties to the smaller biotech company. The biotech company is paid equally whether it co-promotes the drug or just lets its partner handle all sales. However, by exercising its co-promotion option, the biotech company essentially gets a free sales force that can be leveraged to sell other drugs it develops or in-licenses. Therefore, a co-promotion deal can be a big step for a biotech company trying to mature into a fully-integrated pharmaceutical company.

JOINT VENTURES

Some deals between companies involve the creation of a third entity, often called a joint venture (JV), which may be nothing more than a paper company of which each partner owns a portion. The JV may be funded by one partner or both, have scientific and administrative staff from one partner or both, and may receive licenses to each of the partners' relevant technologies. For example, the larger partner may agree to pay for all the work being done by the JV. The JV may, in turn, make payments to the smaller partner for the use of its people, equipment, laboratory space, and intellectual property. At some point, the JV might agree to license a drug to the larger partner, which would pay royalties to the JV. Eventually, that money would find its way to the smaller partner. The JV is really an accounting construct which one or both partners may favor over a direct transaction because of how a JV affects their financial statements.

TERMINOLOGY: LICENSING DEALS, PARTNERSHIPS, & ALLIANCES

Arrangements in which a risk-averse company relinquishes development entirely to another company in

exchange for payments are typically referred to as licensing deals. While most arrangements between drug companies will involve a license (transfer of rights from one partner to another), the terms *partnership* or *alliance* connotes both parties playing an important role in developing and commercializing a product. These terms are not rigidly defined and are often interchangeable.

NEGOTIATING AN AGREEMENT

The goal of a partnership negotiation is for both parties to sign a Binding Agreement that precisely defines each party's future obligations and rights and specifies in great detail what happens if the partnership is dissolved. The process can take a year or more and happens in stages.

After exchanging preliminary proposals, two companies may sign a non-binding Letter of Intent (LOI), a.k.a. Agreement in Principle, saying that they will make a good-faith effort to find mutually agreeable terms on which to base a partnership. Such LOIs are of limited value because they are not legally binding (e.g. how do you prove bad-faith?). The goal of the LOI is primarily to establish that both parties are on the same page. A well-defined LOI may include highly detailed terms that need only be legally codified by attorneys before the document can be called a Binding Agreement. Until the Binding Agreement is signed, either party can change its terms, regardless whether an LOI has been signed.

Sometimes, the buyer is not confident about the merits of the seller's drug candidate and may want to test a sample of the compound before making a final decision. However, the buyer may not want to risk someone else licensing the drug candidate during the evaluation period. One solution is to negotiate a Binding Agreement right from the start stating that, if the buyer loses interest in the candidate (i.e. does not advance the candidate into further development by a certain date), the license may be terminated and right to the compound returned to the seller. The onus is then on the seller to be proactive about terminating the agreement.

An alternative is to give the prospective buyer a sample of the drug candidate for evaluation and the *option* of signing a binding agreement within a certain period of time. If the buyer likes the compound, the buyer will exercise the option and sign a binding agreement. The burden is on the buyer to be proactive about securing rights to the drug candidate. If the buyer loses interest for any reason during

the evaluation period, the buyer can simply let the option expire and implicitly relinquish claim to licensing the drug candidate. Until the option expires, the seller may not license the candidate to anyone else. Therefore, the seller may demand compensation for the opportunity cost of waiting for the buyer to make a decision.

If you are on the buy-side, you can negotiate for an option from a stronger position if the seller does not yet know how valuable the drug candidate is to you. If you wait until after the evaluation to finalize a binding licensing agreement, the seller will then know that you consider the candidate valuable and will try to drive a harder bargain. Therefore, it is important for the buyer to try to pre-define the terms of the Binding Agreement before taking an option. The pre-defined Binding Agreement should be included as an appendix to the Option Agreement. Conversely, it benefits the seller to try to defer negotiation of the Binding Agreement until the buyer expresses a desire to exercise the option.

The final Binding Agreement can be an extremely thick document. It must delineate which partner has control in certain circumstances, how decisions are made, and each partner's recourse in the event of disagreement or breach of contract. It is especially critical to define the consequences to each party of terminating the agreement. Any contingency omitted from the Binding Agreement creates potential for dispute. Leaving dispute resolution to the courts is a losing proposition for both parties.

The Binding Agreement may have built-in options allowing parties to defer certain decisions until later. For example, a pharmaceutical company may agree to fund a biotech company's development of three cancer compounds through Phase II trials. Upon completion of a Phase II trial, the pharmaceutical company will have two months to exercise an option to license each candidate on pre-defined terms. If an option expires, the biotech company may keep the compound for itself, along with all relevant data and intellectual property developed with the partner's help. Allocation of rights to data and IP must be delineated clearly in the Binding Agreement; nothing should be assumed as implicit.

EYE ON THE GOAL

Business development is just one element of a successful biotech company's business plan. Management's job is to build a profitable business; like raising capital, partnering is not an end unto itself but a step along the way.

DEVICE, DIAGNOSTIC, & INSTRUMENT MODELS

MEDICAL DEVICES

Medical device companies rarely go public through an IPO. They are instead groomed for acquisition. Acquisitions of device companies tend to be in the range of \$50M - \$70M, though a few have been much higher. Medical devices typically require 4-6 years to develop, making it feasible to start and sell a company in that timeframe. Whereas early-stage investors focused on drug development often swing for home runs, medical device investors expect to steadily making base hits.

If VCs want to make 10x their money by selling a company for \$50M in 5 years, they must invest at very low valuations, often \$1-2M pre-money, with slightly larger follow-on rounds if necessary. Investing at such low valuations also limits how much capital the VC can deploy at a time, forcing medical device funds to stay small (<\$200M). That's not to say that medical device companies don't raise larger rounds. In fact, three Seattle device companies Vertis, Calypso, and Spiration each raised between \$22M and \$37M in 2002. These numbers, however, are not the norm.

Typical medical device products may have gross margins from 55%-70%, compared to 80%-85% for branded pharmaceuticals. Also, devices are usually marketed directly to surgeons that use them; television ads are uncommon and patient demand does not drive sales as it does for pharmaceuticals.

Medical devices tend to be "low tech" and these companies rarely fail because of technical difficulties. Poor execution by management is more commonly to blame. However, unlike the biotech sector, the medical device field has been around long enough that there are a fair number of experienced managers available to work with startups.

Device investors often bet on management's ability to successfully develop one product, not a portfolio of products, and to sell the company to giants such as Medtronic, Boston Scientific, and Guidant. The neuro/spinal field is most active with 10-12 acquirers, cardiovascular has 4-5, and other fields may have 2-3. The device giants in the medical device sector are relatively risk averse compared to large pharmaceutical companies. They will wait until a small company has reached a late stage of validation, possibly filed for FDA approval, before stepping in to partner with or acquire the company.

Small device companies cannot expect to successfully market their own products when faced with competition

from the entrenched giants. Surgeons primarily trust the products sold by the established manufacturers and are much faster to adopt a device with a J&J label than one marketed by an unknown company, all else being equal. Therefore, the marketing efficiency of the big players creates a significant barrier to entry, and device companies are forced to either sell out to the larger players or at least partner with them.

DIAGNOSTICS

Diagnostics have a reputation for being a particularly difficult business. In 2003, Abbott Laboratories' 200 diagnostics generated \$3B in sales, averaging \$15M per product. Pioneering companies rarely enjoy more than a few years of market exclusivity before others jump the low regulatory hurdles and launch me-too products, often forcing the innovator to lower prices and, consequently, profit margins to remain competitive. In certain cases, diagnostics require novel instrumentation and must justify the expense of purchasing the instrument and allocating space in the lab for it. Promoting your instrument as having a smaller "footprint" (area it takes up on the floor or bench) can differentiate it from competing products. When customers are sensitive to capital equipment cost or footprint size, they may be more receptive to buying diagnostics that can be read without instruments or by instruments they already have.

INSTRUMENTS

Selling a single line of instrumentation, robots, or medical imaging equipment rarely generates significant or steady recurring revenues for a small company. Charging a high price for an instrument shifts the buying decision from the end users (scientists or physicians) to the relatively unreceptive administrators who must approve significant expenditures and can tie up the purchase in bureaucracy.

A more attractive alternative may be the Razor Blade model; sell or lease the instrument cheaply but charge for disposables. Even then, healthcare providers and researchers alike are loath to install a new piece of equipment in their facility or switch to a new way of doing something. Consequently, if sales of disposables generate most of the profits, it may make sense to manufacture disposables that better utilize the capabilities of equipment customers already have.

DRUG PRICING PRINCIPLES

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Pharmaceutical pricing and utilization are influenced and, in some cases, controlled by a patchwork of government laws and regulations overlaying a diverse web of private insurance plans, self-paying individuals, and charity healthcare services. Biotech companies need to understand how to integrate these factors into their product development plans. Although this chapter focuses on pharmaceutical pricing in the U.S., foreign pricing systems are also discussed.

GENERAL PRINCIPLES

A new therapeutic's price reflects a combination of factors: the price of competing treatment options, the value provided to patients and society, and an assessment of what the market will accept. As a "real" benchmark, the first is easiest to grasp. However, with a breakthrough medicine -- one for a disease with no pre-existing treatment options -- appreciating the latter two factors becomes essential. In these cases, a starting benchmark can be the price of an existing medicine for a disease of comparable severity affecting a similarly sized population. For example, the first biologic treatment for advanced rheumatoid arthritis (TNF-alpha inhibitor), entered the market at roughly the same annual treatment cost (about \$12,000) as the previously approved first biologic for multiple sclerosis (beta-interferon).

When comparing a new biotech medicine with existing treatments for the purpose of setting a price, first consider its relative clinical effectiveness. This includes not only the efficacy seen in clinical trials, but also the drug's side effects, its interactions with other medicines or foods, dosing intervals, and other characteristics that influence the patient's compliance.

Then consider the drug's economic value for payers. The new drug must either demonstrate cost savings over competing pharmaceuticals or show that it can reduce overall healthcare costs. Pharmaceutical-specific cost savings are direct and can be calculated simply: compared to an older once-a-day medicine, a new medicine dosed once a week yields cost savings even if each individual dose costs three times as much. Overall healthcare savings are difficult to calculate comprehensively as one must quantitate the value of shorter hospitalizations, fewer emergency room visits, eliminating the need for tests to monitor side-effects such as liver or bone marrow toxicity, and other benefits a drug may offer.

Ideally, real-world studies will demonstrate both clinical and economic value. For example, a once-a-week medicine produces better compliance, better control of

the patient's disease, reduced ER visits and hospitalizations, and, thus, lower overall healthcare costs. During the clinical development stages of any new pharmaceutical or biotech medicine, a company should include plans for collecting this type of information to demonstrate the value of the new medicine to potential partners and payers. Sometimes, such pharmacoeconomic studies are included after FDA approval either in Phase IV trials or as part of Phase III trials for additional indications.

Pharmacoeconomic data and information about competing treatments enable the biotech company to "ballpark" the launch price of its new medicine. To fine-tune the process, a company may hire a consulting firm that anonymously market-tests pricing scenarios for new treatments. These consultants assemble patient and payer groups to ask test groups questions aimed at gauging market response to a new drug; i.e. "What would you think of a new medicine that did X, Y & Z and that was priced at A per dose, or B per month of treatment?" However, there are no exact formulas for introductory pricing. For example, Pfizer launched Zithromax® at a premium compared to similar antibiotics believing that the drug presented major advantages over its competitors. This was not born out by its initial market performance because payers and prescribers (i.e. insurers and physicians, respectively) did not agree. In response, the manufacturer lowered the price of Zithromax®, leading to increased sales volume.

The ultimate "value" of a medicine in both clinical and economic terms is often not well understood until late development or even post-approval. For example, the cholesterol-lowering power of Lipitor® was not appreciated until its Phase III trials, prior to which its development had almost been terminated because it was going to be the fourth or fifth medicine of its type on the market. Lipitor® eventually became the most frequently prescribed branded prescription drug in the US. Also, the market value of Diflucan®, a potent antifungal, increased significantly post-approval when the number of patients with compromised immune systems grew dramatically due to HIV/AIDS and advanced cancer treatment.

US PRICING AND DISTRIBUTION

Although one often hears references to the "price of a medicine" in the United States, this is really an oversimplification, since for any given medicine there are a wide range of prices. At the high end, retail prices vary

not only by city, but among local pharmacies. At the low end, free medicines are delivered as samples and through patient assistance programs.

GOVERNMENT PROGRAMS

In between full retail and free, prices range widely, influenced by the patient's insurance status and other factors. The lowest prices are generally paid by government programs such as Medicaid and the Veterans' Health Administration (VHA). Under Federal law, state Medicaid programs receive a 15.1% discount off the average manufacturer price (AMP) or the "best price" at which the company sells a medicine to any private sector customer in the United States, whichever is lower. AMP is the proprietary price at which the manufacturer sells the medicine to wholesalers, while Average Wholesale Price, or AWP, is a published "list price" compiled by industry analysts. A frequently cited source for AWP's is the Red Book, published by the Medical Economics Company, the same company that publishes the Physicians' Desk Reference.

Many Medicaid programs use a "Preferred Drug List" to exert pricing pressure on manufacturers. Drugs that aren't discounted below the minimum price may be excluded from the list and thus can only be prescribed with prior authorization from the state Medicaid agency. This imposes a level of administrative burden that can act as a powerful deterrent against physicians prescribing an expensive medication, ultimately hurting sales of the drug.

The VHA receives discounts that are similar to Medicaid's, although the formula is different. In addition, the VHA uses a bidding process for the "closed classes" of its National Formulary system to secure prices below those that are legally required. Securing coverage by the VHA for medicines excluded from its closed classes is even more difficult for physicians than obtaining prior authorization for a drug from Medicaid.

Medicare currently pays only for a limited number of outpatient prescription drugs -- mostly cancer chemotherapy agents, administered as intravenous infusions in a clinic or doctor's office. However, new Federal legislation has created a limited and voluntary Medicare prescription drug benefit for all Medicare enrollees, starting in 2006. In addition, for 2004 and 2005, this law included transitional prescription drug discount cards and, for low-income Medicare beneficiaries, a \$600 annual subsidy. The law also changes Medicare's methods of paying for the medicines it already covers. Specifically, before 2004, Medicare reimbursed the doctor or clinic 95% of the Average Wholesale Price (AWP), a system that has been repeatedly criticized in government reports for over-reimbursing doctors and clinics. Starting in 2004, Medicare's reimbursement amounts for some of these medicines decreased to 80-

85% of AWP and in the future may be subject to "competitive acquisition program" pricing.

Although the new law precludes the Federal government from dictating prices or formularies, there will likely be pressure in the long run for the government to reduce the prices it pays for prescription medicines, just as it currently does for all healthcare products and services. Expensive biotech medicines may find themselves particularly vulnerable to this pressure, since the government may represent a large part of the U.S. market for these drugs, particularly if they are used primarily by the elderly and if private plans manage to avoid providing Medicare prescription drug coverage to the high risk/high cost patients using these therapies.

Overall, there will likely be considerable uncertainty over the next 5-10 years about how Medicare will price or pay for medicines, particularly new medicines, within the new benefit. Clearly, the government's continued leveraging of its legal and buying powers to minimize spending will have significant pricing implications for pharmaceuticals. The effect on drug sales depends, in part, upon whether lower prices can be offset by increased usage due to expanded insurance coverage for millions of Medicare beneficiaries.

How the changes in Medicare will ultimately affect seniors' prescription drug coverage and use will depend upon Congressional modifications to the new law, the Federal government's implementing regulations, the rate at which seniors enroll in the new benefit (inasmuch as it may initially prove of only limited value to them) and employers dropping or modifying their retiree coverage in response to the new law.

PRIVATE MARKET

In the private insurance market, discounts and rebates vary by company and medicine, with the Medicaid "best price" often creating a floor for markdowns. Contracts frequently provide for variable discounts depending on a drug's market share, rather than strictly on the volume of units purchased. Private insurers can affect a drug's market share by using prior authorization, formularies, and financial incentives. Private payers create financial incentives for patients by placing medicines in "tiers" requiring different co-payments. For example, a plan might require that patients make co-payments of \$10 for generics, \$20 for "preferred" medicines, and \$40 or 50% of the cost for "non-preferred" medicines. Within some plans, if a medication is not "on formulary" it is classified as non-covered or "excluded," requiring patients to pay 100% of its cost. Health plans and insurance companies may also create financial incentives for physicians to use certain medicines. Particularly in staff-model health systems, these incentives can take the form of risk sharing, bonus pools, or other systems where the

physician is partially responsible for the total cost of prescription drugs used by their patients.

One effect of the new Medicare pharmaceutical benefit law is to make Medicare beneficiaries more attractive to private managed care plans. Early trends indicate that managed care plans are boosting their pharmaceutical benefit and lowering premiums for Medicare beneficiaries, with the likely effect of increasing enrollment. This will place a greater percentage of the pharmaceutical market under the restrictions of managed care plans.

By establishing incentives for physicians, prior authorization policies and formularies create de facto pharmaceutical expenditure-control programs. Therefore, when formulating a compelling pricing argument, a biotech company needs to appreciate each customer's internal budgetary operations and incentives for cost control. Those with direct pharmacy spending budgets will probably be more stringent in imposing limits on drug prices and usage. Health systems that take a more integrated approach may view pharmaceutical expenditures within the context of overall healthcare spending and recognize, for example, that spending more on drugs may reduce hospitalization costs. Generally, vertically integrated health systems, such as staff-model HMOs, tend to have more integrated budgetary approaches and are thus more open to cost-saving arguments for expensive biotech products. Yet, a system that includes both physician groups and hospitals must still pay for the fixed cost of maintaining hospitals and may not derive savings from a new drug's ability to prevent hospitalizations.

A private health insurance system may also rely on a third-party company, called a pharmacy benefit manager (PBM), to develop and manage formularies, negotiate discounts, and manage prior authorization processes. (Integrated health systems like HMOs and the VHA may have their own internal PBMs.) In some cases, PBMs have their own internal financial incentives that can affect pharmaceutical usage.

None of these market pressures are likely to remain static. Most programs, whether private or governmental, change their pharmacy systems and contracts every year in response to new approvals of branded and generic medicines and other events. The resulting changes in prices and sales volume for individual medicines can be dramatic.

FOLLOW THE MONEY

Complex behind-the-scenes financial transactions paralleling the distribution chain also affect potential drug revenues. As a general rule, the manufacturer receives 70-75% of the retail price of a medicine, 5% goes to the wholesaler, and 20-25% percent to the pharmacist. These

revenue distributions can be influenced by rebates and discounts, as well as by the individual payment policies of different payers. For example, companies pay state Medicaid programs a quarterly rebate: 15.1% of either the AMP or the best price to private purchasers in the US. Additionally, the Federal rebate formula increases this percentage if the company has raised its price by greater than the Consumer Price Index. Because of the retail markup on drugs, pharmacies have traditionally been able to offer discounts (usually 10%) to seniors who lack prescription drug coverage. Some payers try to drive down their retail payments for medicines to near the pharmacist's actual acquisition costs, while compensating pharmacists with a higher dispensing fee. A biotech company should "follow the money" to understand how economic incentives influence the various links of the distribution chain.

MARKET SEGMENTS

Pharmaceutical customers can be broadly divided into two categories: institutional decision-makers and individual prescribers. A biotech company will typically have one or more sales teams assigned to each segment, either directly or through a marketing partner. The decisions made by an institution will vary according to its type – for instance, long-term care facilities will differ from tertiary care hospitals. Sales forces for institutions may be divided between those focusing on managed care plans and those directed towards hospitals and nursing homes. Virtually all institutions have a Pharmaceutical & Therapeutics (P&T) Committee that decides which medicines to stock and may also establish guidelines or rules for the use of certain high-cost treatments. Consequently, a pharmaceutical sales force often includes specialists focused on institutional P&T Committees.

Individual prescribers, technically free to use any FDA approved medicine, typically develop their own personal formulary based upon their training and the formularies of their patients' managed care plans. Sales forces targeting physicians may be divided into groups focusing on specific medical specialties, particularly if the biotech product is used predominantly by only a few types of physicians, e.g. nephrologists, oncologists or rheumatologists. However, even in the case of specialized drugs, it is important to market to internists and general practitioners as they provide needed specialty referrals and educate patients about new treatment options.

OTHER DEVELOPED COUNTRIES

Most other developed nations, including Canada, Germany and England, have more uniform health systems than the U.S. In these countries, the government is essentially the sole purchaser and uses its monopsony power to establish reimbursement amounts for all

medicines. Therefore, companies trying to introduce a new drug in these countries face a “fourth hurdle” after the three initial market entry barriers of discovery, development and approval.

These government-managed markets also involve discounts and rebates, usually tied to either total volume of sales or profits. In some countries, reference pricing systems enable the government to set a price based on either the price of the drug in other countries or the price already established for other treatments, branded and generic, that address the same condition. Furthermore, countries such as France have instituted policies to support local industries, providing government reimbursement for products which in the US would be sold as nutritional supplements.

Pricing differences between countries results in transshipment of medicines across national boundaries. This “parallel trade” practice is legal in the EU, and drug companies try to limit it by restricting supplies to wholesalers in countries where their products are low-priced. Increasingly, drugs are now coming into the U.S. from Canada, Mexico and elsewhere, even though it raises significant safety concerns. Since US laws and regulations only allow individuals to carry a 90-day supply of medication for their own personal use across the border, shipping medicines from outside the country is illegal in almost all cases.

DEVELOPING COUNTRIES

International pricing comparisons and purchasing are likely to put more downward pressure on U.S. prices. However, there is a flip side to globalization; developing countries are creating a growing middle class with the discretionary resources to spend on healthcare. The

lifestyle and longevity of these populations also lead to chronic diseases typical of developed nations, including cardiovascular diseases, diabetes, cancer, and Alzheimer's. While this trend presents opportunities for increasing sales volume in international markets, actually generating revenues and profits will require that developing countries enforce intellectual property rights and establish market-oriented healthcare systems.

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CLINICAL DRUG DEVELOPMENT

Kenneth B. Klein, MD.

Endpoint

This chapter addresses the range of tasks involved in getting a compound from the laboratory to the pharmacy, highlighting both common pitfalls and methods that work consistently. The discussion will center on clinical development of a *new chemical entity*, that is, a unique molecule with potential as a medicine. The development of biologicals (e.g. monoclonal antibodies) in general follows similar lines; vaccines and medical devices are developed differently and are outside the scope of this chapter.

The earlier stages of clinical development are emphasized since these are most relevant to the entrepreneur. Since the *Entrepreneur's Guide to a Biotech Startup* is directed primarily toward an American audience, the focus will be on FDA requirements. Note, however, that most promising compounds should be developed with worldwide regulatory approval and marketing in mind.

GETTING FROM THE LAB TO IND

The IND (*Investigational New Drug Application*) seeks the FDA's authorization for the first administration of an experimental drug to humans. Because the IND must outline the initial thinking about the compound's entire clinical development, this first formal communication with the FDA (a.k.a. *the agency*) is of crucial importance.

COMPONENTS OF THE IND

The FDA web site offers extensive information on the form and content of an IND, as well as other pertinent documents. See <http://www.fda.gov/cder/regulatory/applications/> for a general overview and helpful links.

The major components of the IND are as follows:

- *The Introductory statement and general investigational plan* is a 2-3 page overview of the compound and a summary of its intended development. The emphasis is on describing the general design and goals of the first proposed human study.
- *The investigator's brochure* is a stand-alone document of about 50 – 100 pages which provides a comprehensive review of the compound. The brochure is written for clinical investigators who will perform the human studies involving the compound as well as their IRBs (institutional review boards), who must approve each study. The FDA has endorsed the ICH (International Conference on Harmonization) guidelines for the format and content of an investigators' brochure. These guidelines may be found within the following document: <http://www.fda.gov/cder/guidance/959fnl.pdf>.
- *The proposed initial protocol* is the heart of the IND. When the FDA accepts an IND they are in effect giving permission to begin this first human (Phase I) study. The protocol does not have to be as detailed as for Phase II or III studies; the FDA is interested in an outline that includes key elements such as the number and type of subjects to be enrolled and the dosing schedule. Greater detail is reserved for safety-related sections, e.g. how adverse events will be monitored, the sorts of toxicity that are expected, and the stopping and dose-adjustment rules.
- *The chemistry, manufacturing, and control (CMC) information* section details the synthetic steps involved in manufacturing the compound and describes the analytical techniques that will be used to identify it as well as potential impurities. A distinction is made between *active pharmaceutical ingredient* (formally called *drug substance*) and *drug product*; the manufacture of each must be described separately. The active pharmaceutical ingredient (API) refers to the chemical compound; drug product is the actual formulation (e.g. intravenous solution, capsule, oral suspension) that will be administered in the Phase I study. The focus of the CMC section is to convince the agency that both API and drug product are adequately characterized as to strength, purity, and stability to justify administration to humans.
- *The pharmacology and toxicology information* section summarizes the animal data concerning the pharmacologic actions of the drug, as well as its safety. It is composed of two major sub-sections:
 - *Pharmacology and drug distribution*, a 5-6 page summary of 1) the drug's pharmacologic effects and mechanism of action and 2) the absorption, distribution, metabolism, and excretion (ADME) of the drug in one or more animal species.
 - *Toxicology integrated summary*, is a fairly hefty section, usually 10 – 15 pages long, plus supplementary tables and figures. There are no precise requirements for toxicology studies, not even for the animal species to be tested. The

sponsor is expected to make and justify such decisions based on the nature of the compound, its proposed human use, its probable toxicities, and the design of the Phase I study that will be supported. The goal is to present a package that will convince the agency that the drug is likely to be safe in the population and for the indication in which it will be tested.

ASSEMBLING THE IND

Once the decision has been made to file an IND, a major milestone in the life of a company, any delays can seem intolerable. It is important to plan how the required information will be generated so that the document can be assembled as efficiently as possible.

The *investigator's brochure* (IB) cannot be completed until all the other components of the IND are available, as it includes summaries of pharmacology, chemistry, manufacturing and toxicology. Usually the pharmacology and chemistry portions of the IB can be written up relatively early since the relevant work is generally complete before the decision is made to file the IND. To speed up IB production the other sections of the IB may be written, at least in outline form, before the final data are available. Toxicology testing is often the rate-limiting step in IND filing. Not only must the animal studies be planned and completed, but subsequently the histology must be evaluated, plasma drug levels assayed, and preliminary data tables and reports compiled.

A company filing its first IND must usually contract out much of the work. This typically includes (1) manufacturing the drug substance and product, (2) developing the analytical techniques for assaying the compound, metabolites and contaminants, (3) performing and analyzing the toxicology studies, and (4) designing the initial human protocol and 5) often, even writing and assembling the IND itself. There is no shortage of contract research organizations (CRO) available to help. The challenge is finding the right one. Apart from the basic issues of cost and relevant expertise, there must be a good fit in terms of style.

One approach is to work with a large CRO that will take charge of the entire process, including managing any necessary sub-contracting. Indeed, some promise a *turnkey* operation—just hand over your compound and they will do everything up to and including actually filing the IND. The other approach is to select more specialized, usually smaller CROs with expertise in a relatively limited area such as regulatory filings, toxicology, manufacturing, or designing and carrying out Phase I studies in a specific therapeutic area (e.g. oncology). When taking this second route, it is necessary to actively manage and coordinate the work of multiple contractors. For example, the company must be sure that

drug product and the appropriate analytical techniques are available in time to allow the *toxicokinetic* component of toxicology studies to proceed without delay. Coordination can be handled either in-house or by a consultant familiar with all aspects of the IND process.

THE IMPORTANCE OF EXPERT REGULATORY PLANNING AND ADVICE

No matter which method the company takes - using one major CRO, multiple smaller ones, or a hybrid of the two approaches - the key to a successful IND filing is the advice of an individual or group with extensive regulatory experience. Ideally they would have previously dealt with the Division of the FDA that will process the IND and supervise the subsequent New Drug Application (NDA). Each Division (e.g. Cardio-Renal, Oncology, Pulmonary) has its own style of interacting with the sponsoring company and its own interpretation of the regulations; having an advocate who has a personal relationship with the relevant FDA Division members is invaluable in enhancing the chances of a successful IND submission. For example, the IND toxicology requirements of each Division can vary considerably; a knowledgeable consultant can suggest a package that the Division is likely to accept that may be less extensive than the regulations appear to require.

A company should request a *pre-IND meeting* with the agency to discuss key components of the proposed application, particularly the Phase I study and subsequent development plans. Having an experienced individual to represent the company's interests at such a meeting is invaluable. He or she can help secure the FDA's agreement on specific IND contents, negotiate agreements on what data might be deferred until after the IND is submitted, and 'read' the agency's attitude on specific issues that arise.

A STRATEGIC APPROACH TO CLINICAL DRUG DEVELOPMENT

If FDA says nothing to the contrary, thirty days after the IND is filed the company may initiate the submitted Phase I study. Though this is the culmination of years of research and planning, it is merely the beginning of the long and arduous process of turning a chemical into a marketed medicine. Because human testing is by far the most expensive and time-consuming part of drug development, the clinical development program must be designed to be as efficient as possible.

PLANNING AHEAD BY WORKING BACKWARDS

It is common for pharmaceutical companies, and particularly newly emerging ones, to take the development

Recruit Allies Early*Inserted by Editor (P. Kolchinsky)*

The connections that a company forms with key opinion leaders (KOL) in the clinical community during development can dramatically impact how quickly the drug will penetrate the market once it is launched and how well it sells. If the KOLs follow the progress of the drug and are convinced of its utility, they will be instrumental in educating the rest of the medical community in how and when to prescribe the drug. Pharmaceutical companies make a concerted effort to recruit the right people to serve as clinical trial investigators or advisors, usually starting at Phase II.

of their compounds one step at a time. The assumption is that you need to see the results of one study before designing the next. Although true to some extent, it is a poor argument for not planning ahead. The best way to plan ahead in drug development is to think backwards. Even before the first Phase I study is initiated, the company should begin to consider how the drug's package insert will read. That is, as soon as enough information is available about the molecule to make a reasonable guess as to its ultimate clinical utility, the company should begin to construct a model of how they would like to see it used in patient care. If the compound is being developed as an anti-depressant, does its pharmacology make it most suitable for bipolar disease, general depression, or another indication? If it has antineoplastic properties, which malignancy would be the most appropriate first clinical target? Or perhaps the compound is so promising that it deserves simultaneous development in multiple indications. Such decisions depend not only on the underlying pharmacology but on the unmet medical need, the size of the potential market, and the nature of current and pending competition.

THE PRODUCT PROFILE

The company should formalize its vision for the compound by constructing a *target product profile*, which describes its key potentially achievable features. The typical target product profile specifies an indication, route and frequency of dosing, and some sense of efficacy and safety compared to any currently marketed products with which it will compete. Depending on the therapeutic area and the competition, additional attributes such as pricing, cost of goods, and launch date may be relevant. A companion *minimally acceptable profile* should be drafted as well. If the accumulating clinical data begin to show that the compound's attributes are clearly falling below the minimally acceptable profile, the company should maintain discipline and cut its losses by halting the drug's development. Only very rarely should the minimally acceptable profile be adjusted to accommodate unfavorable data.

PLAN ALL THE WAY TO AN NDA

Many emerging biotechnology companies have no intention of taking their compound through a complete clinical development. This process, culminating in the filing of an NDA, requires considerable capital and expertise to which a young company may not have access. A typical exit strategy is to license the development rights to a large multinational pharmaceutical company after a successful Phase I study or after *proof of concept* (usually in Phase II) is established. Even if this is the intent, the company should draft a complete clinical development plan. This is important for two reasons:

- It is not possible to optimally design the early clinical studies unless the entire clinical development trajectory is articulated. This is because earlier studies must be carefully designed to lay the groundwork for subsequent ones.
- Investors and potential partners want assurance that the company has a clear vision for the development and commercialization of the product.

THE CLINICAL DEVELOPMENT PLAN

The clinical development plan should summarize the proposed design, timing, and logic behind the clinical trials that will be included in the NDA filing. Having a robust clinical development plan in place early on offers numerous benefits:

- The plan serves as a reality check on timeframes. Biotech startups often substantially underestimate the time to NDA filing. Unlike most laboratory experiments, a large clinical trial may take two years or more from protocol design to initial data analysis. The frequency with which eligible patients are referred to trial sites is an under-appreciated factor. Even a trial that only involves treating and evaluating a patient for a month may still require a year or longer to enroll all the necessary patients.
- The plan helps to ensure that the proposed studies will satisfy regulatory requirements. The ICH general guidance to clinical trials (see <http://www.fda.gov/cder/guidance/959fnl.pdf>), which is endorsed by the FDA, discusses the numbers of patients and duration of exposures expected for marketing approval.
- The plan defines the magnitude of the clinical development effort. Projecting the full gamut of anticipated studies, particularly their length and patient numbers, allows an estimate of the resources and cost that will be required to complete the clinical component of the NDA.

- Having a plan facilitates discussions with various in-house experts as well as consultants. For example, even before the start of Phase II, if the company toxicologist sees that the plan calls for a six-month Phase III study, he or she knows that it is not too soon to begin scheduling (and requesting a budget for!) the toxicology studies required to support such extended human drug exposure. Meanwhile, commercially-oriented staff can consider whether the proposed studies will allow them to make desired commercial claims. If not, they can negotiate with the clinical team regarding modification of trial design, or even the inclusion of additional studies to generate data relevant to marketing.

The clinical development plan should be referred to frequently in the course of the compound's development to maintain the discipline and rigor of the clinical program. Of course, information from recently completed clinical studies, new competitive intelligence, advances in science, and approvals of other products may lead to modifications of the plan. Such modifications may affect both the development timeline and the ultimate product profile.

CLINICAL DEVELOPMENT TEAM

The compound's clinical development should be closely managed by a dedicated team comprised of experts in these essential areas:

- *clinical*: A senior clinician usually has a key leadership role on the team due to a familiarity with the therapeutic focus of the development program as well as with the mechanics of clinical trials.
- *basic sciences*: Especially early in the development of a compound, the basic science representative provides a vital perspective as to what can realistically be pursued as a clinical target. He or she can also facilitate additional laboratory studies to support the emerging clinical program.
- *toxicology*: All too often the rate-limiting step in advancing the clinical trial program is adequate *tox coverage*. The toxicology expert must monitor planned trials and ensure that supporting toxicology data are available in time to avoid delays.
- *manufacturing/formulation*: Just as with toxicology, another potentially rate-limiting step is the availability of appropriate *clinical trial material*, i.e. drug product. Especially when drug manufacturing is contracted out, lead times may be very long. Not only must the specific formulation for each clinical trial be manufactured, but stability studies must be done to ensure that the synthesized material will meet FDA stability requirements for as long as the trial is anticipated to run.
- *statistics/data management*: The project statistician will analyze data from each clinical trial and will synthesize information from individual trials into critical sections of the NDA, (e.g. the *Integrated Summary of Efficacy* and the *Integrated Summary of Safety*). For example, he or she must ensure that the primary endpoints of all key studies are compatible. The data management representative is responsible for preparing a database appropriate to the design of each proposed trial.
- *commercial/marketing*: Not all approved drugs generate profits, often because their profile was not tailored for commercial viability during development. For example, a twice-daily antibiotic may have a hard time competing against equivalent or even slightly worse once-daily drugs. The marketing representative on the team must help direct development so that the drug is positioned to sell well following approval.
- *regulatory*: A regulatory review of all clinical studies is essential to ensure that their design and conduct will be acceptable to the FDA. Close contact with the FDA must be maintained by someone experienced in dealing with the agency. The *end of Phase II meeting* is a particularly important opportunity for the company to present its proposed Phase III program and gain valuable feedback before such plans are finalized.
- *project management*: A project manager must coordinate the various efforts described above, track progress, and quickly identify and resolve problems.

What if a CRO is running the clinical development? It is rare for even the most committed CRO to have the same passion for a project as does the sponsoring company. Therefore, the company should maintain close contact with and supervise the CRO. In addition to having a lead *contact person*, it is useful to have an in-house 'shadow' clinical development team to monitor progress; company employees with expertise in all the relevant areas should regularly liaise with their CRO counterparts. If the full panoply of expertise is not available within the company, it should consider hiring consultants in such areas to advocate for the company in dealing with the CRO.

THE MAJOR TASKS OF EACH PHASE OF CLINICAL DEVELOPMENT

Traditionally clinical development is divided into three phases, though these designations have no clearly-defined meaning. Mechanically pushing a compound through

each phase may distract from the most important task of clinical drug development: individualizing the design and sequencing of studies to optimally advance the compound.

Roughly speaking, *Phase I* refers to small (8-60 subjects), usually short studies designed to elucidate the drug's basic safety profile, pharmacokinetics, and sometimes pharmacodynamics. Phase I usually involves healthy volunteers. The drug is typically first administered to *patients* in Phase II trials, which are of medium size (50 - 250 patients). Such studies may provide the first evidence of efficacy, identify the main side-effects in patients, and determine the clinically relevant dose range. Phase III studies are generally much larger (300 - 1000+ patients). They are designed to refine dosing and provide evidence of efficacy and safety in a more diverse group of patients than Phase II, mimicking actual clinical practice as much as possible.

EXPLANATION OF POWER AND P VALUES

The chance that a trial outcome is really a false positive result is called a P value, and a trial must show that a treatment has a positive effect with a $P \leq 0.05$ to be considered statistically significant (i.e. 5% or lower chance that the result is due to chance). Clinical trials are often described, for example, as being 90% *powered* to show a 20% treatment benefit versus placebo. Power is defined as the probability that if a drug can yield a meaningful difference in a clinical endpoint, the trial will show it with $P \leq 0.05$. Important variables for calculating power are the number of subjects in the trial and the definition of *meaningful difference*. The less dramatic a drug's effect, the larger the trial must be to achieve 90% power.

PHASE I

Phase I lays the groundwork for the entire subsequent development. Skipping on vital Phase I studies in a rush to proceed to Phase II may cripple the clinical program and ultimately undermine the NDA. Too often during the design of critical Phase III studies one hears someone say, "if only we knew *this* about the compound," referring to such things as the highest well-tolerated dose, the kinetics of dosing three versus two times daily, or another parameter that could have been easily obtained in a Phase I study.

The main task of Phase I is to determine whether the drug merits further clinical testing and, if so, to provide key information necessary for designing these trials. Establishing the drug's safety profile is critically important; unacceptable toxicity will prevent even the most efficacious drug from being approved. Of course what constitutes *unacceptable toxicity* may be very different for an antihistamine and an anti-cancer compound. Escalating single doses, then multiple doses, should be administered until either the unit dose is ridiculously high

or, more commonly, dose-limiting side-effects occur. It is vital at an early stage to know the most common side-effects associated with a new drug and how these are related to dose.

The second major Phase I task is to determine the drug's basic pharmacokinetic (pK) profile. Carefully designed studies should establish whether the formulation chosen for clinical development can produce therapeutically-relevant plasma drug concentrations. For example, unless reasonable blood levels can be achieved when the drug is given orally at the highest safe dose, it does not make sense to use such a formulation in a proof of concept study. Either the company must develop a new oral formulation or select an alternative route of administration that results in better bioavailability. Early pK studies also determine the drug's half-life, which will help establish how frequently the drug should be dosed. Occasionally, insurmountable pK issues identified in Phase I result in the termination of a project.

A third Phase I task, applicable to some but not all drugs, is to characterize the compound's basic pharmacodynamics (pD), usually as a function of plasma drug level. A drug designed to lower blood sugar, depending on its mechanism of action, might be studied in either normal volunteers or people with diabetes. The goal would be to establish the relationship between drug level and plasma glucose. Important information may be obtained even from a small Phase I study on the lowest dose of drug that is associated with the desired benefit; in such a case, both the lowest and highest doses for subsequent efficacy testing could be elucidated in a single study. In the case of a cytotoxic drug designed for the treatment of malignancy, study subjects would necessarily be people with cancer. Pharmacodynamics would be measured using a surrogate for antineoplastic effect, possibly levels of certain lymphocyte populations.

It is important to recall that *Phase I* refers to a type of study, not a chronological order. Many of the Phase I studies that regulatory authorities require for approval are best performed only after it is certain that an NDA will be filed, including studies on drug interactions, fed/fasted pharmacokinetic differences, pK and pD as a function of age and gender, and kinetics in renal and hepatic failure. There is no point in doing such trials before proof of concept is established since the results are seldom relevant to the patient population enrolled in early efficacy studies.

PHASE II: EMPHASIZING PROOF OF CONCEPT

The most important traditional task of Phase II is to establish *proof of concept* (POC), that is, the first credible evidence in the target population that the drug actually does what it is being developed to do. For certain conditions (e.g. migraine), POC can sometimes be

obtained in a Phase I study, whereas for others (e.g. anxiety) it is not achieved until Phase III. Cancer is an example of a field where Phase III results often fail to live up to expectations set by positive Phase II data, even when the Phase II endpoint is survival. Phase II cancer studies sometimes lack proper placebo control arms, are not blinded, or are not randomized properly. Instead, these elements of a proper trial design (discussed below) are reserved for Phase III studies while the Phase II studies use historical or case-matched controls instead of placebo arms. Human bias in trials is very real and significant – without proper placebo controls, randomization, and blinding, trial results cannot serve as Proof of Concept.

The validity of the POC trial depends on how well it is designed, conducted, and analyzed. A properly done study that is clearly negative is a strong argument for terminating the development of a drug, whereas a positive outcome will lead to a huge investment of resources. Because the stakes are so high, every effort must be made to ensure that the POC results are trustworthy. Perhaps the most common, and ultimately the most costly, mistake emerging companies make is to under-fund and under-power a POC trial “because we don’t yet know if the drug works.” A so-called *exploratory study*, the clinical research equivalent of a toe in the water, seldom provides useful information.

Below are some key elements of a robust POC trial.

- It must be designed to answer an appropriate *clinical* question. This is not the time to do *mechanistic* studies, no matter how fascinating the information may be. The problem is that mechanistic endpoints (e.g. a measure of how the drug alters physiology) do not reliably predict actual clinical utility. For example, in a POC study for the treatment of irritable bowel syndrome, it would be inappropriate for the primary endpoint to be some aspect of gut motility. Rather, it must be a validated measure of clinical response. If a surrogate marker is employed, it should be a well-documented predictor of meaningful clinical effect (e.g. tumor regression in cancer trials).
- It should be placebo controlled, randomized, and double-blinded.
- It should involve a patient population that resembles that which will be the ultimate market for the drug.
- It must explore a wide enough range of doses to ensure that a negative result is not due to under-dosing.
- It should be designed to begin the process of identifying the optimal clinical dose(s), including the documentation of dose-response relationships.
- It must be sufficiently *powered* so there is little likelihood of erroneously concluding that the drug does not work. Typically the power of a POC study is set at 90%, (i.e. there will be only a 1 in 10 chance of a false negative result).
- It should characterize the nature and frequency of the most prominent side-effects to be expected in actual patients.

Phase II trials also help quantify a drug's benefit versus placebo so that enough patients are recruited in Phase III trials to have a good chance (90%) of showing that the observed benefit is statistically significant. If a drug shows a weak benefit to the patient in Phase II trials, many patients will be required in Phase III to demonstrate that this weak benefit is, in fact, statistically significant ($P \leq 0.05$).

PHASE III: EMPHASIZING GENERAL PRINCIPLES OF CLINICAL STUDY DESIGN

The major task of Phase III is to conduct two independent clinical trials that conclusively prove that the compound is effective and safe. Such studies, required for the regulatory approval of most drugs, are called *pivotal trials*. Their design and execution are critical since the success of the NDA depends to a great extent on their outcome. The specifics of Phase III study design are highly dependent on the nature of the molecule being developed, the therapeutic target, the particular efficacy endpoints employed, and the results of earlier clinical studies.

It is generally recognized that meaningful clinical trials must be appropriately *controlled*, *randomized*, and *blinded*. Despite the Helsinki Declaration on Human Experimentation, the control group in most clinical trials receives a placebo rather than, as required, “the best proven therapeutic method.” This is because a placebo control generally makes it much easier to show that the experimental drug is effective. To maximize the likelihood that patients receiving the experimental drug and those receiving the control drug are not meaningfully different in any other way, treatment must be randomly assigned, usually by a standard computer-generated paradigm. Finally, to prevent knowledge of the patient's treatment from influencing patients and investigators, both must be blinded to treatment assignment, i.e., the experimental and control medications must appear identical in all respects. The trial is *unblinded* for analysis only after the study is completed.

The following are under-appreciated key principles:

- *Begin with a clear, simple objective.* Because clinical trials are so costly and time-consuming, there is a strong temptation to try to answer many questions in a single study. For example, scientists may be tempted to discern a drug's mechanism of action by measuring various physiologic parameters during the trial. When employed judiciously such ancillary measures are acceptable. If they dominate the trial, however, they can be distracting.
- *Design and power the study around a single primary question.* The most important question that the study seeks to answer should be operationalized in the *primary endpoint*. The success of the study depends on whether the primary endpoint is both significantly different, both clinically and statistically, between the experimental treatment and the control.
- *A clinical trial must be designed as one in a chain of studies.* The study should both take into account the results of previous trials and produce data suitable for refining the features of subsequent ones (e.g. selecting patient population, trial length, drug doses).
- *Answer the essential questions without generating unnecessary data.* All data generated during clinical development will be included in the NDA submission and may find its way into the package insert. You may not like the answers you get to questions you did not have to ask.

PRACTICAL CONSIDERATIONS

While beyond the scope of this chapter, the following practical issues are worthy of careful study before proceeding with drug development:

- *Study planning and budgeting:* Carefully constructing and administering the study budget (which may be in tens of millions for a Phase III trial), deciding on optimal methods of data collection in multi-center trials (e.g. the use of web-based data forms, standardizing instructions for the administration of subjective evaluation instruments); coordinating the timely availability of all study supplies (e.g. study drug, properly translated patient diary cards, case report forms).
- *Study initiation:* Selecting investigators and study sites that can reliably recruit a sufficient number of patients and deliver high quality data; employing techniques to speedily obtain *institutional review board* and regulatory approval of the protocol; putting in place various methods to enhance the rate of patient recruitment

(often the major determinant of the time to trial completion); motivating study personnel to work well and hard.

- *Study conduct:* Efficiently monitoring the performance of individual sites and the trial as a whole; timely identification of sites and investigators with quality and productivity problems; optimizing way in which data are brought from the study sites to the central location where QA and data entry are done.
- *Post-study activities:* Streamlining data analysis and interpretation; coordinating the production of data summaries, manuscripts, and the *final study report*.

Optimally managing these and a multitude of other activities requires extensive experience in actually running clinical trials. A company serious about clinical development should have such practical expertise available in-house and/or acquire it by working with knowledgeable consultants and CROs.

FDA TAKES ACTION

Section added by P. Kolchinsky, Editor

The Prescription Drug User Fee Act of 1992 (PDUFA I) allowed companies to pay the FDA to review an NDA faster, assigning more people to the process, perhaps. At first, the FDA promised a response within 12 months of the filing date and eventually pushed this goal down to 10 months. However, a response does not guarantee completion of the review process. By the so-called PDUFA date, the date by which the FDA is expected to give its response, possible verdicts include:

- **Approval:** The company may proceed with launching its product.
- **Non-Approvable:** Also known as a Complete Response Letter, a non-approvable letter might require that the company run lengthy additional clinical studies before the FDA will consider giving its approval.
- **Approvable:** An approvable letter indicates that the FDA agrees that the drug is safe and effective but want more information, which the company must assemble and submit to the FDA. A requirement for a Class I resubmission is considered minor in that it usually involves paperwork, such as a reshuffling of existing clinical data or agreement on how the drug will be labeled, and if any clinical trials are required, these may be done as Phase IV post-marketing studies. Class II resubmission can be more laborious, possibly involving additional clinical studies prior to approval or upgrade and reinspection of

manufacturing facilities. If the required information is provided in a timely manner, the FDA will usually review a Class I within 2 months and a Class II within 6 months of resubmission.

If the FDA decides to convene an Advisory Committee (AC) to guide its decision, this meeting will usually take place prior to the PDUFA date. The FDA will usually follow the advice of the AC, but it does not have to.

FDA approval of an NDA should not be confused with Acceptance for Filing of an NDA, which indicates that the application is complete and occurs automatically 60 days after submission of an NDA, unless the FDA raises issues during the 60-day period.

EVEN FASTER

The FDA issues a number of special designations that can speed a much needed drug through development and/or the review process.

Fast Track: At the time of IND review or during subsequent discussion with the FDA, the sponsoring company can request the drug be granted Fast Track status. A Fast Track designation allows for more interaction with the FDA throughout development as well as “rolling” submission to the FDA of the various component of the NDA (i.e. preclinical package, clinical package, CMC) as they are completed.

Accelerated Approval: Drugs that receive Accelerated Approval do not require as much clinical data in their NDA and may be reviewed, for example, on the basis of only Phase II results. With the FDA's consent, such drugs may also be approved on the basis of improvements

in surrogate endpoints, which can take less time than showing a clinical benefit.

Priority Review: An NDA that has been assigned Priority Review within 60 days of submission will be acted on within 6 months of submission. All NDAs are considered for Priority Review regardless whether the sponsoring company requests it.

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Endpoint's clients include multinational pharmaceutical companies, emerging biomedical ventures, biotechnology investment firms, contract research organizations, regulatory agencies and national health services.

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MEDICAL DEVICE APPROVAL

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Taking a new medical device through the FDA to reach final approval is usually complex and time consuming. The following chapter is only a basic survey of the regulatory landscape facing medical device companies and will reference additional information worth reading.

For detailed FDA Medical Device approval advice, visit <http://www.fda.gov/cdrh/devadvice/>. Registration, listing, and labeling forms/instructions available from this website are **highlighted** below.

The Center for Devices and Radiological Health

If your organization is conducting research to commercialize a product that might be classified as a medical device you will need to register with and report to the Center for Devices and Radiological Health (CDRH). A company will deal with different offices of the CDRH throughout the process. While the CDRH review process can be complex, their decision is fundamentally based on whether the benefits outweigh the risks.

The regulatory process may start with *registration* and *listing*, which are free and simple. Registration involves notifying the CDRH that your company is in the medical device business. Listing involves submitting a description and classification of the device your company is developing. However, neither registration nor listing is mandatory until 90 days before the device goes to market and many times a company might register and apply at the same time.

If your device is novel or being approved for a new use, you will likely file a Premarket Approval Application (PMA), which involves a good deal of data, time, and money. In those cases where a company wants to bypass the application process, it may either file for an *exemption* or, more likely, request that all or part of your device be recognized as *substantially equivalent* to a previously marketed device. The requirements for applying for substantial equivalence depend on how the CDRH *classifies* your device. The majority of relevant medical devices fall under the Class II or Class III categories, in which case they would usually file what is referred to as a “five-ten-K” (510(k)) application. Other than exemptions, which are discussed later, the 510(k) will always be the preferred application option because it is faster and much cheaper than a PMA.

Following approval, the CDRH becomes a law enforcement body. For as long as the device is marketed for public use, the CDRH will implement surveillance programs, monitor compliance, and enforce both good

manufacturing practices (GMP) and post marketing performance standards.

REGISTRATION, LISTING AND LABELING

ESTABLISHMENT REGISTRATION

Any place of business under one management, at one physical location where a medical device is manufactured, assembled or processed for commercial distribution is considered an “establishment” requiring registration with **Form 2891**. Registering your establishment with the CDRH is very simple and there is no fee to do so. It is meant to provide the FDA with little more than the name, type and location of the medical device manufacturing facilities along with the name and address of its owner/operator, whether that owner is a person or corporate entity.

Any owner of an establishment must register within 30 days of commencing any activity that might be seen as requiring registration, including the start of production or the import of a device for commercial distribution. Also, keep in mind that you may not introduce the device for distribution or export unless you are registered and listed at least 90 days prior to that distribution date.

Note: Foreign establishments should be aware of many additional regulations not discussed here.

PRODUCT LISTING

Product listing is fairly easy and free. Listing is meant to provide the CDRH with a general description and classification of the type of device you plan to manufacture or distribute. The on-line listing **Form 2892** includes links to help you find information necessary for completing the form, including databases of product codes and guidance instructions for completing the forms. The primary reason for properly identifying the device's classification is so that you pursue the correct development and regulatory path. The CDRH will not tell you whether you have misclassified your device until it reviews the full marketing application (i.e. PMA or 510(k)), at which point the accuracy of the listing will be the least of your concerns. If the device must be reclassified following review, changing the listing at least 90 days prior the marketing will be relatively simple.

Owners are responsible for keeping data on their listing forms current and must be sure to update it when there is either a name change in the marketed device or when any additional intended uses might cause a change of the

device classification. Failure to do so may tarnish your image at the FDA.

LABELING

The FDA develops and administers labeling regulations pertaining to how medical devices are used. Before marketing clearance is obtained, the manufacturer must ensure that the device is labeled according to those regulations or risk seriously complicating the approval process.

Sometimes a company may choose not to list a use, knowing that doctors might decide to buy and use the device *off-label*. Generally, a company would do this when proving safety and efficacy for the unlisted use would incur significant cost or result in an unfavorable classification. For example, if a die applied as a diagnostic had been in use prior to laws that would require classification and it was later discovered to have new properties that might be used in a new, high risk technique, a company may choose not to report it and allow doctors to simply buy the product as currently marketed. By doing so, however, doctors may be taking unreasonable liability risks, which will obviously affect the new technique's commercial and practical success.

Ultimately, the CDRH Secretary determines the intended uses of a device. At any time, the Director may require that the label include appropriate information regarding a novel use not identified in the proposed labeling if there is a reasonable likelihood that the device will have this novel use. Performing the now needed trials for the novel use may pose a significant and unanticipated financial burden to the company and its investors. Therefore, when filing a PMA or 510(k), a company should consider including as many accessories and uses as possible to avoid unnecessarily filing for changes or equivalence.

MEDICAL DEVICE CLASSIFICATION

When you list with Form FDA-2892 you will need to determine the *Class* of your device. Although your device will be listed under one of 16 *panels* (medical specialties) and given a number identifying it within that panel, it can only be classified as a Class I, Class II or Class III device. Consult a regulatory attorney if there are ambiguities regarding classification. It can be the most critical regulatory element since class impacts regulatory requirements substantially.

Shortly after passage of the Medical Device Amendments of 1976, the Office of the Secretary organized panels of experts to provide review and recommendation to FDA regarding the classification of over 1800 device types. Their recommendations have been codified in classified regulations found in 21 CFR 800-1299. After discharging these responsibilities, these same panels converted to the advisory panels used today. The panels continue to make

recommendations to FDA on issues ranging from classification to the approvability of PMAs.

To find the classification of your device, as well as any potential exemptions, go directly to the product code classification database and search for a part of the device name, or, if you know the device panel (the medical specialty) to which your device belongs you can go directly to the Code of Federal Regulation and find the classification for your device by reading through the list of classified devices. You can also check the classification regulations and the precedent correspondence for information on how various products are regulated by the CDRH.

Class I: These devices do not present an unreasonable risk of illness or injury and are generally exempt from the marketing application process. Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

Although many Class I devices will be exempt from the marketing application process the FDA has identified what are referred to as *general controls* to ensure safety and efficacy of even these low risk devices. Various general controls will apply to Class I devices as the CDRH deems necessary. These controls include but are not limited to:

- Registration and listing
- Compliance with adulteration & misbranding regulations
- Compliance with Quality Systems Regulations (formerly Good Manufacturing Practices or GMPs)
- Record Keeping and reporting requirements
- Repair, replacement and refund practices

Class II: Class II devices may help support or sustain human life and pose some risk of injury or ailment. When general controls alone are insufficient to provide reasonable assurance of safety and effectiveness but information to provide such assurances is available through what the FDA calls *special controls*, a product will be listed as a Class II device. Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

Special controls include but are not limited to:

- Development and dissemination of guidelines, including guidelines for the submission of clinical data for applications aimed at getting recognition of substantial equivalence to a previously marketed device.
- Performance Standards
- Post-market Surveillance
- Patient registries

- Recommendations for compliance improvement

Class III: These are high-risk devices and require PMA filing providing reasonable assurance of safety and effectiveness. Examples of Class III devices that require a PMA include replacement heart valves, silicone gel-filled breast implants, and implanted cerebella stimulators. When considering the classification of your device, keep in mind that safety, efficacy, and classification are judged relative to the needs of the intended patient.

THE PREMARKET APPROVAL APPLICATION (PMA) – FDC ACT §515

Premarket Approval Applications (PMAs) are required for all Class III and some Class II devices in order to give reasonable assurances of safety & efficacy. For the most part they will require human clinical trials, a good deal of money, and a much greater time commitment than any other type of device marketing application required by the FDA.

The PMA review is a four-step process consisting of:

- Filing Review – FDA staff conducts meetings, administrative checks and limited scientific review to determine whether a PMA is suitable for filing and further review. The agency will notify the company of the application's status within 45 days after receiving their PMA. The FDA has developed a checklist of **refuse-to-file criteria** to assist applicants in meeting threshold criteria;
- Consideration – FDA personnel conducts an in-depth scientific, regulatory, and quality system review;
- Panel Review - Review and recommendation by the appropriate advisory committee;
- Final deliberations, documentation, and notification regarding the FDA's decision.

COLLABORATION MEETINGS

The FDA Modernization Act provides for two early, formal collaboration meetings with the Secretary, scheduled only upon your written request. These one-day meetings are intended to provide clear direction for testing/development and will help you understand what will be required in order to get your device through the PMA process successfully. Prior to these meetings you must submit an extensive formal package. You should ask the Secretary about this package and begin its preparation as soon as you feel confident that you will bring a new device to market.

In essence, these meetings help you create a *PMA Shell* from which to structure the entire application. These meetings should not be taken lightly as agreements

reached in these formal meetings are binding on both the company and the agency. It will be difficult for either party to deviate from the agreement after signing, so have someone at these meetings who is empowered to make critical decisions for your company as needed over the course of the day. By the end of these meetings the FDA should determine whether clinical studies are necessary to establish efficacy and, if so, how they should be conducted.

Other means of interacting with the FDA include phone calls and informal meetings, which may be useful prior to a formal meeting.

PMA STRUCTURE

A PMA can be viewed as a compilation of sections and *modules* that together become a complete application. The term *module* is used to identify a set of data and information addressing an aspect of the device. Information included in such a module ranges from pictorial representations of the device to clinical study data. A module may begin as the simple identification of the issue to be addressed and later developed into a detailed listing of the specific test results to be submitted. What is needed for each module will ultimately be decided by agreement between you and the FDA.

The PMA Shell is an outline of those sections or modules that will be necessary to complete the PMA. It will include all modules needed to support filing and approval of the total medical device. The FDA requires that the Shell be submitted in advance of the completed PMA.

As the information required for each module is reviewed and accepted by the FDA staff, the shell is filled with these completed modules. If you make any design or technical changes to the device after the module submission, you have to file supplements to the relevant module, identifying the changes and their effects. Once the module is complete and accepted by issuance of a *status letter*, it is considered closed and can only be reopened if there is good reason to do so. Once all modules are closed, the PMA is complete and can be submitted.

The filing date is the date that the FDA receives a complete PMA. The PMA may still be rejected for filing up to 45 days later. Technically, the FDA has 180 days from the day of filing to review the PMA and render a decision. In reality, the review will take longer, particularly since any substantial changes will restart the 180-day clock.

After the FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the internet announcing the data on which the decision is based and providing interested persons an opportunity to

petition the FDA within 30 days for reconsideration of the decision.

PMA SUPPLEMENTS

Making a change affecting the safety or effectiveness of the approved device requires filing a PMA Supplement. Such changes include:

1. New indications for use of the device
2. Labeling changes
3. Using a different establishment to manufacture, process, or package the devices
4. Changes in sterilization procedures
5. Changes in packaging
6. Changes in performance or design specifications, circuits, components, ingredients, principle of preparation, or physical layout of the device.

SUBSTANTIAL EQUIVALENCE - PREMARKET NOTIFICATION, 510(K)

If a your device has equivalent materials, performance and uses to a previously approved product, you may be able to bypass many of the hurdles posed by the PMA by filing what is referred to as *Premarket Notification* for the equivalent part.

The term *five-ten-K* is derived from section 510(k) of the FDC Act and is another way of referring to an application for *Substantial Equivalence* or *Premarket Notification*. All three terms indicate an attempt to demonstrate that a newly introduced device is so similar to a predicate device (an already legally marketed device to which you claim equivalence) that the PMA process or other special controls are not necessary to show safety and efficacy. A substantially equivalent device is defined as:

A device that has the same intended use as a predicate device, does not raise different questions of safety and effectiveness, and has either the same technological characteristics as the predicate device or has different technological characteristics but demonstrates it is as safe and effective as a predicate device.

Any establishment wanting to market a device intended for human use in the U.S. will most likely have to, at the very least, submit a 510(k). Any change to the device's intended use or any significant change or modification made to a predicate device that may affect safety or efficacy will require premarket notification no later than 90 days before marketing.

There is no specific 510(k) form to be filled out. The application must be constructed and submitted according to specific formats (see CDER website for information on the **510(k) Submission Process** links to **Title 21 of CFR 807**). You will have to include various types of data to

establish your device as substantially equivalent and otherwise support that claim. Additionally, a summary and citation of all adverse safety and effectiveness data related to both your device and the predicate device must be included.

Most significantly, if a company successfully applies for Class III premarket notification, they may forgo the rigors and expenses of a PMA. The 510(k) only costs about \$2000 and is worth the expense if there is any chance that any part of your device might gain equivalence status.

The CDRH has recently introduced a New 510(k) paradigm that presents device manufacturers with two additional optional approaches for obtaining market clearance. The *Special 510(k) Device Modification* option utilizes certain aspects of the Quality System Regulation (formally known as GMP), while the *Abbreviated 510(k)* option relies on the use of guidance documents, special controls, and recognized standards to facilitate 510(k) review.

SPECIAL 510(k): DEVICE MODIFICATION

The Special 510(k) may offer a less burdensome option than the standard 510(k) application and the Office of Device Evaluation (ODE) will be processing the Special 510(k) within 30 days of receipt.

There is a common understanding as to what types of device modifications may be made through a Special 510(k) application. Where evaluation is intended to ensure the modified device continues to meet user requirements as opposed to patient safety and effectiveness the Special 510(k) will likely be the appropriate and preferable avenue.

Modifications to predicate devices that do not affect a device's intended use or alter its fundamental scientific technology should usually qualify for the Special 510(k), or 30-day change as it is often referred. Such modifications might include:

1. Changes to formulation or type of material used
2. Energy type
3. Dimensional specifications
4. Software or firmware
5. Packaging or expiration dating
6. Sterilization

The Special 510(k) relies more heavily on quality system regulations (or GMPs) to ensure safety and effectiveness than does the standard application. To utilize it, manufacturers must have a systematic set of requirements and operating procedures for design and development that can act independently to ensure safety and efficacy.

Note that if a clinical investigation is necessary to answer safety and effectiveness questions relating to a particular modification, a Special 510(k) will not likely be the appropriate avenue.

ABBREVIATED 510(K)

This option allows for the streamlining of substantial equivalence review. It can be utilized by manufacturers when device-specific guidance documents exist, a special control has been established by the FDA, or when the FDA has recognized a relevant *consensus standard*.

The CDRH is developing device-specific guidance documents to identify device information that might standardize certain types of marketing authorizations. You may be able to reduce 510(k) review time by submitting a *summary report* outlining your adherence to the guidance documents.

As in the case of guidance documents, summary information that describes how special controls (as described under the Medical Device Classification, Class II section) have been used to address a specific risk should also reduce the time and effort to prepare and review 510(k)s.

In addition, the CDRH is developing individual *consensus standards*. The Modernization Act authorizes them to recognize all or part of national or international standards through publication of a notice in the Federal Register. Recognized standards could be cited in guidance documents or individual policy statements, or established as special controls (as described in the Medical Device Classification section) that address specific risks associated with a type of device. Certain aspects of a medical device might be broadly applicable and if a standard is approved for such applications and combined with modified review procedures, the FDA should be able to streamline the review of 510(k)s covered by the standard. To learn about qualifying for such a standard, see [Consensus Standards Database](#).

EXEMPTIONS

A 510(k)/GMP Exemption gives an establishment the legal right to manufacture and distribute a device to the public without going through the approval application process, while an Investigational Device Exemption permits use of an unproven device for clinical studies. These are the two primary types of exemptions.

510(K)/GMP EXEMPTIONS

The 510(k) exemption applies to almost all Class I devices. These devices are identified and listed as exempt from FDA marketing approval and often times from quality systems regulations (GMPs) as well. However, they are still subject to various appropriate general controls, applied individually as deemed necessary by the CDRH.

The FDA has also published a [list of Class II devices](#), subject to certain limitations, that are now exempt from marketing approval by the FDA prior to distribution. If you think there is a chance you might get on that list, you may want to contact your regulatory attorney. See Appendix of Links for web site to exemptions and list of exempt Class II devices.

Note: When dealing with one of these devices you must still file for the exemption. You will, however, be saved the substantial costs of premarket approval or recognized substantial equivalence. Also, Class II devices are never exempt from GMP requirements and are still subject to other general and special controls.

INVESTIGATIONAL DEVICE EXEMPTION (IDE)

An Investigational Device Exemption (IDE) allows a device to be used in clinical studies to collect the safety and effectiveness data required to support a marketing application. Although the term *exemption* might often indicate a reduced workload, getting an IDE is, to the contrary, an involved process. Even after receiving approval to move forward, compliance with IDE regulations will continually demand your attention and keeping the Institutional Review Board satisfied can be a nagging responsibility.

An Institutional Review Board (IRB) is an impartial board of at least five respected citizens of diverse backgrounds that act as watchdogs for the rights of patients participating in investigations or studies. The IRB is necessary for the approval of almost any study. They are primarily responsible for:

- Approval of the written protocols for treatment and data collection.
- Guarding against financial and other conflicts of interest;

Table 3. Medical Device 2003 Regulatory Filing Fees for Small Businesses

PMA application	\$154,000	\$58,520 (free for 1 st PMA)
180-Day Supplements	\$33,100	\$12,582
Real-Time Supplements	\$11,088	\$4,213
510(k)	\$2,187	\$2,187
Exemptions	Free	Free

- Categorizing your device as a Significant Risk study or a Non-Significant Risk study; and
- Assuring that fully informed consent is given by each participant.

The IDE regulations differentiate between Significant Risk (SR) and Non-Significant Risk (NSR) devices. Only the SR devices require submission of an entire IDE Application. For NSR devices the CDRH calls for only an abbreviated version of the IDE. If the device investigation is designated as NSR, the investigation may begin immediately at the institution represented by the approving IRB. In case of an SR designation, both the IRB and FDA must approve all parts of the exemption application before the trial may begin. An SR device is defined as one that:

- Is an implant
- Is used in supporting or sustaining human life
- Is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or
- That otherwise presents a potential for serious risk to the health, safety or welfare of a subject

An NSR device is one that does not meet the SR definition. The FDA website offers further guidance on **SR vs. NSR designation**.

COSTS

The Medical Device User Fee and Modernization Act of 2002 outlines new user fee payment procedures for applicants seeking market approval. The increased fees outlined by the Act are significant, must be paid at the

time of submission, and the payment process involves jumping through some hoops.

If you qualify as a small business the application fees are either reduced or waived. A small business is one that reports gross receipts or sales of no more than \$30 million. You must include in that calculation the receipts of any affiliate, partner, or parent firms and such receipts will be counted in determining your small business status. This is something to keep in mind when structuring your company because the cost increases are significant for larger businesses. The FDA waives the PMA fee for Small Businesses filing their first PMA, but not if your affiliates or partners have filed a PMA in the past.

In reviewing the fees in Table 3, note that 180-Day Supplements may outline a significant change in components, materials, design, specification, software, color additives, or labeling to your already approved PMA. Real-Time Supplements cover minor changes.

ABOUT THE AUTHOR

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Mr. Pimentel has experience with government proposals and performance contracts, licensing & contract management, technology evaluation, project management, stock purchase & corporate governance. He was a co-founder and Executive Vice President of Crosslink Medical, where he became interested in medical devices. Mr. Pimentel also served as Assistant Agreements Specialist at Massachusetts General Hospital's Corporate Sponsored Research and Licensing and was a finalist in the 2002 MIT 50k Entrepreneurship Competition.

EQUITY

The principle underlying equity distribution is simple. If you and two friends each put a dollar into a joint bank account, you would each own one-third of the bank account. After many years of accumulated interest payment, the money in the account will double to six dollars, and you still own one-third of the account, which is two dollars. If you agree to let a fourth person deposit four dollars in the account, there will be ten dollars in the account, but you and your two friends will each only own 20% instead of 33% of the account. This is referred to as dilution of equity. When the account grows to \$20 from accumulated interest, you will still own 20% and will be entitled to \$4. Just because you used to own 33% of the account and were later diluted to 20% does not change the value of your original investment; your money would have increased from \$1 to \$2 to \$4 even if the fourth person hadn't invested his \$4.

Unlike a bank account, a company has some intrinsic value even before any money is invested. The value comes from the idea, the people, and investment of time and energy that went into putting everything together. This value is referred to as *sweat equity* or founders' equity; it belongs to the founders of the company. This intrinsic value is also equal to the pre-money valuation of the company prior to its first financing. The pre-money value of the average biotechnology startup is rarely more than \$2M - \$3M. If an investor gives the company \$3M based on a pre-money valuation of \$3M, the total valuation of the company after financing will be \$6M and the investor will own 50% of the company.

SHARES AND OPTIONS

To allocate ownership of the company conveniently, the company is divided into shares (a.k.a. stock). Upon incorporation, a certain number of *authorized* shares are created. Authorized shares issued to shareholders are referred to as *outstanding* shares. Ownership in a company is calculated as a percentage of *outstanding*, not *authorized*, shares. If a company only has 1,000 outstanding shares, then 100 shares represents 10% of the company.

Ask your corporate attorney to register about 10 million shares at the time of incorporation. It will be easier to attract employees by offering them 10,000 shares out of 10 million than by offering 100 shares out of 100,000. Furthermore, investors like to buy cheap stock. A company with 1,000 outstanding shares valued at \$1000/share has the same capitalization as a company with 1,000,000 outstanding shares valued at \$1/share. Though the percent ownership is the same in both cases, paying \$1000 for 1000 shares may feel like a better deal to some investors than paying \$1000 for one share.

Upon incorporation, each share is assigned a nominal value, often \$0.01 or less. The value of the shares thereafter is determined by the price others are willing to pay. If an investor is willing to give the company \$5M for one million shares, each share becomes worth \$5. If the company has a total of five million shares outstanding after the purchase, then the company's valuation is \$25M. Next time the company raises money, an investor might be willing to pay \$10 per share, setting an even higher valuation for the company and increasing the value of other shareholders' stock. If people are only willing to pay \$1/share during a later financing, the value of everyone's stock will drop to this price.

A company will often reserve a pool of shares to incentivize employees and consultants. Rather than give away the stock, the company may grant *options*, which give the right to purchase stock from the company at a set price. There are many tax and accounting implications to granting options. Your corporate attorney and accountant can help create a valid stock option plan document, which the board of directors must approve.

When a new employee is hired, he might be offered options to purchase 50,000 shares at \$1 each. Someday, when the company's stock is worth \$10/share, the employee may exercise his options to purchase all 50,000 shares and then sell them, thereby increasing the number of shares outstanding. Therefore, make sure to account for the stock option pool when calculating dilution. If you own 1 million shares of a company with 4 million total shares outstanding, you own 25% of the company. However, if the company has 1 million shares reserved for employee stock options, you will only own 20% of the company once those options are exercised. In this case, 20% represents your *fully diluted* share of the company.

There are two types of options: incentive and non-qualified. ISOs (**I**ncentive **S**tock **O**ptions) have tax-favored status and may be granted only to employees. To qualify as an ISO:

- The exercise price must be at least equal to the FMV (**F**air **M**arket **V**alue) of the company at the time of the grant,
- Be granted within 10 years of the plan's adoption,
- May not be granted to an employee who owns more than 10% of the company's voting stock unless the grant price is 110% of FMV and exercisable within 5 years of the grant,
- The aggregate FMV (as of the grant date) for which ISOs are exercisable for the 1st time by the employee during any calendar year may not exceed \$100,000 (*excess over \$100,000 is treated as non-qualified*),

Table 4. The tax implications of NQO and ISO options.

To the Employee	NQO	ISO
Option Granted	No tax unless option has a readily ascertainable market value	No tax
Option Exercised	Difference between option price & market value @ exercise is taxed	No regular tax; AMT (Alternative Minimum Tax) may apply
Stock Sold	Post exercise spread taxed as short- or long-term capital gain (loss)	If held 2 years from grant date <i>and</i> 1 year from exercise date, then spread taxed as capital gain or loss
To the Employer	NQO	ISO
Option Granted	No tax deduction unless option has a readily ascertainable market value	No tax deduction
Option Exercised	Tax deduction equals difference between option price & market value @ exercise	No tax deduction
Stock Sold	No tax deduction	No tax deduction on qualifying sale. Tax deduction on disqualifying disposition.

- Be exercisable within 10 years of grant date, and
- May not be transferable by the employee except upon death.

An NQO (Non-Qualified Stock Option) is not as tax favored as an ISO but provides the company greater flexibility. NQOs may be granted to consultants and advisors, in addition to employees. They may be granted at any exercise price, and any vested amount may be exercised. Table 4 illustrates the tax implications of each type of option.

Because shares have a monetary value, they must be purchased or, if granted, recorded as an expense by the company and as taxable income by the recipient. At startup, shares are only worth their nominal value; as a company matures, the share price will increase and the person may no longer be able to afford to purchase the shares or pay associated taxes. At this point, it makes more sense to grant options, which are essentially as good as shares. However, a tax form section 83(b) election must be filed with the IRS within 30 days after exercising NQOs or else the recipient will pay income tax rates (as opposed to the lower long-term capital gains tax rate) on the difference between the FMV on the vesting date and grant date. Needless to say, consult an accountant and attorney regarding tax issues and options.

VESTING

It does not make sense to grant 50,000 options to an employee on the first day of employment. The person might exercise the options after a month and then quit. Instead, the options are vested (become available to the person) in installments over time. After the first year on the job, the employee might receive 10,000 shares (one-year cliff vesting). Each month thereafter for another

four years, more options will vest until the employee has all 50,000 options. At that point, the company may offer him another set of options on a new vesting schedule. If the employee quits or is fired, he will retain only the vested options and forfeit any claim to the remainder.

Before venture capitalists invest significantly into a company, they may insist that founder's stock be subject to vesting. Founders who have already been with the company for several years may find themselves stripped of some or all of their stock and have to work it back again. The VCs want to make sure everyone remains highly motivated. Additionally, the employment agreements that founders sign may have a mandatory buy-back clause that can force you to sell your vested shares back to the company if you quit or are fired for good reason. You will not be in a position to dictate the buy-back price, either.

Vesting may be accelerated if a founder is terminated without just cause, resigns for a good reason, or suffers death or disability. The individual typically may receive shares/options that would not have otherwise vest for another year, depending on the extent of acceleration. Acquisition or merger may also trigger accelerated vesting of all unvested shares, though VCs will often negotiate for only partial acceleration so as not to suffer extra dilution.

COMMON VS. PREFERRED STOCK

Shares of the company that do not come with any associated rights are considered *common*. *Preferred* shares, on the other hand, offer certain advantages. A company can issue more than one *series* of preferred stock, each with its own provisions.

Although preferred stock cannot be traded in the public markets and its value is independent of the value of

common stock, preferred stock is almost always convertible to common stock. One preferred share will usually convert into one common share, though anti-dilution provisions may increase this conversion ratio. An investor with preferred stock will hold onto it as long as he feels he needs the protection the preferred stock offers, but when the price of the common shares is attractive enough, he may decide to convert his preferred shares to common and sell then those shares. When calculating shares-outstanding, only the common shares count. A company with 1 million common shares and 100,000 preferred shares, each convertible into 10 common shares, essentially has 2 million shares outstanding on a fully diluted basis.

Founders almost always receive common stock, whereas investors want the protection of preferred stock. In the event of liquidation, preferred shareholders are paid back first. If the preferred stock also comes with a cumulative dividend right (a dividend is money paid per share by a company to its shareholders), investors are allowed to collect their original investment and accumulated annual dividends (typically 5%-8%/year) before common shareholders have a chance to salvage their investments.

Investors can also negotiate for *participating preferred* stock, which allows them to double-dip when a company is sold. Following sale of the company, these shareholders take out the amount of their initial investment plus any accumulated dividends, then convert their *participating preferred* stock into common stock and split what remains of the sale proceeds with the rest of the common shareholders, sometimes with a cap (e.g. the preferred shareholders might limit their total proceeds to a multiple of their original investment). In the simplest case, consider a company with one million common and one million *participating preferred* shares that is sold for \$10M. The common shareholders might think they are entitled to 50% of the \$10M. However, the *participating preferred* stockholders will first collect their original investments, say \$5M, and then split the remaining \$5M with the common stockholders. The preferred investors therefore receive \$7.5M and the common stockholders will only receive \$2.5M from the sale proceeds, half of what they expected. Truly aggressive investors may negotiate for *participating preferred* stock with dividend preferences.

Furthermore, entrepreneurs do not always realize that owning a majority of the company may not necessarily give them control over the company. Preferred stock can stipulate that the shareholder, such as a venture capital firm, has the right to elect a director to represent its interest in the company. The preferred stockholders may also negotiate "drag along" rights. This means that they can compel the other shareholders to sell their stock if the preferred shareholders wish to sell their shares to an outside party. The investors may also require that the

company obtain permission before hiring a new employee, purchasing an expensive piece of equipment, or entering into a merger agreement; so called *negative covenants* are fairly common in VC financing agreements.

Each financing usually involves a new series of preferred stock. Investors participating in the first financing will receive Series A shares, those participating in the next financing receive Series B shares, and so on. These shareholder agreements may stipulate that with respect to certain decisions, management must receive approval from a majority of the investors of *each* series. Therefore, a small investor who represents the majority of a small series may be able to obstruct management and a majority of other investors while owning only a tiny fraction of the company.

The entrepreneur should evaluate the terms of any preferred stockholder agreement carefully with his attorney to appreciate these issues of control.

LIQUIDATION

Shareholders of a private company do not have many options when it comes to selling their shares and converting their "paper money" into real money. The ideal exit involves an IPO or acquisition of the company.

Investors may negotiate for preferred shares with Redemption rights. This provision allows the investor to demand that the company purchase his shares within a certain period (typically 5 years) if no other exit option exists. The investor would receive his original investment plus any accrued dividends. Venture capitalists will rarely exercise their redemption right since the financial burden of repurchasing stock can easily bankrupt a company. Instead, the VCs may extend the deadline for redemption in anticipation of a more profitable exit and, as "payment" for doing the company this favor, may demand an increase in their preferred-to-common conversion ratio.

Prospective investors negotiating a shareholder agreement may include a clause granting them "piggy-back" registration rights. This means that if the company registers its shares for a public offering, investors have the right to include their shares in the offering. Typically, the clause obliges the company to pay for the associated registration costs.

A shareholder of a private company may try to sell his shares to an outside buyer, but there are often clauses that require that these shares first be offered to other shareholders. Investors may require co-sale rights that allow them to also sell a portion of their shares in the event that a founder tries to sell shares. Such bureaucracy may ward off prospective outside buyers.

After a company does an IPO, there is a lock-up period of 6 months during which the pre-IPO investors may not sell their shares. Before legally selling (or buying) stock, company insiders with significant equity stakes must register their shares with the SEC, thereby letting the market know of their intention to sell. Outside investors may interpret this as a vote of non-confidence in the company's future. Consequently, the stock price may drop between the time an insider declares his intent to sell and the actual time of sale.

ANTI-DILUTION PROVISIONS

Even before financing, you may need to offer stock to people who will not want to risk dilution. For example, a technology licensing office (TLO) may give you a license to a technology in exchange for some payments, royalties, and 5% equity. However, they stipulate that they want to own 5% of the company *after* it has received financing. If the investors value the company at \$3M dollars pre-money and invest \$3M, the investors will own 50%, the TLO will own 5%, and the founders will own a total of 45% of the company post-financing. Had the TLO not demanded the anti-dilutions provisions, it would have owned 5% of the company before financing and then only 2.5% after financing, leaving the founders with 47.5%. Using anti-dilution provisions, the TLO passes the burden of dilution to the founders.

An investor can also request Pre-emptive Rights, which guarantee the investor the right to purchase enough stock at each subsequent round so that he can maintain his original stake in the company. A modified form of this anti-dilution provision is called Pay-to-Play, which requires that an investor continue to invest in the company in order to maintain certain rights, including Pre-emptive Rights. Both these clauses may make it difficult to raise money from VCs. If you try to raise \$5M in a second round of financing, there may be a number of VC firms interested in making an investment of this size. However, if you only need to raise \$3M after all the investors from the first round exercise their pre-emptive rights, then some VC firms will decide that making such a small investment is not worth their time. On the other hand, it is always reassuring to new investors when old investors want to put more money into the company.

Investors in a given round will often demand provisions that ensure that their investment will not be excessively diluted if a company subsequently goes on to sell shares at a lower price. Such provisions increase the preferred-to-common conversion ratio.

For example, a company has 1.5M shares outstanding. In Round 1, VC1 acquires 40% of the company by paying \$2/share for 1M newly-issued preferred shares, each convertible to one common share. After Round 1, there are 2.5M shares outstanding. In Round 2, VC2 purchases

2.5M newly-issued preferred shares at \$1/shares. The fair market value of the VC1's investment is now only \$1/share, or half of the original price.

- Without any anti-dilution provisions, there would be 5M shares outstanding after Round 2. VC1 would own only 20% of the company (1M of 5M shares).
- *Full-ratchet* anti-dilution provisions in VC1's term sheet would issue him enough additional common shares upon conversion to adjust his price/share from \$2 to \$1, the same price VC2 paid. In this case, the conversion ratio would be adjusted to 2 common shares per preferred share, entitling VC1 to 2M common shares. Full-ratchet would set the VC1's ownership stake at 33% (2M out of 6M after the second round), much better than the 20% he would own without any anti-dilution provisions.
- *Weighted-average* anti-dilution would adjust VC1's effective price/share to an average of the Round 1 and Round 2 price/share weighted according to the number of shares purchased by each. The formula is as follows: $(\$2/\text{share} \times 1\text{M shares} + \$1/\text{share} \times 2.5\text{M shares}) / (1\text{M shares} + 2.5\text{M shares}) = \1.29 . The new conversion ratio is calculated by dividing VC1's original share price by the new effective price $(\$2/\$1.29 = 1.55)$. Therefore, after Round 2, VC1 would be entitled to 1.55M shares and would own ~28% (1.55M out of 5.55M shares).

Full-ratchet favors VC1 while weighted-average favors the entrepreneur and new investors. Of course, most entrepreneurs would prefer to omit anti-dilution provisions altogether, but investors will almost always demand them.

EQUITY DISTRIBUTION

FOUNDERS

Division of equity can have a profound effect on the dynamic between founders. The bitter disagreements that may arise from these discussions can foreshadow disaster down the road. Some may work together on a startup for a prolonged period of time before finally sitting down to decide what each founder's share will be. Others may divide the company amongst themselves before any significant work has been done. There are problems with both scenarios.

In the simplest of cases, partners divide the company equally. However, this agreement assumes that each partner has contributed and will contribute equally to the company, which is rarely the case. If there is a lead founder who has clearly done more work and will continue to contribute more to the company than others,

he deserves a larger share of the company. However, a team leader may not feel comfortable making such a claim on his own behalf. The lead founder may hope that one of the other founders will suggest it out of fairness. On the other hand, a founder may have an exaggerated opinion of his contribution to the company and try to insist on a larger share of the company than he deserves. Ultimately, a distribution that gives too little to some and too much to others for the sake of diplomacy will lead to unrest among the founders. Those who feel undervalued may cut their productivity to a level they feel is on par with their stake in the company. Unfortunately, those who got too much probably won't increase their contribution proportionately.

When distributing equity among founders:

1. Do not discuss equity until it is clear who is and is not a founder. Allow enough time so that potential founders can prove their dedication and abilities by actually contributing to the startup.
2. Discuss equity distribution before investors become involved. Your attorney should prompt you to settle this issue before incorporation.
3. When you finally decide to divide up the founder's stock, assemble all the founders for a conference and have an open discussion at which everyone can present what they have contributed to the startup and what they can contribute in the future.
4. Do not be afraid to ask for what you believe is your fair share. Be mindful of others' contributions.
5. Once all the proportions are established, factor in vesting schedules, mandatory buy-back clauses, and all the other legal gadgets that will make sure that everyone will continue to work for their shares or risk losing them. You can agree that people who contribute above and beyond what is expected of them can be rewarded with additional options.
6. Decide what happens if a founder wants to quit or wants to sell his shares. Founders should be required sell their shares to the company and the other founders before being permitted to sell them to an outside party. This ensures that the remaining founders retain more control of the company.
7. Finally, put all of the above terms into writing in a Shareholder's Agreement. Any objections to the terms should be voiced *before* signing the document. Once signed by all the founders, this agreement will dictate the rules of fair play.

DIRECTORS AND SCIENTIFIC ADVISORS

At the pre-financing stage, you can compensate directors and advisors with founder shares that vest over 3-5 years, subject to restrictions that you should discuss with your attorney and accountant. There are two ways to think about how many shares to give to each director/advisor:

1. The average board member should be compensated between \$25K and \$50K per year in stock. If the person will be with the company for four years, the stock should be worth between \$100K and \$200K at the end of the 4th year, and one-quarter of the stock should vest each year. This method is cumbersome and inaccurate because it requires you to estimate your company's current valuation and rate of growth. You will have a hard time justifying your math.
2. If still a startup, offer between 0.1% and 1% of the company, depending on how badly you want that person to join. Very rarely should a non-founding director or advisor receive more than 1% of a company.

The two methods described above may not give you different answers. Depending on growth estimates, 0.1%-1% of the company today may be worth \$100K or more after 4 years, allowing for dilution from financings.

In addition to shares, directors and scientific advisors may be compensated for their time with cash. Some say \$1,000 per meeting; others suggest 2%-3% of the CEO's annual salary (\$3,000 - \$5,000 per year). Assuming that you have quarterly meetings, these two calculations yield equivalent estimates. You will likely need to compensate them for their expenses. Cash compensation is not as commonly discussed as stock, but you should bring it up with each board member early on to avoid disputes. Board members who recognize that the startup has little cash to spare may not expect to receive cash at first.

CEO

Although a seasoned CEO may be the most expensive recruit, this individual may have the most to contribute to the value of the company. Founders overly eager to retain cash and equity may end up owning a larger piece of nothing if the company fails.

Based on a 1998 PricewaterhouseCoopers (PWC) Survey of medical device firms, the CEOs of private companies with valuations under \$5M were paid \$120K - \$130K per year and CEOs of companies with valuations greater than \$25M were paid \$180K. CEOs received \$50,000 worth of stock options each year. Keep in mind that salaries have increased by as much as 6%-10% per year for some positions and may be higher than reported here. At the startup stage, industry experts estimate that CEOs should receive about 10% of the founder stock of the company, vested over 4-5 years.

You get what you pay for. Experienced CEOs know their own worth and will calculate the value of what they are offered in much the same way investors calculate how much their contribution is worth. Also, if a CEO joins the startup team before the first financing, consider including that person as a founder, particularly if the CEO then goes on to raise money.

A CEO who is also a founder should distinguish between equity granted for being a founder vs. being a CEO. When venture capitalists finance a company, they may insist that founders and management agree to a vesting schedule. Founders may be allowed to hold onto part of their equity and have the rest vest over time. Likewise, a founding CEO may be able to keep the founder portion of his equity but agree to vesting of the CEO portion. In the event that the founder CEO is replaced, he will only have to forfeit rights to the CEO portion of the stock options and will continue to receive founder options as long as he remains with the company in some capacity.

CFO AND OTHER EXECUTIVES

According to the PWC survey, smaller companies (<\$25M valuation) typically hire controllers for about \$60K - \$100K. Larger companies hire CFOs at >\$140K and grant them about \$20K worth of stock options each year. Industry experts tend to address equity compensation using percentages, suggesting that the CFO of a startup should receive between 2%-4% of a startup company, vested over four years. If a CFO is hired at a later stage, the equity allocation may be much smaller.

In smaller companies with \$0-\$12M valuations, salary ranges were between \$70K and \$90K for Heads of Operations, R&D, Marketing, and Business Development. Their annual stock option grants were \$15K-\$30K.

MANAGEMENT AND EMPLOYEE OPTIONS

The founders should set aside 10%-20% of the company for management options and another 10%-20% for employee options. You will need to use these shares to recruit people, give them incentive to stay with the company, and reward them for performance.

When employee/management options are allocated after an investment round, the investors and other shareholders are diluted equally. When options are set aside prior to financing, only initial shareholders experience the dilution. For example, an investor purchases 50% of a company for \$12M and receives 4M shares at \$3/share from a total of 8M shares outstanding. If the company issues 2M shares for the employee option pool (bringing the total number of shares that will be outstanding to 10M), the investor will be diluted down to 40% ownership. However, if the investor insists that the 2M shares be set aside for the employees before he purchases 50% of the company, then he will own 6M shares of a total 12M outstanding at only \$2/share. The investor thus protects himself from dilution at the expense of the original shareholders and the employees. In this case, \$2/share is referred to as the *fully diluted* share price.

Not surprisingly, investors will negotiate with management over the size of options pools and insist that these shares be set aside prior to investment so that investors are not diluted. Strong companies that can afford to haggle with investors may be able to compromise by setting aside a small pool pre-financing and then issue additional shares later on when the investors also have to suffer dilution.

RAISING MONEY

Raising money is one of the most challenging steps in forming a company. This section discusses when to raise money, the pros and cons of angel and venture capital, and the role of loans and venture leasing. Government grants are discussed in the next chapter.

ANGELS

Angels are high-net-worth individual who invests in private companies. These people are "accredited" investors, who, according to SEC guidelines, must have a net worth of at least \$1M or earn >\$200K annually. The typical angel invests between \$25K and \$100K at a time in one company, with an average of ~\$60K per deal. Most angels have invested in several companies each year for over a decade. Angels will occasionally form networks or groups that may meet regularly to review companies.

Consult your corporate attorney prior to accepting money from angels. It may be advisable to have the attorney put together a Private Placement Memorandum (PPM), which is a more detailed version of the business plan with many legal warnings about the specific and general risks of investing in the company. By essentially stating, "Buyer beware: Invest at your own risk", a PPM mitigates the risk of an angel successfully suing the company for fraud.

THE 3 F'S

Inexperienced angels may fall under one of the 3 F's... friends, family, and fools. They may be doctors or lawyers who are willing to give "dumb" (silent) money but do not have enough relevant experience to contribute advice or connections. Worst case, such investors are meddlesome and fickle, insisting that they have a right to make management decisions or running away with their money when they discover just how difficult starting a company can be.

Angels may demand protective provisions that transfer risk to the company or other investors. Accepting their investments on bad terms (such as aggressive anti-dilution clauses) can make it difficult to raise money later. As always, consult an attorney before signing any agreements.

The best angels to have as investors are those who have started their own companies in the past in your industry and can give you valuable guidance (a.k.a. "smart" money). They can help you recruit people, raise more money from venture capitalists, identify customers, and prepare for business development negotiations. However, because these angels have done it before, they may feel that they know how to do it again even better than you. Be careful that they do not try to take over and run the show. One entrepreneur reported that an angel investor

proclaimed himself the Head of Business Development and promptly screwed up both a licensing negotiation and frightened off several venture capitalists with his aggressive tactics.

Scientific advisor and Board of Directors may also qualify as angels. In fact, those members who truly believe in the success of your startup may consider investing, and some companies require that a new Director invest in the company as a show of faith.

MEETING ANGELS

As with most investors, angels prefer to hear about startups from their trusted sources; your corporate attorney, technology licensing office, or advisors should be able to introduce you to angels and other investors. Networking is important for finding and developing these connections. Attend meetings of the MIT Entrepreneurship Forum (www.mitforumcambridge.org), which has 11 chapters in the US and a few in other countries. Go to investor conferences sponsored by industry organizations such as the Mass Biotech Council (www.massbio.org) and BIO (www.bio.org).

SMALL INVESTMENTS

Gathering the \$2M-\$5M that most biotechnology startups need in their first few years can be difficult when the average angel only invests \$60K/deal. Even angel groups usually cannot collect more than \$1M. Angel financing is most practical when the entrepreneur needs <\$500K and can then raise more significant investments from venture capitalists later. Even such a small amount of money, by biotech standards, can increase your venture's credibility. \$500K may be enough to secure an office, CEO, license agreement, and advisors.

ANGELS AS MENTORS

Many experienced angels not only profit from startup investing, they also enjoy it. They report that they want to give back to the entrepreneurial community from which they came. Recognizing that someone once took a chance on them, these angels are willing to overlook inexperience if a promising entrepreneur is pleasant to work with and demonstrates a willingness to receive guidance. Therefore, when approaching an angel, discuss how their contribution of experience (not just money) could make the company stronger.

An angel does not have to answer to anyone when making an investment and may be less concerned with an exit strategy than a venture capitalist. Consequently, an angel may be more willing to work with you to grow your company into a successful long-term business. In the event of crisis, a venture capitalist may exercise his right

to replace the CEO whereas an angel may be more forgiving and allow the CEO to work through the problems.

ANGEL GROUPS

Angel groups tend to be local associations of angels who meet regularly to hear entrepreneurs pitch their ideas and to discuss investment opportunities. In most cases, an individual member will pre-screen a startup on behalf of the group. Each angel in the group decides independently whether to invest in a particular deal and can be an active or passive investor. Your corporate attorney or investors may know of angel groups in your area.

ONLINE MATCHING SERVICES & BROKERS

During the dot-com boom, a number of online matching services emerged promising to connect startups with angels. Some services pre-screen the plans before posting them. Most of the deals posted on these sites are related to information technology (IT); for the most part, neither the services nor the investors are sophisticated enough to evaluate biotechnology ventures. A typical matching service may take ~5% cash commission and 2.5% in warrants (options to buy stock at a fixed price, usually the price/share set by the investors) of the funds transacted through its network. Therefore, a matching service which raises \$1M at \$5/share may receive \$50K cash and warrants to buy 5,000 shares of stock at \$5/share at some point in the future (typically within 5 years). In a few cases, the services have their own venture funds that co-invest alongside angels.

Individuals or firms that promise to raise money for a company are called *brokers*. Just like online matching services, brokers will usually take their commission in cash and equity. Rates for independent brokers may be as high as 8%-10%. Technically, a broker must be registered, in accordance with SEC guidelines, as a *broker-dealer*, which involves passing various tests. Many individuals who raise money on commission are not technically *broker-dealers*. If you do not catch this when you sign them on to help you with fund raising, then your lawyers will probably spot the omission later. Some companies have chosen to adhere to the spirit of their agreement by structuring a consulting agreement in which the unregistered broker is compensated at an hourly rate for as many hours as is necessary to pay off the commission.

From an investor stand-point, brokers rarely pass for qualified references. "You should really take a look at this great startup", lacks the ring of sincerity when it comes from a broker trying to earn a commission. Therefore, unless a broker has a successful track record, their services are unlikely to add much value. Some brokers will negotiate onerous clauses that entitle them to a commission on **all** funds raised in that round, not just the funds the broker brings in directly. The broker may fail to

raise any money but will still be entitled to a commission if management succeeds in raising capital. Such terms are absurd; brokers should be compensated only for the money they raise. Furthermore, many investors are not happy knowing that part of their investment is going into a broker's pocket, legitimately so if the broker were not instrumental in bringing the investor to the company.

Investigate a broker's background carefully before working with one. Check references, particularly previous clients, and look for a strong track record.

INVESTMENT BANKS AS BROKERS

Many investment banks offer startups consulting services and may help them raise money from wealthy individuals, including their own high net-worth clients. Such services range may be free or commission based. The goal of the investment bank is to secure the company's future investment banking business.

VENTURE CAPITAL

Venture capitalists (VCs) are fund managers who invest other people's money in private companies. The people and institutions that provide the money are called the *limited partners* of the venture capital firm. In exchange for managing the money of the limited partners, the VCs typically receive a 2% of the fund as an annual management fee and a 20-30% *carried interest* (a.k.a. *carry*) in fund's returns. If the VCs invest a fund of \$100M into 10 companies and are able to sell their equity after 6 years (though 10 years is more typical) for a total of \$800M, the VCs will have realized a 700% return on investment (ROI). At a 2.5% management fee and 25% carry, the VCs would receive about \$18M over 6 years (for salaries and expenses) and a carry of \$175M. The limited partners would receive about \$620M at an average *internal rate of return* (IRR) of 35% per year. In fact, a few long-standing venture capital firms consistently give their limited partners a 35% rate of return, significantly beating out the public markets over the long-term.

During the 90's, VC funds swelled to unheard-of proportions. It became common for a VC firm to have over \$1 billion under management. With larger funds, the average size of each deal also increased, making it difficult for companies with small initial capital requirements (<\$5M) to justify the attention of many VC firms. Yet, not all companies qualified for larger investments, particularly those that lacked good management, a credible business strategy, solid IP, etc. Venture capitalists who continue to fund such raw startups may only do a few per fund, maybe only one each year. These ventures require considerable coaching, and one of the venture capitalists may need to step in as interim CEO.

BEING A VENTURE CAPITALIST

From their vantage point, VCs have an informed perspective on the industry's future. The large respected firms have first- or second-hand knowledge of most of the startups looking for financing at any given time. As Directors, VCs sit in company board rooms, where the good, bad, and ugly are discussed without the layers of PR varnish the rest of us try to see through. Seems everyone either wants a piece of a VC or wants to be a VC. On the surface, it would seem that VCs have it made.

Yet, VCs must answer to their limited partners and have the unenviable responsibility of making money for the LPs regardless of the economic climate. VCs must stay ahead of the trends, but not too far ahead, and pay heed to changing demands on technology, business models, and management. While the most experienced firms will survive an economic downturn with a few bruises, many VCs lose their jobs either due to bad luck or once their incompetence comes to light. In certain circumstances, VC can face personal bankruptcy. There's nothing grand about being a failing VC, regardless of the prestige the title carries. It's not a job to be coveted lightly.

VENTURE CAPITALISTS AS PARTNERS

Venture capitalists do more than just provide money to companies. They also serve as valuable advisors, capable of guiding a company through many phases of growth. The best venture capitalists have hands-on experience turning startups into mature companies, allowing them to better relate to entrepreneurs. They have extensive networks and can help recruit employees, executives, directors, customers, and other investors. One entrepreneur indicated that he could have gotten financing on better terms from angels but instead chose to accept an investment from a highly respected venture capital firm.

Evaluate VC firms based on the companies in which they have already invested. There may be opportunities for your company to work with other companies in the VC's portfolio. At the same time, be careful of approaching VCs who have already invested in a competitor. Not only are they likely to turn you down, but you may also find that news of your activity has leaked to the competitor.

VENTURE CAPITALISTS AS INVESTORS

VCs have a reputation for taking advantage of entrepreneurs, demanding majority equity stakes and the right to fire the founding CEO on a whim. Indeed, VCs are savvy investors and know the value of their money. When they have a strong bargaining position, which is almost always, they will negotiate for more equity and control than the founders are happy to relinquish. However, VCs are not so blind as to rob entrepreneurs of all incentive to succeed. If you were dealing with an experienced VC in your field, many entrepreneurs would

advise you to accept an offer even if the terms seem a bit harsh. As long as you have an experienced corporate attorney on your team and have reasonable expectations, you should be able to negotiate acceptable terms.

Venture capitalists' terms frequently include clauses that tax the founders and other shareholders in the event of missed milestones. For example, if a company fails to finish a prototype or secure a license by a certain date, the company must issue additional shares to the VCs (or accordingly change the preferred-to-common conversion ratio), giving the VCs a larger stake in the company without additional investment. On the bright side, such terms really motivate management to succeed.

Identifying good venture capitalists is not always easy these days. Because of the rapid proliferation of funds, there are many venture capitalists distributing other people's money who are not necessarily qualified to do so. Eventually, the ones who poorly invested their first fund may find that they cannot raise another and will leave the industry. Taking money from a poorly respected firm may prevent you from being able to raise money later on from the good firms. When selecting a VC, look for those with a successful track record of co-investing with other reputable VCs.

Some firms have a reputation for stringing a company along for months, professing a deep interest but without offering a term sheet and telling the company not to talk with other VCs. When such a firm finally decides not to follow through, the entrepreneur is left out in the rain, having lost valuable time. A company should agree to exclusive negotiations for a specified period only if a VC has put forth a term sheet. Otherwise, the company owes a VC no loyalty and should hold multiple discussions in parallel.

In other cases, venture capitalists develop reputations for being difficult and controlling. For example, when a company goes on to raise a second round of financing, an existing VC shareholder may insist on providing the additional funds. This type of deal is known as an "inside round" and only makes sense if the insiders are willing to match or beat terms offered by outside investors, who are in the best position to objectively establish fair value. Of course, if the company's current VC investors are unpleasant, other VC firms may not want to come on-board.

MEETING THE RIGHT VC

Venture capitalists receive thousand of plans each year, more than they can process, are focus on those that came in from trusted sources. More importantly, VCs often specialize in particular industries and, at any one time, are likely to prefer a company with a specific business model, technology, disease focus, etc.

Before you seek out venture capital you should have:

- A well-written, organized business plan.
- An Executive Summary, no more than 1-2 pages.
- A qualified scientific advisor.
- At least one business-savvy individual, ideally on your management team but possibly on the Board of Directors.
- An experienced and respected corporate attorney.
- An option or rights to key intellectual property.
- If applicable, a list of people who have agreed to join the company once it is financed.
- Answers to every question about any aspect of your product, technology, customers, competitors, business model, etc.
- Confidence to say, "I don't know, but I can find out", when appropriate.

After assembling all these pieces, you may find that you are already connected to VCs. At least your corporate attorney should be able to put you in touch with a few firms. A reputable technology licensing office can also have enough influence to get you in the door. Find an opportunity to meet CEOs of other biotechnology companies, possibly through your scientific advisors, technology transfer office, or local biotechnology industry organization. As fellow entrepreneurs, CEOs of small companies may be willing to give you advice and put you in touch with their VCs.

Once a VC has seen a deal, a clock begins to tick. The deal becomes "stale" over time. Do not blanket the VC industry with copies of your business plan. Most VCs may not even respond, but if you approach them after six months, they will assume that there is something wrong if you are still looking for money after all that time. Focus on several VCs at a time and if things do not work out after a few weeks, move on to new firms that have not yet heard of you. Even so, VCs are well connected and exchange information, so even the new firms may already know that you have been looking for capital unsuccessfully for some time.

Good VCs create trends rather than ride them. Still, if proteomics companies are making the news, venture capitalists will take notice and may consider that sector hot. To assess how "hot" your idea will sound, read biotechnology trade journals such as BioWorld and In Vivo. A university tech transfer office may subscribe to these publications. If nothing else, keep track of the latest news on BioSpace.com and sign up for the email bulletins issued by Venturereporter.net

PRESENTING TO VCS

An experienced businessperson on your team should lead the presentation since the central topic is usually the business model. A scientific founder's role should be

limited to discussing the technology and science. Keep in mind that both the people and the idea will be subject to careful scrutiny. *At no time should members of the presenting team interrupt each other or the investors.*

Keep it simple and clear. Too much glitz makes it look like you are masking a bad idea. The VC should already have a copy of your business plan and will probably have questions. You might simply be asked to introduce yourself and your idea informally before the VC starts asking questions. The presentation may become conversational, but never let down your guard because you are always being judged.

Though one should always put one's best foot forward, do not hide anything significant from the venture capitalist; they will dig deeper and discover if they had been initially misled. The success of one venture is not worth ruining one's entrepreneurial career by acquiring a reputation for dishonesty.

WHAT VCS LOOK FOR

Visit the websites of a few dozen venture capital firms to read what most of them want. By the tenth site, you will be able to recite the clichés by heart:

- Experienced management team
- Large and growing market, >\$500M.
- Proven technology or concept
- Intellectual Property
- Little or no competition.
- Attractive business model.
- Multiple exit opportunities: Sale or IPO – preferably within 5 years.

The management team is the most important element. Venture capitalists would rather invest in a great management team with a poor technology than a great technology with a poor management team. The rationale behind this philosophy is that a bad management team will mismanage a great technology whereas a great management team will figure out a way to make the company successful regardless of the starting technology. Investors won't like a scientist without business experience insisting on being CEO just because the company was his idea.

The VC's goal is to earn at least a 35% return overall for his fund, which might mean shooting for a 55%-65% return in case a few companies fail. A 55% annual rate of return means that the VC must expect a \$3M investment will be worth \$30M in five years. A company should appreciate these targets if they hope to appeal to a VC's bottom line.

"NO" DOES NOT MEAN "NO"

Venture capitalists hate missing a great deal. Consequently, their rejections are rarely absolute. They fear misjudging a company that will later make money for other firms. Bessemer Venture Partners has even compiled an amusing anti-portfolio of missed opportunities (www.bvp.com/port/anti.asp), proof that VCs are not without humor.

In the rejection, The VCs may say that your company's focus does not fit with their current strategy. However, "No" really means "Not now". They may suggest that the company strengthen its management or further develop an area of the business plan. Follow their suggestions and, when you think you have made important progress, make another pitch. Be politely persistent.

Because VCs may be indirect ("*The venture is promising but too early in its development for our firm, so please let us know when you are raising the next round.*"), some entrepreneurs may not recognize a VC's way of expressing disinterest. Entrepreneurs must be very careful not to misrepresent one VC's comments when speaking with other investors. Prospective investors can easily pick up the phone to figure out what their peers at other funds were really thinking when they turned the entrepreneur away.

KEY ISSUES

CALCULATING PRE-MONEY VALUATION

Pre-money valuations are mostly grounded in opinion, not fact. The quality of the technology, business model, and management team affect the investor's estimates of risk and future valuation, from which the investor back-calculates a pre-money valuation for the current round. Estimates are often so adjustable that, regardless of data, almost any number may be justifiable. Consequently, it all comes down to negotiation and leverage merely rationalized with subjective math.

For example, an investor who wants to invest \$3M will calculate how much the investment should be worth in five years in order to justify the risk. For a low-risk company, the investor may be happy with a four-fold return (\$12M). If it is a high-risk proposition, the investor may feel that only a 10-fold return (\$30M) would justify the risk. If the investor wants a ten-fold return (\$30M), then he will calculate how much of the company he would need to own now so he has \$30M worth of equity in five years. If the investor estimates that the entire company could be worth \$150M in five years based on the value of comparable companies, he would have to own 20% of the company five years from now to make \$30M. Because each round of financing dilutes the equity stake of all previous investors, these calculations can be somewhat complex. For example, the company's financing activity

in the coming five years will dilute current shareholders 2-fold, then our investor must own 40% of the company now in order to own 20% of the company 5 years from now. He will therefore value \$3M as equivalent to 40% of the company, and the other 60% will have an intrinsic value of \$4.5M. In this case, \$4.5M would be the investor's estimate of the company's current pre-money valuation. But if another credible investor offers to invest at a \$6M pre-money, the first investor might agree to match or beat the offer, if only because the other party's interest serves as external validation of the startup.

If a prospective investor feels a company is solid and that the entrepreneurs could easily raise money elsewhere, a five-fold return on \$3M over five years may justify the risk he feels he would be taking. Such a strong startup might have a projected valuation of \$300M in five years. The investor would only need to own 5% of the company in five years to recover \$15M and would have to own 10% today (assuming 2-fold dilution due to future rounds of financing). If 10% of the company is worth \$3M, then the other 90% is worth \$27M, a very attractive pre-money valuation for the founders.

However, some startups are of such a low quality that when the investor calculates how much equity it would take to make the investment worthwhile, the result is very high, maybe 90% or more. The founders and employees may be left with too little equity to remain motivated. Investing at a higher valuation might leave the entrepreneurs and employees with more equity and happier, but the investor might not earn an attractive return on his investment.

Share price is calculated from the valuation and number of shares outstanding at the time of the financing. If the founders have issued one million shares to themselves prior to financing and an investor gives them \$3M for 50% of the company, then the investor will be issued one million new shares (the founders do not transfer their own shares to the investor because they are not the ones receiving the money). The company now has a total worth of \$6M with 2 million shares outstanding valued at \$3/share.

DISCUSSING VALUATION

Investors are often straightforward in asking "What valuation do you have in mind?" Rather than set a starting point for negotiations, this question may be intended to discern whether the entrepreneur's expectations are realistic. If the response is astronomically high, the entrepreneur will appear naïve or delusional. Time is on the investor's side; after being rejected by enough investors, the entrepreneur will lower the valuation until it falls into investors' negotiating range.

Entrepreneurs should identify solid comparables that justify the valuations they ask for. Consider the environment in which those companies raised their rounds; financings done in 2000 are unreasonable comparables because most valuations were uncharacteristically high. If investors turn down a deal because of valuation, the entrepreneur should take the time to find out why the investors think their particular estimate is reasonable. The goal is to prepare for the next investor meeting.

Some investors value all seed-stage startups at under \$2M, regardless of the concept, IP, etc. Investors may expect these companies to raise a small amount of capital (\$1M or less) and prove that they deserve more money. If a biotech company justifiably needs \$7M, a reasonable valuation might be between \$5M and \$12M. If you try to raise less money, the valuation might drop. If you can prove you need to raise more than \$7M, the valuation might increase. It's not an exact science; at the end of the day, many early-stage biotech investors simply want to own 40%-60% of the company.

CASH AND SECOND CHANCES

Disappointing clinical results or other bad news can put a company in a position of weakness from which to negotiate additional financing. Raising money in a *down round* (i.e. at a lower valuation than the previous round) damages current shareholders through excessive dilution and hurts the reputation of the company by essentially announcing its failure to the world (since financing events draw the investment community's attention). Having a strong cash reserve allows a company to weather disappointments with minimal effect on current shareholders.

The shares of public companies trade daily. Therefore, the real-time effects of a public company's successes and failures on investor sentiment are constantly reflected by the share price. The share price of private companies, however, remains static between financing because shareholders are restricted from trading their shares. Therefore, if a private company falters, this mistake need not drive the share price down as long as the company can recover before it needs to raise additional fund.

TAKE THE MONEY

A company should raise as much money as possible when it can, not just when it needs it, because you never know when the opportunity to raise capital will come along. Investors, after all, can be fickle. One day they offer more money than you ask for and the next they may not offer any capital at all.

Management should select investors from the start who will be able and willing to invest in future financings. In bad times, these investors will be more likely to let the

company raised money in a down round since they will also have the means to buy shares at the lower price. Most VCs that participate in one round of financing will allocate additional capital for investing in subsequent rounds. Angel investors or small funds, however, may not take such a disciplined approach.

If investors exercise undue control either through negative covenants or board representation, they may prevent a financing from going through or may limit the amount of money the company may raise in a round. They may prefer that the company raise a little money now and then raise more after achieving milestones that may justify a higher valuation, thereby minimizing dilution. The burden of executing these multiple financings, of course, falls to management and may impede progress, particularly if the financing climate turns cold.

RENEGOTIATING FINANCING AGREEMENTS

While investors may negotiate all sorts of protection into their contracts, including aggressive anti-dilution provisions and board seats, once signed these contracts are not set in stone. During negotiation of a new financing round, the prospective investors may demand that all previous contracts be renegotiated before investing in the company. For example, new investors contemplating investing in a down round may demand that old investors forfeit their anti-dilution rights. The entrepreneur must then secure the signatures of all or a majority of the old investors (according to the agreement) indicating that they forfeit their rights. If a few shareholders would rather sabotage the financing than let the new investors have their way, they certainly have the power to do so.

The best way to avoid having prospective investors dictate financing terms is to negotiate from a position of strength, when the company is not desperate for capital and several funds are competing to invest.

CONVERTIBLE DEBT

An angel investor who agrees to provide \$100,000 in seed capital may not want to decide how much the investment is worth. Instead, the angel can provide the capital in the form of a loan that will convert to stock at the valuation established at the next round of financing. If a VC sets the share price of the next round at \$5, the angel will receive 20,000 shares.

However, by investing at an earlier stage, the angel has assumed greater risk than the VC. The angel should be compensated more generously and may stipulate that the \$100,000 loan convert at a 20% discount to the valuation established at the next round. If the share price at the next round is set at \$5, then the angel's \$100,000 is converted at \$4/share to 25,000 shares. In this case, the

angel receives 5,000 more shares than without a discount. If an angel requests an overly aggressive discount, subsequent investors may not appreciate having to split the pie unfairly and may be discouraged from investing.

Until it is converted into stock, the loan will appear as debt on the balance sheet. When negotiating convertible debt financing, verify that the loan does not need to be repaid if the company fails to close a next round. Instead, the agreement should stipulate a default valuation at which the loan will convert into preferred shares after a certain period of time. Though default conversion will favor the angel investor, it will, at least, remove the outstanding debt from the balance sheet.

BOOT-STRAPPING

"Boot-strapping", the concept of pulling oneself up off the ground up by the bootstraps, refers to the practice of funding a startup directly with the cash generated from sales, a practice rarely seen in the biotechnology industry. Most biotech startups do not have revenues in the first year but must still invest significantly in equipment, space, licenses, and human resources. Bootstrapping may be feasible in the rare instances when a customer is able to pay up-front for a product or the entrepreneur is able to self-finance the startup (e.g. using bank loans) until it can generate cash from sales.

LOANS AND VENTURE LEASING

Banks will usually extend loans only to companies that already have assets and cash-flow. Unless you are willing to mortgage your house and invest your personal funds into the company, getting a significant bank loan will be almost impossible at the seed stage.

Some banks have venture leasing programs that lease equipment to companies in exchange for equity and interest payments. Startups eager to conserve cash may find venture leasing an effective way of leveraging a small amount of equity to get access to expensive equipment. For example, a startup that has recently raised money at \$5/share may lease \$1M worth of equipment in exchange for warrants to purchase 20,000 shares at \$5/share (\$100,000 of equity + regular lease payments). For more information on this, read more about debt funding in the **Accounting & Finance** chapter.

INCUBATORS

Incubators are firms that provide a mix of resources and funding that startups need to grow into self-sufficient companies. Traditionally, they provide space, shared administrative staff, office equipment, possibly seed financing and interim management, and business expertise, all in exchange for fees, equity, or both. Incubators may manage multiple startups at any one time.

There were only a handful of incubators in the 1980's, many of them government-affiliated non-profits dedicated to promoting small business growth in a particular region or state. With the economic boom of the mid-late 90's, the number of (mostly for-profit) incubators exploded. Most focused on internet companies, claiming that they could turn an idea into a public company. On average, these incubators took a 35% stake in the company in exchange for space, shared equipment and staff, and advice. After the 1999 stock market crash, many of these incubators had to close or change their business models.

Biotechnology incubators also have a sordid past. The Massachusetts Biomedical Initiative (MBI-www.massbiomed.org) started off as an organization that incubated companies in its Worcester facility and provided seed funding. MBI burned through its cash reserves before its investments could generate revenue; the resulting financial crisis was typical of what spurred many incubators to change the way they operated. These days, MBI is considerably more cautious and rents out its space to paying companies.

Present-day incubators have a reputation for picking only the best startups and then taking equity at low valuations with aggressive anti-dilution provisions that make it difficult for the startup to raise a next round. There is a belief that most companies that are accepted into an incubator are probably good enough to get VC or angel financing and operate independently right from the start. On the flip side, incubators that lack the experience and credibility to attract high-quality companies may stigmatize those companies they do manage to recruit.

The term 'incubator' is no longer popular. Instead, Venture Creation Firms and Startup Accelerators have taken their place. In some cases, the euphemistic name masks the same old incubator concept. In other cases, these firms take a more sophisticated approach to starting and growing companies. Whether the newer incubator models will succeed where so many others have failed remains to be seen.

GOVERNMENT GRANTS

Betsy M. Ohlsson-Wilhelm, Ph.D. and Katharine A. Muirhead, Ph.D.

SciGro, Inc.

The Small Business Innovation Development Act of 1982 requires that federal agencies with R&D budgets in excess of \$100 million set aside a percentage (currently 2.5%) of their extramural research budget to fund innovative research in small businesses. Though grants are available from a variety of agencies including state governments, local governments, and foundations, by far the largest amount of money to support biomedical research is available through federal programs, primarily the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, associated with the National Institutes of Health and the Department of Defense. The NIH operates one of the largest SBIR/STTR programs focusing on biotechnology and biomedical products.

Many other governmental agencies also have SBIR/STTR programs but may differ in the number of solicitations (i.e. calls for applications) per year, deadlines for receipt, guidelines for money and duration of each phase, adherence to guidelines, and the number of awards possible per company prior to commercialization of a product. The DoD maintains a commercialization index; if your company does not make good use of its SBIR funds, it will not get more. The DoD SBIR program strives to achieve an 80% commercialization rate for those products that receive support.

Grants are in theory an attractive way to obtain seed funding without having to distribute equity. Grant applications take time to prepare and there may be a lag time of 6 to 9 months from submission until receipt of funds. Once the funding comes through, the company is restricted to following an approach it may consider out-of-date (since startups change their direction frequently). A company should carefully assess whether or not to include grants as part of its fund-raising and business development strategy. The most critical goal for a small business is getting its first product to market.

Before applying for government grants, consider the following key questions:

- **Is the proposed work a critical path activity?** Would the company carry out the proposed work even if no grant funds were available?
- **Will the proposed work shorten the time to market for the first product?** Could the company solve a technical problem faster if it had more money? Keep in mind that some solutions require more time rather than more dollars.

- **Will the funds arrive in time?** What is the time frame in which the company needs the money to do the work? Does the company's need match the timeframe in which money would be received if the grant application were funded? Would it make more sense to seek funding for a project later in the product development plan?
- **What is the chance of success?** Is the company a competitive grant applicant? Most grant programs receive many outstanding applications; keep in mind that you are competing with companies that have up to 500 employees and established track records.
- **Can we afford it?** Can the company afford the time, resources and/or missed opportunities that writing a successful grant application and managing the interaction with the granting agency will cost? Even the simplest grant application will require ~1 person-month to prepare and administer.

Winning a grant does not substitute for getting a product to market. Business conditions and priorities change, sometimes very rapidly. It is possible that doing the project in the way you proposed when you were writing the grant is no longer in the best interests of the company by the time the grant is awarded. If this occurs, you must be prepared to grit your teeth and decline the award.

Many of the committee members who review your grant application are academicians, who may or may not recognize that good science is necessary but not sufficient for making good products. Therefore, well-reviewed grants do not substitute for the money and advice coming from real investors or corporate partners.

HYPOTHESIS VS. ENGINEERING APPROACH

Grant applications are typically either hypothesis driven or follow an engineering approach.

Hypothesis driven grant applications identify questions/unknowns critical to product development. The usual approach is to form a testable hypothesis with quantifiable outcomes. One then tests the hypothesis experimentally, using appropriate methods and controls. Results are analyzed and interpreted and any new unknowns critical to product development are identified. This process is then repeated until all critical unknowns are identified and under control. It is important to identify the minimum information needed to proceed to the next phase of product development. If the company is seeking general scientific, rather than product specific, information to extend a platform technology, it should

apply for an R01 grant, the same program that supports basic research at universities and other research institutions. Companies are eligible for many programs supported through the R01 mechanism; information on R01's can be found at <http://www.nih.gov/funding>.

The engineering approach is commonly used with medical devices. In this case, an innovative and practical solution to an important unsolved commercial problem is presented, target performance specifications are set, and a novel prototype is developed. The prototype is then tested against the proposed target specifications and improved until the target specifications are met. Again, the company should be clear as to what the minimum performance specifications are to allow the company to proceed to the next phase of product development. Perfection can exact a tremendous opportunity cost.

Most granting agencies require that the proposed research be truly innovative, either scientifically or technically. They are not interested in funding development of "me too" products. If you are developing the n^{th} beta-blocker -- don't bother applying. Abstracts of successful awards can be found in the CRISP database located at <https://www-commons.cit.nih.gov/crisp/>.

UNCLE SAM AS AN INVESTOR

The government is interested in catalyzing commercial development of novel technologies and prototypes, new products and services, new knowledge, and new businesses. It accepts its return on investment in the form of taxes, both corporate and personal, rather than equity. The government, therefore, is a patient investor that adds value without diluting equity. In addition, the grant programs provide free due diligence for third party investors, as well as leverage for investor and/or partner capital. The government does retain limited intellectual property rights (so-called "walk-in" rights), to be exercised only if your company is unwilling or unable to provide the product at a rate consistent with national needs.

In fiscal year (FY) 2002, the NIH made SBIR grant and contract awards totaling \$484M. Data on SBIR and STTR awards can be found at

<http://grants.nih.gov/grants/funding/sbir.htm#data>.

SUMMARY OF GOVERNMENT PROGRAMS

For quick facts about the different programs listed here and lists of relevant web links, visit <http://www.evelexa.com/startups/grants.htm>.

SBIR PROGRAM

The NIH SBIR Program offers two stages of grant support to small companies. Phase I SBIR grants are intended to support rapid determination of initial

feasibility, allowing the company and the grant program to determine whether a particular product warrants further investment. Phase I grant guidelines are for a maximum of \$100,000 and a maximum period of six months; however, most agencies are willing to consider well-justified requests for larger amounts of money and longer periods of time. If you obtain a Phase I SBIR and successfully meet the objectives you described in your application, you may apply for a Phase II grant, for which the guidelines are a maximum of \$750,000 over a two-year period. The goal in Phase II is to move the product into the market or at least to a stage of development where the company can attract enough capital from investors or partners to complete commercialization.

To qualify for an SBIR grant, the company must be American owned (>51%), independently operated, have a principal place of business on U.S. soil, control its own research space, have less than 500 employees, operate as a "for profit" entity, and be able to carry out innovative research. This means that the company must employ well-qualified investigators and less than 30% of the work (based on the dollar amount spent) can be outsourced in Phase I and less than 50% can be outsourced in Phase II. The company must employ the principal investigator (the person listed as PI on the grant) more than half time during the award period.

If the proposed principal investigator is based at an academic institution, many companies get through the Phase I portion of an SBIR by taking advantage of the fact that many universities have only nine-month faculty appointments, technically giving investigators the summer off. If the company proposes slightly less than six months worth of work during Phase I, an academic principal investigator can be employed full-time for three months during the summer, resulting in >50% employment by the company during the Phase I award period. Universities vary in their reactions to this type of scheme. Some Universities have implemented programs that allow their scientists to take a leave of absence and rent their own space and equipment from the University for use by the company. Be sure to inquire about the policies at an academic founder's institution. If they are not compatible with the SBIR policies, you should consider applying for an STTR grant (see below).

Make sure that your business/administrative people know up front that a variety of assurances will be required when dealing with the federal government. Useful information on such assurances is provided on <http://grants.nih.gov/grants/funding/welcomewagon.htm>.

Assurances will be required regarding the following topics: Human Subjects Vertebrate Animals; Debarment and Suspension; Drug-Free Workplace; Delinquent Federal Debt; Research Misconduct; Civil Rights; Handicapped Individuals; and Age Discrimination. If your company

will be working with human subjects, you will have to comply with new NIH policies regarding education of investigators proposing to use human subjects. See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html> and http://grants.nih.gov/grants/policy/hs_educ_faq.htm

In addition to awarding to grants, some programs also offer SBIR/STTR contracts for particular projects. When applying for a contract (as opposed to a grant), applicants must respond specifically to a research topic described in a solicitation. The latest listing of open SBIR contracts may be found at: <http://grants.nih.gov/grants/funding/sbir.htm#sbir>

STTR GRANTS

An STTR grant funds a collaborative effort between a company and an investigator at a university or research institution. The university/research institution personnel must perform >30% of the research, the company must perform >40% of the research, and up to 30% can be outsourced during Phase I. Eligibility for STTRs is very similar to that described above for SBIRs. The major difference is that the principal investigator does not have to be employed by the applicant company at the time of or during the course of the award. Documents detailing the assignment of intellectual property must be in place so that there will be no confusion over patent rights.

STTRs can be very useful because they bring technology and expertise out of research institutes and into a company while still involving the inventors in the development phase. The STTR funding pool is much smaller than that for SBIRs, and the application is more complex because of the requirement for a budget from the research institution as well as from the company. In 2002, the NIH awarded STTR grants totaling \$30M.

FAST TRACK

Some SBIR/STTR programs allow companies to apply for both Phase I and Phase II grants at the same time, eliminating the 6-9 month gap between Phase I and Phase II awards. Clear, measurable milestones for moving from Phase I to Phase II are key to success and "third party" matching dollars may be required (true of DoD, but not NIH; check with target agencies).

Department of Defense (DoD): DoD primarily funds projects developing military hardware though also includes some biomedical topics. The DoD generally puts out two SBIR/STTR solicitations per year. The Army, Navy, and other branches of the armed forces participate. This program is somewhat different from that of the NIH as the intent is to develop suppliers for the armed forces. Only proposals responsive to the stated research topics are accepted and the topics change for each solicitation. Typically 3 SBIR Phase I awards are made (\$70,000 each) for each topic and a single Phase II award follows.

Frequently, if the Phase II work is successfully accomplished, a contract will be awarded to the company.

NIST/ATP: The National Institute of Standards and Technology (NIST) manages the Advanced Technology Program (ATP), which awards grants to support the commercialization projects that have a high degree of technical risk but an obvious and rapid path to market once the technical hurdles are overcome. In addition, the product being developed must have the potential to significantly impact the US economy; companies developing niche products need not apply. The program funds research on enabling technologies but does not support subsequent product development. Applicants must include a detailed business plan for bringing the new technology to market once technical milestones have been achieved under ATP support.

Up to \$2 million for 2 years may be awarded to an individual company, but the company must be able to match this funding either with cash or in kind, making ATP grants more appropriate for emerging companies than very early startups. This program has been criticized in the US Congress as "corporate welfare" because large well-established companies and consortia can also apply. There are periodic threats to kill the program, but it has had significant successes and has many supporters. It is worth monitoring this program if your company's technology might qualify for an ATP grant.

SPECIAL PROGRAMS

A variety of specific program announcements (PAs) and requests for proposals (RFAs) are made each year and an increasing subset of these utilize both R01 and SBIR/STTRs as the mechanism for funding. PAs are best found by monitoring the NIH's website for special announcements of small business research opportunities: http://grants.nih.gov/grants/funding/sbir_announcements.htm.

STATE/LOCAL ECONOMIC DEVELOPMENT PROGRAMS

Although it would be impossible to cover them all here, most states and many local governments also have various types of grants and/or low-interest loan programs intended to support the growth of small businesses. In general, the amounts of funding available from these programs are relatively small (\$50,000 - \$500,000), and not all of them are appropriate for early startups. It is always worth checking how you might be able to use these programs to stretch investor capital or federal grant money. For instance, Pennsylvania's Ben Franklin Technology program requires matching funds (which can come from an SBIR grant) but will pay for items not eligible for SBIR funding such as market surveys or patent preparation and filing. California has a program in which SBIR recipients can receive additional matching money from the state. Non-profit and charitable foundations

may also be a source of grant funding, particularly for projects that the company has outsourced to an academic collaborator's laboratory.

TIPS ON GRANT WRITING

The NIH provides a variety of tips on the home pages of its various institutes as well as on http://grants.nih.gov/grants/grant_tips.htm. It has also provided a model SBIR Phase I grant application: <http://www.nhlbi.nih.gov/funding/sbir/modelsbi.htm>. A set of DoD SBIR samples are also available at: www.acq.osd.mil/sadbu/sbir/contracts/contract.htm.

Writing successful grants is not something that can be done in 24-hours by cutting and pasting from the business plan. Key questions that must be addressed include:

- What is the product/service being developed? Note that a "platform technology" is NOT a product.
- Are your technology and product innovative?
- Who are the customers and what is the product's commercial potential?
- What innovations are required for success?
- What is the commercialization timetable? Be sure that the timing of the award fits with your business plan.
- Are there significant competitors and why is your company best suited for executing the project?
- Are your key personnel qualified and facilities/resources adequate?

Once you have identified the specific product for which you are seeking funding, it is important to check the interest areas listed in the free solicitation documents on the websites of potential target agencies. If you find what appears to be a match, e-mail and/or telephone the listed contact to discuss your plan and see how it might fit with the goals of the funding agency.

You need to sell the importance of your work, but be realistic with the research plan. Clearly state what you expect to accomplish, when it will be finished, and the metrics by which your success or failure may be gauged objectively. Define the contributions of the key personnel involved with the project. Be sure that your timeline and financial budget are reasonable; the grant application must demonstrate your ability to manage the project. It is also important to follow exactly the format specified by the soliciting agency, e.g. <http://grants.nih.gov/grants/forms.htm>.

Good grant applications usually include a contingency plan at each stage of experimentation, in case things don't work exactly as you anticipate. The application must convince the reviewers that you are well-informed and that you will be able to deal with any unexpected results

effectively. Make sure to get an objective review of your application before submitting it.

GETTING OUTSIDE HELP

National conferences hold seminars to instruct small businesses about the preparation of SBIR and STTR grant applications and to facilitate networking with representatives of target agencies. A list of upcoming conferences can be found at <http://www.zyn.com/sbir/>. If your company decides to include grants as part of its funding strategy but lacks prior experience with grant writing or sufficient scientific staff time to write and edit the entire application, you may increase your chances of success by using outside consultants. A variety of firms provide supporting services ranging from simply providing forms and instruction packages for specific programs to drafting applications based on scientific input from clients. Compensation may include a non-refundable flat fee, hourly fees, and/or a success fee proportional to the size of the award.

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About SciGro, Inc.

SciGro, Inc. offers technology assessment and scientific management services for the pharmaceutical, biotechnology and diagnostic industries. SciGro has a demonstrated ability to communicate new concepts to investors and granting agencies, having written dozens of winning SBIR/STTR grant applications on behalf of clients. For more information, visit www.maconsultants.com/scigro.htm.

IPO: GOING PUBLIC

The Initial Public Offering (IPO) is sometimes considered the coming of age for a growing company. With only a tenth of biotech companies in the US trading publicly, however, not every company will do an IPO. The average biotech company that IPO'd in the 1990's was 5 years old and had raised a total of \$25M before going public at a pre-money valuation of \$75M-\$100M. The exception was the class of 1999-2000, which, after raising an average of \$50M, did initial offerings at an average pre-money of \$300M. Some of the reasons why the genomics bubble of 1999-2000 deviated from the norm are discussed below.

Instead of examining the IPO in isolation, consider it merely another financing event; the public market is just another source of funding and, once a company's stock trades publicly, it must still conduct business as usual. The benefit of becoming a public company is that all the shareholders that got shares prior to the IPO are able to sell their shares on the open market (once the mandatory 180 day lock-up expires). Furthermore, being public facilitates subsequent fund raising because companies have a wider range of options: sell more stock to the public markets (secondary offerings), sell stock to private equity funds (Private Investment in Public Equity – PIPE), or do a convertible debt offering. The downside of being public is having to address the concerns of hundreds and eventually thousands of shareholders and analysts, requiring intense Investor and Public Relations (IR/PR). Public companies also face more complex accounting and auditing obligations. Management can find these new responsibilities distracting.

The IPO is mediated by an investment bank, a.k.a. the underwriter, which negotiates with public equity funds to purchase the newly issued shares. The funds will typically sell some of those shares in the “aftermarket” to eager investors who did not have a chance to buy the shares in the IPO. The investment bank underwriting the IPO will often try to price the shares such that the initial buyers will be able to sell them at a higher price in the aftermarket. Therefore, the IPO is driven by demand from the large funds, who, in turn, try to be attuned to the buying interest of the investment community at large.

The balance between investor optimism and pessimism is tipped by many factors other than the fundamental strength of companies. For example, underwriters must wait for rising markets and periods of liquidity (when investors are buying/selling stock in large volume) to ensure that prospective buyers of the IPO shares will be able to later sell the shares for a profit. When all the variables are aligned and companies begin to IPO, the IPO *window* is said to be open. However, the duration that a window remains open is determined by how the

newly IPO'd stocks perform. If these stocks fall, large funds will stop participating in subsequent IPOs, thereby shutting the window. Investment banks try to make sure that the strongest companies IPO before the weaker ones during any given window.

HISTORY OF BIOTECH IPOs

The first biotech IPO was in 1980; Genentech raised \$35M at a post-IPO valuation of \$250M. The stock nearly doubled in the first day of trading. Cetus followed in 1981 with a spectacular \$120M offering at a valuation close to \$500M. But the average biotech IPOs of the 1980's were decidedly more conservative; companies typically raised less than \$30M with post-IPO valuations of \$100M during the windows of 1983 and 1986-7.

During the windows of 1991 and 1995-6, more companies went public than in the 1980s. The total raised in biotech IPOs in 1995-6 was almost \$2B, more than double the \$900M raised from IPOs and secondary offerings in 1986, though the average size of a biotech IPO still remained about \$28M. The 1997-1998 window was particularly inhospitable for biotech financing in general, due in part to major financial crises around the world. Yet biotech also had itself to blame when platform companies conceded that they would not be able to secure enough revenues from collaborations to become profitable.

What revived investor enthusiasm in 1999 was a combination of hype around the sequencing of the genome and recently enriched hi-tech investors betting that biotech would be the next big wave. Billions in capital migrated to biotech in search of nascent Amgens.

Tularik's IPO in October 1999 marked the beginning of a spectacular period of public financing for biotechnology. Because the company had raised a lot of capital prior to its IPO, concomitantly increasing its valuation to roughly \$400M, the IPO was priced slightly higher; Tularik raised \$100M at a post-IPO valuation of \$500M. More than 60 IPOs followed in the next 14 months, averaging \$85M at a post-IPO valuation of nearly \$400M.

There were three drivers underlying the tripling of IPO values in 1999-2000: the sellers (VCs and companies), the buyers (public equity investors), and the investment banks. Venture capital funds grew in size throughout the 90's and needed to put more money to work with each investment. With the VCs' generous support, startups expanded their operations without regard for revenue, increasing their burn rate. Because companies often try to raise 2-3 years of cash in an IPO, higher burn rates necessitated larger offerings. Companies try to sell no

more than 25%-30% of their stock in an IPO, and raising more money means increasing the valuation. A company that burns \$30M a year and wants to raise \$75M in an IPO by selling only 30% of its stock would need to have a post-IPO valuation of \$250M.

Public equity funds also grew significantly and needed to put larger chunks of money to work without ending up with too large a stake in any one company. If you want to invest \$20M into a company without owning more than 5%, the company would need to be valued at \$400M, not \$100M. Consequently, companies that reached a certain valuation threshold, probably around \$300M, enjoyed the attention of many more funds, whose interest sustained and even further inflated valuations.

The investment banks, working on commission, were certainly in favor of larger IPOs. Sell-side analysts could generate more business for their brokerages because larger valuations meant more liquidity and more shares being traded on commission.

Ultimately, just because the sellers, buyers, and investment banks benefited from uncharacteristically large valuations did not mean that these valuations were deserved. Valuations are derived from earnings, and reasonable projections failed to justify the bubble valuations of 1999-2000. As this realization dawned on investors, their optimism wavered and stocks fell.

Talk of an IPO window wouldn't resume until the end of 2003. Yet when the first of the companies, Acusphere, completed an offering in October of 2003, its stock tumbled by over 25% within a matter of weeks, casting a pall over the market. Several companies announced postponement of their plans to IPO while others pushed forward but lowered their issue price, raising less money than they had hoped.

IN THE AFTERMATH OF THE BUBBLE

In the aftermath of the genomics bubble, a stringent set of challenges facing investors, banks, and companies alike have raised the bar for companies considering their IPO.

With the increased-regulation of the investment banking industry that followed the bubble, Wall Street became more conservative and sensible. While there had long been a Chinese wall between bankers and analysts, the wall gained substance once the SEC called for increased compliance. Consequently, banks can't promise favorable analyst coverage to prospective investment banking clients. No longer beholden to the investment bankers, analysts can be more open about their real opinions on companies. One need only look at how much more often analysts assign SELL ratings to weak companies instead of using the traditional HOLD euphemism. Analysts almost never issued the SELL rating in the 1990s. Unable to

leverage the reputation and celebrity of their respective analysts, investment banks compete with one another on the quality of their services.

Investment banks consistently charge fees of 6-7% for underwriting public offerings, e.g. a \$75M offering generates \$5M in fees. The larger a bank, the less meaningful are a few million dollars in fees and the larger an IPO must be to justify the bank's involvement. Raising \$75M by selling no more than 30% of the company requires a post-IPO valuation of at least \$250M.

Market interest and analyst coverage are also important variables affecting the likelihood of a company going public. Investors want to know when they buy newly issued stock that there will be analyst coverage to stimulate interest in trading of that stock. Since the transaction divisions of an investment bank cannot force analysts to pick up coverage, the companies have to actually merit analyst interest on their own. An important question, therefore, is what qualifies a company for analyst interest.

Banks earn commissions by executing trades for their investor clients. Investors, in turn, have a history of trading through those investment banks whose analysts provide them with good research and guidance. Before an analyst will initiate coverage of a company, the analyst may consider whether the company is likely to attract enough interest from investors that it will generate decent commissions for the bank. Large institutional investors, who generate most of a bank's commissions, may put millions of dollars to work with each investment decision and therefore prefer stocks with enough liquidity to accommodate such large transactions.

The larger a company's valuation (a.k.a. market capitalization), the more liquid its stock tends to be. Word on the street in 2003 was that a company had to have a valuation of \$300M or higher to motivate investment banks to underwrite the IPO. More specifically, a company with this valuation would likely do an offering large enough to generate worthwhile fees for the investment bank and would generate enough trading volume to justify analyst coverage.

EXIT STRATEGY

The conclusion of all this reasoning is that an entrepreneur should plan on growing a company to a valuation approaching \$300M before expecting to IPO. Biotech companies with late-stage drugs addressing significant markets may achieve such valuations 5-8 years after startup, but few tool/service companies can hope to do so this quickly. Depending on the nature of the company, suggesting that investors anticipate an IPO may come off as unrealistic and even flippant.

NETWORKING

Considering how vast the business world is and how little expertise any one person is capable of amassing, one's worth can be approximated by the size (and quality) of one's network. *In business, you are only as good as the people you know.* It seems such a harsh, cynical statement, robbing each of us of the credit we deserve for our personal accomplishments. Yet, forming complex companies (as opposed to small businesses) requires knowledge, stamina, and capital in excess of what any individual can offer. People who know how to work in teams and leverage their networks are more likely to succeed than individualists.

Networking is more than just collecting business cards at cocktail parties. Networking means getting to know someone well enough to spot opportunities for collaboration when they arise. People have to identify each other's skills and needs.

For scientists, rumored to be riddled with social phobias, networking is far easier than they may imagine. The academic environment is a breeding ground for

collaborations and new relationships. If you do not know any entrepreneurs or investors, ask your institution's technology licensing office to introduce you to a faculty member who may have such experience and/or connections. Conferences are about meeting new and old acquaintances, so spend time in the corridors mingling instead of just attending seminars. The people you meet may someday be your colleagues, investors, employees, advisors, co-founders, and competitors. When you finally decide to change career paths or form a company, it will be too late to start networking.

Knowing someone involves more than remembering their face and name. Well-networked people have the discipline to use a database to record not only contact information but also details about the person and the circumstances of the meeting (when/where/who else was there). They find opportunities to interact with the same people on multiple occasions. Like a finger-drawing on a fogged window, a network must be traced and retraced or else it disappears.

The Guide is dedicated to my parents, Alexander and Evelina,
who have set for me the highest example of integrity, creativity, and diligence.