CHALLENGES IN A BIOTECH STARTUP

HEALTHCARE NUTS

HIMT 453
Fall, 2006

Aravind Durai

Bin Li

Sunil Metkar

Monica Pelayo

Natasha Phillips

EXECUTIVE SUMMARY

Biotechnology refers to the large and growing array of scientific tools that use living cells and their molecules to make biological products for many different industries. Human and animal health care, agriculture, forestry, environment, and specialty chemicals are among the industries that have benefited most from biotechnology. The economic promise of biotechnology is extraordinary. At present a $60 billion sector worldwide, it is estimated to become a market of at least $120 billion annually within 10 years. Although this is a high-growth sector, moving a promising research discovery to market is a complex, costly and challenging undertaking.

In this paper we have identified and addressed challenges that are unique to a biotechnology startup. The approach used to compile the information included a combination of interviews with Chicago-based bio-entrepreneurs and research using industry journals, business databases and newspaper articles.

The challenges of starting a biotechnology company in the US include raising capital, building strategic partnerships, recruiting, motivating and retaining top scientific talent and compliance with regulatory bodies. Running a biotechnology company entails challenges in manufacturing, sales and marketing, reimbursement and several other managerial challenges. The goal of this paper is to serve as a high-level guide to an entrepreneur planning to venture into the biotechnology sector.

TABLE OF CONTENTS

The three pillars for any startup company include management, technology and capital. Our analysis assumes that the startup has an experienced management team and scientific board of advisors in place. A second assumption is that a startup has a great technology and associated patents (intellectual property). We also assume that a startup has Freedom-to-operate (FTO) i.e. it is free of third party patents. Given these conditions, the following are the challenges a bio-entrepreneur will face when starting a biotechnology company.

CHALLENGES IN RESEARCH AND DEVELOPMENT (R&D)

All biotechnology (biotech) companies face monumental managerial challenges in the R&D arena. R&D is costly and often the greatest expense in bringing a biologic drug or product to market. Biotechnology research is often times more complex than traditional pharmaceuticals because researchers may not know for years what forms their products will take. Despite these significant obstacles, management at a biotech startup company faces additional challenges. Management must find the perfect balance between cutting-edge science and good commercialization opportunities. Not all great scientific ideas have commercialization potential with measurable outcomes, and a successful management team must have a way to ensure that the scientific staff is working on the one or two products that will help the company prevail. Often times a stellar scientific group has a large set of potentially great novel molecules or products. Big pharma and the established biotechs have the luxury of experimenting with many options to find a blockbuster, but startups have the difficult task of selecting one or two - at the most - to focus on. Management has the exciting and arduous task of marrying the discussions between the scientific and sales and marketing teams to decide on the best molecule or product to focus on. As LeAnne Tourtellotte of Maroon Biotech stated, “One of the keys to our success has been the existence of an excellent board of directors and scientific advisory board. These two groups have worked together intensely to unite our scientific and business strategies in order to achieve key strategic goals. If they had not, we would not be here today”.

CASE STUDY – MAROON BIOTECH

Interview with LeAnne Tourtellotte COO – Telephone interview 11/20/2006

Marrying Funding and Commercial opportunities with distinct Science is the challenge

LeAnne believes that a biotech startup must have fabulous science and a great board of directors but funding is one of the main concerns. She pointed out that the success rate of obtaining Venture Capital (VC)/Angel investor funding is currently lower than those of NIH grants (about 14%). Many federally funded Small Business Innovation Research (SBIR) and Small Business Technology Transfer Program (STTR) grants have success rates ranging from 8 to 20%, with the additional benefit of constructive feedback. This constructive criticism can be utilized to make a more marketable pitch to a VC in the future. In addition, a biotech startup with a technology platform can utilize it for contract research, bringing in additional capital (albeit small).

A well-rounded board of directors and scientific advisory committee is a very important asset for a startup, according to LeAnne. The startup can benefit immensely from the experience that a diversified team like this can bring to the table. She believes that location is very important and so is the presence of a technology incubator whose administrative staff can provide unique networking opportunities.

LeAnne mentioned that is very important for the Founder scientists to remain involved in the startup in order to keep the scientific staff motivated. Equity offerings are also one way to retain top scientific talent.

LeAnne also mentioned that biotech startups should join organizations such as IBIO. Being part of a group like this will help a startup deal with issues like public perception and networking, areas that are important but would not necessarily be a foremost concern for a startup with limited resources.

Biotech startups are no more or no less successful than the pharma giants and well-established biotech companies when it comes to the development of a drug. According to industry standards at the present time, 8 out of 10 drugs will fail in clinical trials[1]. However, for biotechnology startups the stakes are even higher. Large companies have many successful products on the market. A biotechnology startup continued existence depends on the success of the one or two products. Therefore, failure is much more public and highly scrutinized. It leaves investors and the public with little to no incentive to remain supportive of the company.

An additional managerial challenge that biotech startups face is the protection of their intellectual property (IP) in the pipeline. All biotech companies must protect their most valuable asset, IP. However, startups have the added challenge of very limited resources and knowledge to effectively do this[2]. Unverified and unprotected IP can have disastrous effects, not only for the survival of the firm, but also for obtaining funding from investors. LeAnne Tourtellotte addressed this issue with the following comments: “The learning curve for a biotech startup in this arena is steep and difficult.

A startup has to be willing to hire patent and regulatory consultants to help with these issues early-on in the process. You can't do it correctly the first and second time on your own."

Consequently, overcoming the managerial challenges related to R&D may seem impossible for a small biotech startup. However, solutions exist. One approach is to consider mergers and acquisitions with other biotech startups. Consolidation with a complementary company can provide much needed capital for R&D as well as added value for both firms without the downside of having to sell equity and opportunity to big pharma or a large biotech.

It is important to focus research to increase throughput of successful products and to consider outsourcing some of the development to foreign countries where some of the big players have already established operations, such as India and China.

CASE STUDY – GENENTECH

*Interview with **V**ishwa **D**ixit, Assistant Vice-President of Research – Conducted at Genentech, South San Francisco, CA, 11/3/06.*

Attracting and Retaining top talent is key

For a mature biotech company like Genentech, one major challenge is to attract and retain top scientific talent. The Postdoctoral Program at Genentech has become one of its strongest assets in this respect. Genentech researchers have consistently published at a rate of 150+ papers per year and have secured over 6,100 current, non-expired patents worldwide (with 5,400 more pending). Genentech's research organization combines the best of the academic and corporate worlds, allowing researchers not only to pursue important scientific questions but also to watch an idea move from the laboratory into development and out into the clinic.

According to Dr. Dixit, up to 80% of future scientific projects are decided from the grass roots level-up (bottom-up) rather than top-down (the flow of ideas is from researchers to management not the other way around), which happens in big pharma 90% of the time. This helps keep motivation levels very high and align the Scientist's research interests with those of the company.

CHALLENGES IN RAISING CAPITAL

Seed Capital conundrum

Another key challenge for a biotech startup is raising capital. Venture capitalists (VCs) and angel investors, long considered the traditional startup investors, have been pulling

back from seed rounds (see Table 1), just as biotech startups need more money than ever to get off the ground[8,9]. Although angel investors are increasingly attracted to biotech deals, they are investing larger shares of capital into later rounds.

	1999	2000	2001	2002	2003	2004	2005 YTD
Seed round	$8	$32	$35	$29	$6	$21	$8
First round	$579	$1,180	$966	$841	$576	$910	$649
Second round	$613	$982	$1,148	$1,133	$949	$1,587	$658
Later stage	$467	$1,905	$1,033	$947	$1,697	$1,694	$1,074

Source: Dow Jones/VentureOne

Table 1: Venture capital for biopharmaceutical companies by round class ($ millions)

Seed round is the riskiest and both of these investor groups are increasingly risk averse. Seed investments represented only 0.03% of the venture capital funds invested in biopharmaceutical startups according to San Francisco-based Dow Jones VentureOne. In the late 1990s and the first few years of the 2000s, about 80% of angel investments were dedicated to seed funding. In 2005, however, only about half of the total angel investments went to seed rounds. Indeed a significant worry is that the growing seed funding gap may ultimately stifle biotech innovation.

CASE STUDY – PRECISION BIOMARKERS RESOURCES

*Interview with **E**ric **B**remer CSO and **D**avid **P**aul, President – Conducted at Precision Biomarkers Resources, Evanston, IL 11/14/2006*

Biotech is suffering from the Dot.com era

Precision Biomarker Resources is a startup biotech contract research organization (CRO), providing automated, high-throughput micro array services for pharmaceutical, biotechnology and academic researchers. It was incorporated in January 2006 and started operations in July 2006.

Since Precision is an “atypical biotech startup” (CRO) and not a “high-risk, high-reward investment”, but a “steady-stream of revenues” model, it was unattractive to VCs. Their main source of startup capital was leveraging personal holdings (of the management) against bank notes. Dr. Bremer feels that the biotech industry is suffering from the Dot.com bust when it comes to finding capital, owing to financiers becoming risk-averse.

Dr. Paul feels that their main challenge is “Name recognition”. To this end, their marketing efforts are focused on presentations at various national and international scientific conferences / meetings to raise the awareness of the company.

Small business grants (Small Business Innovative Research - SBIR and Small Business Technology Transfer – STTR) from the federal government have traditionally been a source of capital for biotech startups. SBIR and STTR encourage small business to explore their technological potential, provide the incentives to profit from its commercialization and expand funding opportunities in the federal innovation research and development arena.

Various federal departments and agencies including Departments of Agriculture, Commerce, Defense, Energy, Health and Human services and Homeland security, are required by SBIR and STTR to reserve a portion of their R&D funds for award to small business. These programs have the advantage of being non-dilutive. But they are also typically small in scale, ranging from $100K for 6 months in Phase I to $750K for up to 2 years in Phase II. Phase III is the period during which Phase II innovation moves from the laboratory into the marketplace. No SBIR/STTR funds support this phase and the small business must find funding in the private sectors or other non-SBIR/STTR federal agency funding.

Non-traditional funding sources include hedge funds, non-for-profit funding agencies and Strategic Corporate Venture Capitalists. Hedge funds, which are unregistered money-management operations, typically make a wide range of global investments. With more than one trillion dollars under management nationwide, hedge funds are always on the hunt for a wider range of investment vehicles. In biotech, they are meeting an industry always hungry for money. Two private biotech companies, Microbia Inc. and Merrimack Pharmaceuticals Inc., closed a $75 million and $65 million round of funding respectively in early 2006, a large percentage of investment coming

from hedge funds[10]. An early investment in a young research driven company gives big funds an advantage over competitors who may also consider investing in a future stock offering.

Not-for-profit funding agencies over the last 5 years have greatly increased their presence in drug research and development. BIOVentures for Global health (BVGH), a non-profit organization spun out of the Biotechnology Industry Organization (BIO) is supported in part by the Bill and Melinda Gates foundation and the Rockefeller foundation and creates incentives for drug companies to target diseases of the developing world[11]. Other organizations that have non-profit money available for for-profit organizations include Contraceptive Research and Development (CONRAD), dedicated to finding new ways to prevent pregnancy and sexually transmitted infections and Institute for OneWorld Health, which focuses on drugs for dysentery and cholera. Amyris Biotechnology used an agreement with OneWorld Health – via $42.6 million in funding from the Gates foundation to develop an anti-malarial drug, Artemisinin. Amyris used the funding to build its drug development platform and improve its technologies. It will distribute its drugs to developing countries while retaining the R&D experience as well as the rights to technology, which it will use to create products intended for the US market.

Strategic Corporate Venture Capitalists (CVC) are venture capital arms of big pharma, biotech, and medical device companies, which sorely need a startup's ideas, products and technology platforms (See Table 2).

These companies have become victims of their own massive size, requiring unrealistically powerful internal R&D machines to keep their pipelines pumping out innovative new products to replenish expiring patents. Major life sciences companies must supplement their internal discovery and development programs with mergers, acquisitions and in-licensed technologies and products. To accomplish this, they are willing to invest in small startups right alongside traditional VCs to get to the head of the line for an advance preview of devices, drug targets and molecule screens[12]. The primary objective is to promote potential alliances between startups and their parent bio-pharmas, the financial return is not so important. The intention is either to license some of the key assets out of the startups, or if the fit is good enough, acquisition. Takeda

Pharmaceutical and San Diego-based biotech firm Syrrx agreed on a merger in 2005. Takeda's venture arm was considering Syrrx initially as an investment opportunity and later as a collaboration partner. But in the course of these discussions, it morphed into an acquisition.

Table 2: Corporate VC firms and strategies

Company	Size of fund	Strategic focus of fund	Stage focus of fund	Syndication rules	Board
Amgen Ventures (San Diego)	$100 M/four years	Human therapeutics	Seed, Series A, Series B	Coinvest with other VCs	Observer
Astellas Venture Management (Menlo Park, California)	$60 M/evergreen[a]	Therapeutics and technology platform for drug discovery	Seed to mezzanine	Coinvest with other VCs	Observer
Eli Lilly (Indianapolis, Indiana)	$175/evergreen	80% biotech, remainder healthcare IT, medtech	Series A to mezzanine	Invest only in syndicates, will lead, co-lead and follow	Board
Johnson and Johnson (Mountain View, California)	$100 M/year funded off balance sheet investments	Medical devices to biologics, regenerative medicine to small molecules	Seed to mezzanine, clinical stage priority	Lead, co-lead, follow	Board
Pfizer Strategic Investment Group (New York)	Balance sheet investments	'Commercial enablers' diagnostics, systems biology, modeling, healthcare IT and services	Any	None	Observer
Takeda Research (Palo Alto, California)	$10–20 M/year off balance sheet investments	Target, product, enabling technology	Concept, seed through mid-stage	Mostly coinvest, will seed with convertible loan	Observer

[a]Evergreen: gradual injection of capital into a new or existing enterprise.
Source: Paul Grayson, Sanderling Ventures, San Diego

CASE STUDY – ILLINOIS TECHNOLOGY ENTERPRISE CENTER (ITEC)

Interview with **J**im **B**ray, Assistant Director of New Business Initiatives – Telephone interview 11/21/2006

Illinois does not have a big startup environment

According to Jim, the magnitude of the challenge of raising capital depends on location. VCs need to be in geographical proximity to their startup investments, one reason for the less startup money in IL. VCs first look at the Management team and IL lacks the startup managerial experience or talent necessary, believes Jim.

Jim has not seen many Angel investor investments or CVC investments in IL either. CVC investments were the in-thing near the 2001 bubble, but have since shied away from the mid-west focusing rather, in their own backyard.

When queried about the recent trend of VCs starting to invest again in seed and first rounds, Jim says he does see that pattern in IL. He believes that this cyclical return to early stage might be true in the Boston and San Francisco regions.

Contrarians speculate that now that the pendulum of VC investing has swung so far away from seed investing, it will surely start swinging back. This point also came up in discussions with Dr. Craig Shimasaki during the Kellogg Biotech Boot camp. He pointed out a recent change in the trend in that VCs were again starting to fund seed stage rounds. Jim Bray of ITEC, Evanston, however, did not see this trend in the mid-west.

The Financial treadmill

Raising capital represents a continuum of challenges. The first one, concerning seed capital has been discussed above. The other challenge is to continually keep replenishing the capital. A startup could take heart from the fact that big pharma firms are increasingly turning to early-stage deals with biotechs, hoping to fill their pipelines. Even discovery stage and preclinical deals, which offer the least possible assurance of an eventual positive outcome, are on target to breaking new ground this year after years of being either overlooked or undervalued[13]. Of the ten largest disclosed discovery deals ever recorded, eight were signed in 2006. Novartis has emerged as the new discovery dealmaker to know; not only has it announced the largest discovery-stage deal ever (Alnylam), but it has made 4 out of the 15 largest discovery announcements and eight deals in total.

As it is discussed in the next section, startup biotech companies can financially benefit from this increased upstream interest of big pharma by developing strategic partnerships with them.

CHALLENGES IN BUSINESS DEVELOPMENT / STRATEGIC PARTNERSHIPS

Business development (BD) deals or strategic partnerships have emerged as a vital part of resources that small biotech startups leverage to become successful in recent years. "Big pharma is currently confronted with a number of blockbuster drugs coming off patent, so corporations are increasingly looking to biotech startups for access to new products to fill their development pipelines… About one-fourth of the new drugs launched in the past year were the result of collaborations between companies"[15].

There are three major forms of strategic alliances that small biotech firms can utilize[15]: licensing technology, full collaborations on R&D and commercialization, and limited agreements on co-marketing or co-promotion. No matter which option a biotech chooses, the benefits of the strategic alliance with an established partner usually go far beyond just the financial resources. For instance, the established partner can provide the startup with development experience and expertise, regulatory approval support, commercialization capacity (sales and marketing), and manufacturing expertise and resources[16], all of which are essential for the success of bringing the product to the market. Despite all the benefits, there are several significant barriers and challenges in the strategic partnerships that we have identified through our research.

First of all, identifying the right time to enter the partnership plays a key role in a startup's success in the strategic alliance. "The cost and risk to continued development using internal resources must be weighed against the estimated value and other benefits of structuring a licensing deal"[17]. Each firm must analyze its situation carefully to determine the right time to look for strategic partnership. They should avoid starting too early when the valuation is low, or too late when cash is scarce.

The next key question is how to identify the right strategic partner. In order to identify and prioritize a list of most appropriate strategic partners, comprehensive research must be carried out in order to examine the strategic synergies with potential partners. One key point that LeAnne, COO of Maroon Biotech, mentioned during the interview is the importance of finding a partner with "strategic fit" with your firm in terms of company's vision and culture. It is critical to make sure two companies have "mutual understanding of each other" and want to head into the same direction. In addition, during the initial research, the firm also needs to assess both scientific and commercial viability of each

potential strategic partner to demonstrate the benefits to them so that the firm can at least pass the initial screening[17].

Third, management faces a key challenge of how to be successful during the deal negotiation. The key is to be prepared before the negotiation. It is imperative to list the IP portfolio, summary of clinical data, analysis of market potential, etc.

Last but not the least is the issue of balancing collaboration with control, a central issue in the strategic alliance. Management must consider the best approach to leverage the resources gained from the partnership while still maintain enough control of the company and business processes to prevent any major interruptions in innovation. Academic research has shown that mergers between small biotech and pharmaceutical firms have resulted in slower R&D growth relative to similar firms that did not merge[18]. In practice, LeAnne of Maroon Biotech also raised concerns on this issue. She believes that this is the number one challenge that biotech startups facing during the BD process. From her experience, she advises biotech entrepreneurs to establish a clear ownership of the IP from the collaborations very early on.

CHALLENGES IN SALES AND MARKETING

"People outside the biotech industry tend to assume that marketing biotech products should be easy because of a built-in demand for the cutting-edge products that extend life, or enhance the quality of life. Surely they think customers will beat a path to your door the minute your exciting new product gets FDA approval. In fact, nearly the opposite is true"[19].

Unlike funding, where most people agree on its importance to the success or even survival of the biotech startups, the understandings of the marketer's role in the company are often mixed. Because most of the small biotech companies are founded and managed by scientists, marketing is often introduced late, "as if the marketer's role only becomes important once there is a product available for sale"[19]. Interestingly, LeAnne (COO, Maroon Biotech) and Eric Bremer (CSO, Precision Biomarkers Inc.) seem to agree with this view. They believe there is very little role for marketing to play during the early phase of R&D process. Furthermore, they think that the firm should focus on pure sciences, and not let sales and marketing interfere in this process.

However, as we identified through our research, there are several key reasons why management of the biotech startups should get marketing involved early in the product research and development process. First, marketing needs to be involved early to better assess market potential and commercial viability to guide investment decisions. Based on the analysis of the market size, growth rate, and unmet medical need[19], the firm can determine the therapeutic area to focus on and develop the product to ensure a high commercial potential. In addition, management should involve marketing in the clinical trial design process as well to make sure that the end points of the trials are commercially meaningful. For example, an end point of "15% reduction in cholesterol level" would have a very different commercial implication than the end point of "10% reduction on cardiovascular associated mortality and mobility events" for a cardiovascular product. Furthermore, it is important to align the company's scientific messages with its marketing messages early in the pre-market process to ensure a successful launch[19]. It is critical for scientists and management to start communicating the potential value of a product at conferences and seminars or though scientific publications before the product launch. This enables them to get key opinion leaders on board early enough to build a solid foundation for a successful launch.

When a biotech firm finally is able to complete the clinical trials and get the FDA approval for its product, management must develop a strategy to tackle the sales and marketing challenges it will face. Like pharmaceutical companies, biotech firms face a complex market place, which includes patients, physicians and insurance/payers. How biotech firms tailor the marketing strategies to target different players in the markets is very different from traditional seller/buyer markets. A unique challenge biotech firms face is how to be effective on a more focused or so call "targeted" marketing. This is because most small biotechs compete in niche markets for certain less-populated diseases. Therefore mass marketing vehicles, such as DTC, will not work in these markets. In addition, key customers comprise of mostly specialists instead of primary care physicians (PCPs). So biotech firms usually need a small but more knowledgeable sales force.

Last but not the least, pricing and reimbursement represent key challenges for the biotech startups. As we mentioned above, most biotech products are specialty products

serving a small patient population. Therefore, the biotech firms have to charge a relatively high price per regimen in order to offset the high investment cost. Although biotech companies have often escaped the increasing public scrutiny regarding rising prices that big pharma had to deal with, the situation is now changing. The increasing emergence of biologics for common diseases, such as Genentech's Xolair for the treatment of asthma, is increasing the visibility of biotech companies, and with this increased visibility comes increased scrutiny[24].

Startup biotech companies now have to consider issues related to reimbursement as early as the pre-clinical stage of development. An added challenge is that startup biotech companies do not have the benefit of strong lobbying powers with payers or experience on how to navigate the Healthcare Common Procedure Coding System (HCPCS). Additionally, many of the large biotechs and big pharma are creating in house health economic groups that are helping to derive financially based health outcomes. In order to confront this challenge, management at a biotech startup should create a solid reimbursement plan that includes the following components[25]:

1. Build a cost-benefit value proposition into the clinical trials.
2. Develop relationships with payers and collect data on reimbursement on the current market, if one exists, or the potential market. This data should be incorporated into a strategy to gain a formulary status and payer education plan. Dr. C from L Corporation attributed much of the company's early success to the expertise of the individual who worked with the payers to secure reimbursement. (see: Case Study – L Corporation)
3. Create product support for physicians and consumers to work through the initial challenges with coding, billing claims and other reimbursement questions.

Ultimately, a successful reimbursement strategy should enable a biotech startup to convince payers and consumers that the product provides both a health and cost benefit over the competition. Accomplishing this will help ensure the much needed success for a startup.

Given the broad range of challenges in sales and marketing, small biotech firms usually choose to ally with established firms to leverage their extensive and experienced sales

and marketing forces to successfully launch and promote the products as discussed previously[26].

CASE STUDY – OHMX CORP

Interview with Jodi Soriano, Director of Business Development – Telephone interview 11/28/2006

Marketing now needs to work very closely with Research and Development.

Jodi believes that one of the reasons why many biotech companies fail is because they develop products with minimal market needs. She believes that there is a paradigm shift in that both Science and Marketing now drive the development. The marketing department needs to translate the customer's needs to its researchers, likewise it is important for Scientists to have "Business oriented" heads.

Ohmx Corp. is a startup biotech diagnostics company on its "Biochip" platform and has raised about $3 million in its 2.5 years of existence. All of its capital comes from high net worth angel investors. Jodi believes that one of the biggest challenges for a biotech startup is raising money - and the mid-west is a more difficult place to raise capital. She attributes this to the lack of sophisticated investors who do not understand the timelines on a return on investment in a biotech company.

Biochips are a potential IP minefield according to Jodie and Ohmx has ensured that it has a very strong patent strategy and portfolio plus the Freedom to Operate (FTO). She believes that finding really good IP attorneys who understand the science and can serve as a bridge between the scientists and the business people is very important.

Jodie also believes that it is very challenging for a startup biotech company to form strategic partnerships. A startup needs a very strong value proposition and founder scientists with a very successful track record to garner licensing and partnership deals.

CHALLENGES IN MANUFACTURING

After a biotech startup makes a promising discovery, successfully trials it, rolls out its marketing plan, and posts healthy sales forecasts it faces manufacturing challenges. It has to effectively meet the drug's market needs while working in a highly-regulated environment and with a limited budget. Four main challenges have been identified in the manufacturing arena, along with proposals for viable solutions to each.

Production capital requirements

A startup biotech cannot invest heavily in an expensive manufacturing facility without a marketable product. However, the moment it creates a blockbuster drug there will be excess demand and manufacturing capacity must ramp up immediately. With a fixed initial budget and no revenue inflow, startups often lack sufficient funds for

manufacturing investments. They might be tempted to cut corners in manufacturing and quality control but this often results in the factory not meeting the FDA regulations and consequently its shutdown, leading to significant economic costs (FDA fines, opportunity costs, stock price). To counter this, a biotech startup could:

1. Partner with a large pharma with established manufacturing infrastructure,
2. Turnkey outsource manufacturing to a CMO (Contract manufacturing organization), or
3. Keep a key part of the manufacturing process in house and outsource the rest.

Availability of Human and other Resources

Many biotech startups are located near research universities given the highly scientific workforce needed to perform drug discovery. University locations are often not the most cost-effective for manufacturing plants. A startup should investigate location options where local governments offer financial and infrastructure incentives for biotech manufacturing in order to attract this sector.

Scale-up to mass production

"FDA notes that problems often occur during scale-up to mass production and that poor product design and inadequate characterization and testing can cause problems after a product comes to market."

A startup could investigate collaborative programs offered by the government or FDA. For example FDA recently published the Critical Path Opportunities List, which maps out a number of "scientific projects" for improving the testing and production of biotech therapies. In its March report, FDA recognizes that problems in the characterization, testing, and quality management of medical products can delay clinical trials and even completely block drug development.

.

CASE STUDY – INTERGENETICS INC

Interview with Craig Shimasaki, CEO – Conducted at the Biotech Boot camp - Northwestern University, 11/18/06

FDA mostly prevails.

"After testing 8,000 women and conducting 13 years of research into a genetic test that can assess a woman's breast cancer risk, Oklahoma City-based InterGenetics was ready to launch its OncoVue test nationwide last January".

The Food and Drug Administration called and summoned InterGenetics Chief Executive Officer Craig Shimasaki to Washington. The rules had changed one month before the scheduled commercial launch at 50 breast cancer centers nationwide. InterGenetics had to put its commercial launch plans on hold.

Shimasaki was told that the CLIA — an acronym for federal Clinical Laboratory Improvement Amendments — guidelines under which InterGenetics had built its testing procedures and laboratory were no longer sufficient for the FDA.

"They said the algorithm, the software, makes the whole thing regulated by the FDA," Shimasaki said. "I paused for a minute and said, 'this is not the direction I received four years ago and it's also a contradiction to all the things that are being done right now.'"

The FDA was adamant. InterGenetics was forced to delay the launch.

Anticipated income from thousands of tests at $397 each did not materialize and Shimasaki went back into the venture capital market to raise another round of investment capital that would carry the company until it could begin actual sales.

Shimasaki had already raised about $12.5 million in capital, but now is putting the finishing touches on another investment round of approximately $5 million to $7 million.

An FDA spokeswoman said the agency did not issue new rules by with it regulated InterGenetics. It merely developed "guidance" to clarify the definition and status of what it calls in vitro diagnostic device multi-variant index assays. "We believe this complements, rather than contradicts, the controls already in place by CLIA and (the Centers for Medicare and Medicaid Services)."

"(The new requirements) caused the centers to have more administrative responsibilities," Shimasaki said. "We lost some of the centers that really couldn't handle that kind of extra administrative work load."

For now, InterGenetics is earning income from the tests being conducted in Oklahoma City, Edmond, Chicago, Boise, Idaho, and elsewhere, Shimasaki said. It is unclear when the FDA will declare the test period over and let the company roll OncoVue out unrestricted."

Dr. Shimasaki said: "We did not completely foresee this from the FDA" and then exclaimed "but when life hands you lemons learn to make lemonade. We are now positioning our product as one with FDA approval as opposed to CLIA approval which we feel will add more credibility to our product" Dr. Shimasaki also shared his thoughts on the management skills required to make a startup successful (see Appendix B). When queried about his thoughts on the challenges in raising capital given that VCs are increasingly moving away from seed and first stage rounds, Dr Shimasaki mentioned that the trend appears to be changing. He thought that VCs, as a result of becoming risk averse since the tech bust, now had a lot of money to invest and were slowly starting to come back to seed rounds.

Implications of noncompliance

"FDA regulations concerning good manufacturing practices are very strict and factories that fail an inspection may be promptly shutdown, possibly resulting in product recall and millions of dollars in lost sales"[33] Significant attention to detail is essential to satisfy the stringent FDA regulations and one could elicit a warning letter for lack of sufficient written procedures. If these issues are not addressed immediately then there could be a significant impact on earnings, new-product launches, and supplies of existing products. One way a company could address this is through extensive training of all its employees whose actions could come under the jurisdiction of the FDA and continuously monitor FDA's stance on compliance issues that have relevance to the company.

OTHER CHALLENGES

We devoted the preceding sections to the main challenges identified from our research. However, there are several other challenges that also impact the success of the startups. In this section, we briefly touch on them.

Human resource management imposes a key challenge. While startup teams tend to be extremely under staffed, and usually made up of high caliber scientists, it is important to keep a reasonable balance in the workload assigned to the team members. The best results are achieved by focused teams; however, it is often the case that scientists find themselves working on public relations, marketing, and other tasks outside of their area of expertise. This might be a reflection of the lack of resources. The recommendation is to draw boundaries and seek alternative resources when the balance is at risk. Many tasks can be carried out in collaboration with universities, via internships, apprenticeships, thesis dissertations, research projects, etc.

Public Relations (PR) play an important supporting role. It is an important channel to communicate the current state of affairs, to preach on all the strengths of the startup to attract and retain investors, talent and potential partners. PR activities should be ongoing, starting with the foundation of the startup.

A lack of understanding of the industry by the regulatory bodies adds another challenge to startups. As a result of the lack of standards, the constant changes of policy is an

ongoing risk for different areas of the business, such as product submission, R&D, manufacturing, clinical trials, etc. Startups should proceed according to current policies, and constantly check for updates. Dr. David Paul, President of Precision Biomarkers, pointed out that the FDA should become a best friend. As opposed to public perception, the FDA should be thought of as an important partner that cooperates with firms. Dr. Paul suggested seeking FDA's advice well ahead of time, in order to be able to make pertinent changes, if any.

CASE STUDY – L CORPORATION

*Interview with **Dr. C**, CEO and Founder – Conducted at the University of Chicago, 11/06/06*

A model for success

"I knew there had to be a better way to diagnose and treat kidney stones." Dr. C made this statement as a young nephrologist at the University of Chicago more than 30 years ago, but he never could have imagined the journey that this statement would take him on.

Dr. C endeavored to solve this problem and began doing research funded primarily by NIH grants in order to develop a diagnostic test that would examine a patient's kidney stones, categorize the nature of their disease and create a customized treatment plan.

When queried about how his product was considered biotechnology, he responded: "Biotechnology is not just biologic drugs and vaccines, biotechnology can also include diagnostics and services. This is the beauty of biotechnology. You have to think outside the box sometimes."

Once Dr. C had created a system that was superior to anything on the market, he approached his employer and the technology transfer office to start a company.

With limited capital (less than $500k) and support, Dr. C founded L Corporation. He described the early corporation as a partnership amongst three main players with key skill sets: scientists, data experts and public relations/management.

Dr. C set up L Corporation in a somewhat run-down research facility in what is now the medical district near the University of Illinois at Chicago. Dr. C negotiated deep-discounts for equipment and other capital expenditures with the promise of free advertising for the companies once the company achieved a certain level of success and renown.

Once the L Corporation was fully functioning, the company did not have the means to fund a sales force or a marketing department. Dr. C sought out the thought leaders in the field. Dr. C was able to convince one key thought leader that he should use this product and within a small window of time, the others followed. Dr. C also established a relationship with a large, national consortium of nephrologists.

In order to ensure that providers would pay for the diagnostics and services, Dr. C hired a well-connected and experienced executive with extensive knowledge of the reimbursement landscape. The L Corporation had to leverage resources in order to pay for his salary. Dr. C credits this individual with convincing all of the largest insurance providers as well as Medicare and Medicaid to fully reimburse for the product. A key element in Dr. C's success was clear understanding of health economics and the ability to convince payers that his product could significantly reduce the on-going cost of care.

Now, in 2006, ten years after incorporation, L Corporation, is the leading provider of diagnostic testing and disease management for patients with kidney stones. They have been the targeted for acquisition by large competitors as well as other large biotechnology companies looking to expand into diagnostics.

Key lessons from Dr. C:

- Know your customer and know what they want.
- Insure that you have great advisors, both involved in and outside of the industry.
- If there is a choice in location, do careful research and pick a state that actively encourages biotechnology firms to incorporate.
- Publish, publish, publish.
- Be patient – it takes a very long time for opinions to change regarding care. Go after the thought leaders.
- Even when you are small and have no money, pretend you are big. This is the only way to compete with the larger companies with more resources and a recognized name. This will also buy early credibility.
- Pick a great name for both your company and your products.
- Do not undertake expansion too early or soon after starting-up, focus on your niche.

Given the typical long life cycle of the products in the biotech industry, post-market surveillance was not considered to be a challenge that an average startup would be likely to face, according to the people interviewed and researched media. However, this topic should not be completely disregarded. Post-market surveillance might require several types of resources, which are, however, beyond the scope of this paper.

CONCLUSION

Despite the many challenges described above, the biotech industry is one of the most exciting and challenging industries in which to undertake a startup venture. Hopefully the insights from the case studies and the analyses can be used to effectively address some of the managerial challenges one would encounter in a biotech startup. LeAnne Tourtellotte stated, “All startup companies, biotech or other, face a list of 10-15 managerial challenges at all times and have limited resources to solve these issues. The current situation of each firm will determine which issues are most urgent and significant, and hopefully a good management team will execute the best course of action.” Peter Johnson, Executive Director of Corporate Strategic Planning, Eli Lilly and Company, echoed this sentiment when he stated, “All strategy is situational.” Successful bio-entrepreneurs with a solid product who can effectively identify and prioritize the key managerial challenges and subsequently develop a strategy to address these challenges stand a good chance for success. Biotech startups do face several challenges that no other industry startups face, but also face incredible and unique promise if they succeed: the chance for the next breakthrough life-saver that will improve the lives of generations to come.

REFERENCES

Research and Development

1. Pisano, G. "Can Science Be a Business? Lessons from Biotech," Harvard Business Review, October, 2006, pg. 114-125.
2. Levine, D. "Biotech's Next Big Discovery: Profits?" San Francisco Business Times. June 23, 2003.
3. Chang, H. "Biotech Innovators and Investors Assess Challenges, Opportunities" Stanford GSB News, January 2002.
4. Bode-Gruel and Gruel, J. "Determining the value of drug development candidates and technology platforms" Journal of Commercial Biotechnology, Jan 2005.
5. Burow, S. and Berghammer, J. "Patent Protection in the Biotechnology Industry: A Unique Approach to Obtaining Fast Patent Rights" Intellectual Property & Technology Law Journal, August 2006.
6. Ausman, D. "Creating the High-Output Mind-set" Modern Drug Discovery, January 2001.
7. Goodall, S. "The Promise of the East: India and China as R&D Options" Bioentrepreneur, July 2006.

Raising Capital

8. Hildreth, Michael S. "Strength and Stability: The Americas Perspective" Ernst and Young Biotechnology Report 2006.
9. Lawrence, Stacy. "Seed capital conundrum" Nature Biotechnology, December 2005.
10. Heuser, Stephen "Startups turning to hedge funds" The Boston Globe, May 29, 2006.
11. Yajnik, Juhi. "Getting your gates - How one company used the growing non-profit funding pot to jump start its development program, and how you can do the same". The Scientist, Vol. 20 (11), Nov 2006, pg. 71-73.
12. Mack, George. "Big Pharma wants you" Nature Biotechnology, September 2006.
13. Lawrence, Stacy "Fishing farther upstream" Nature Biotechnology, November 2005.
14. George, John. "Top challenges for biotech firms are finding scientists, money" Philadelphia Business Journal July 7, 2006.

Business Development / Strategic partnerships

15. Bryant, T., Ferri, Lisa, Jung, J. "Partnering with IP: An investor's checklist", Venture Capital Journal. Wellesley Hills: Apr 1, 2006. pg. 1.
16. Friedman, Yali "Building Biotechnology – Starting, managing, and understanding biotechnology companies". ThinkBiotech LLC: 2006.
17. Ranan Lachman, Marc Samet, "The Top Five Drivers of a Successful Out-licensing Process", BioPharm International. http://www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=157249&pageID=2

Sales and Marketing

18. Danzon,Patricia et al, "Mergers and acquisitions in the Pharmaceutical and Biotech Industries", NBER working Paper No. 10536, May 2004.
19. Stegall, Allen "Science doesn't sell itself: The special challenges of marketing biotech products", Medical Marketing and Media. New York: Oct 2001.Vol.36, pg. 78.
20. Nair, P.N. "India poised to play a major role in biotech/pharma, post 2005" Pharmabiz.com November 11, 2006.

21. Economy & Business; Biotech Industry Banks on Medicare Law for Help on Drug Bills" The New York Times, December 1, 2003.
22. Author Unknown "Biotech breakthroughs drives the need for reimbursement strategy" The Journal of New England Technology, July 2005.
23. Stoiber, W. "Consolidation challenges in Europe's life science sector – Making it happen" Journal of Commercial Biotechnology Volume 10, Number 1, September 2003. pg. 29-34.
24. Pollack, A. "Economy & Business; Biotech Industry Banks on Medicare Law for Help on Drug Bills," The New York Times, December 1, 2003.
25. Maioli, C. "Biotech breakthroughs drives the need for reimbursement strategy," The Journal of New England Technology, July 2005.
26. Warner, S. "High-Priced Biotech Drugs: Are They Worth it?" The Scientist, December 2004.

Manufacturing

27. Arlene Weintraub "Drug makers, Heal thy factories" "Immunex .sales skyrocketed to $650 million within two years…was caught with severe production shortfalls." Business Week July, 2001.
28. Tania Anderson "Growth in contract manufacturing boosts biotech industry" Baltimore Business Journal - July 21, 2006.
29. Author Unknown "FDA raises concerns about Lilly drug plant" Wall Street Journal. March, 2001.
30. Koehler, Gus A. "Bioindustry: A Description of California's Bioindustry and Summary of the Public Issues Affecting Its Development" 1996.
31. Kolchinski, Peter , "The Entrepreneur's guide to a Biotech Startup" 4th. Edition. 2004.
32. Stafford, Jim "InterGenetics works to overcome delay - Rules changed just a month before launch" NewsOK October, 2006.
33. Wechsler, Jill "Regulatory Beat: FDA Encourages Innovation in Biotech Manufacturing and Product Development" BioPharm International May, 2006.

Other Challenges

34. George, John "Top challenges for biotech firms are finding scientists, money" Philadelphia Business Journal. July 7, 2006
35. Gillis, Justin. "Biotech Regulation Falls Short, Report Says; Pew Study Calls for Better Oversight" The Washington Post Apr. 1, 2004. pg. E03.
36. Laing, Jonathan R. "End of Endotronics? The rise and fall of a biotech company" Barron's National Business and Financial Weekly Mar 23, 1987. pg 16.
37. Mentha, Michael D. "Regulating Biotechnology and Nanotechnology in Canada: A Post-Normal Science Approach for Inclusion of the Fourth Helix" Presented at the International Workshop on Science, Technology and Society: Lessons and Challenges, National University of Singapore. April 19, 2002.
38. Technology Administration "To market to market: bringing the science of biotechnology to the marketplace" A bio-vision roundtable. Washington, D.C. May 20, 2002.
39. Author Unknown. "FDA may change handling of safety issues" Yahoo! News November 9, 2006.