Early-Stage Valuation in the Biotechnology Industry

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Abstract

Biotechnology (or biotech) has impacted almost every aspect of human life. It has reorganized industries, drastically changed healthcare, helped to improve the environment, and led to important changes in laws and ethical norms.

Among the various biotech fields, medical biotech has been by far the most influential, beneficial, and controversial. It has generated not only superlative discoveries to improve the lifespan and quality of human life, but also the greatest amount of wealth for all the players involved, and the greatest volume of public debate.

Several important trends are shaping the future of the pharmaceutical (or pharma) and biotech industries. The biotech industry is characterized by the presence of strong clusters in all countries. The pharma and biotech industries are experiencing an outsourcing phenomenon, mainly due to a lack of in-house expertise and efficiencies. Diagnostics and therapeutics are increasingly converging, a trend that will lead to predictive and precise diagnostics and personalized and preventive medicine. The first few years of the twenty-first century have witnessed significant changes in the pharma/biotech alliance landscape. Today we are seeing the "omic"-ization of the biotech industry: most of the emerging technologies are genomics, proteomics, cellomics, and pharmacogenomics. In addition, the biotech industry faces uphill ethical issues, including excessive marketing, third-world drug availability, genetic engineering, stem cells, and cloning.

The medical biotech industry faces several challenges. First, science, the human body, and disease are, essentially, complex. Second, unlike other high-technology industries, the biotech product development cycle is very long, even after proof of concept. Biotech projects take between ten and twenty years to become successful and cost over $200–300 million before a product reaches the market. Third, delivery of most biotech products and therapies is complex and can be painful, often involving intravenous delivery. Fourth, the preceding three factors pose significant challenges for research and development (R&D) financing. In addition, there are certain outside determinants that influence the biotech industry, including regulation, demography, reimbursement climate, and big pharma companies.

Stem cell research is one of the most fascinating areas of biology, but it raises questions as rapidly as it generates new discoveries. The greatest potential application of this research

is the generation of cells and tissues that can be used for cell-based therapies. A stem cell is a special kind of cell that has a unique capacity to renew itself and to give rise to specialized cell types. Through the process of differentiation, stem cells form various tissues and organs, and the combination of these differentiated materials develops into the whole human body. This class of human stem cell holds the promise of being able to repair or replace cells or tissues that are damaged or destroyed by many of our most devastating diseases.

Diabetes mellitus is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. Diabetes mellitus is a type I diabetes—also called juvenile-onset diabetes or insulin-dependent diabetes—and develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the insulin that regulates blood glucose. Type II diabetes, also called adult-onset diabetes or noninsulin-dependent diabetes, may account for 90–95 percent of all diagnosed cases of diabetes. There are more than 194 million diabetics worldwide, with this number expected to exceed 333 million by 2025.

Insulin is currently the most effective drug for controlling hyperglycemia and is widely accepted as the gold standard for treating type I diabetes and even late-stage type II diabetes. However, physicians and patients are reluctant to use insulin until other less effective drugs have been attempted. This is mainly because insulin therapy is invasive and painful: patients must take insulin intravenously.

One of the most promising ways to cure diabetes is to restore the function of islet cells biologically, either through islet cell transplantation or by engineering cells to restore the insulin secreting function. Islet transplantation, a procedure that can restore insulin production in patients, is a highly promising area of research.

Based on analysis of stem cell research, diabetes market opportunities, and the development of stem cell therapies, it is possible to place a value on a company in the early (preclinical) development stage of a stem cell therapy for diabetes. Such an exercise involves valuing a company based on three different approaches—(1) the discounted cashflow model, (2) the royalty or licensing model, and (3) the comparables valuation model. Sensitivity analysis based on market, pricing, costing, R&D, and development stage can further lead to precise valuation range for a given company.

For biotechnology companies, various drivers play a critical role in company valuation, including people (management team), alliances and partnerships, intellectual property rights, R&D and technology, funding and financing, market opportunity, and therapeutic area.

Early-Stage Valuation in the Biotechnology Industry

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In layman's language, biotechnology (biotech) entails the use of techniques based on living systems—plants, animals, or microbes—to make products or improve other species. Biotech is a symbiosis of biology/science and technology/engineering. It is perceived to improve the quality of life on two fronts: (1) through gains from the social value of its products, and (2) as an engine of economic growth and development. Biotech has impacted almost all aspects of human life. It has reorganized industries, drastically changed healthcare, helped to improve the environment, and led to important changes in laws and ethical norms. This paper evaluates progress in biotech by considering important recent technologies and their applications.

Biotech's industrial applications are rooted in the distant past, an overview of which appears in Table 1. The modern biotech industry has created large, highly profitable industrial outlets of great value to society, such as the fermentation, biopharmaceutical, and food industries; the modification of microorganisms, plants, and farmed animals for improved food production; improved plant and animal breeding; and environmental remediation and protection. Biotech research is opening up more areas where its application is proving to be a boon, including the following selected industrial applications: healthcare; industrial chemicals and industrial enzymes; biosensors; bioelectronics/biochips; insecticides, fungicides, and herbicides; the food industry; the flavor and fragrance industry; waste treatment and pollution cleanup; oil production and processing; and microbial desulphurization of coal.

According to a survey of more than 3,000 firms in the United States, published by the U.S. Department of Commerce in October 2003,[1] a broad range of industries is engaged in biotech. Survey respondents identified themselves within more than sixty four-digit classifications for U.S. industry, from "paints, coatings, and adhesives"

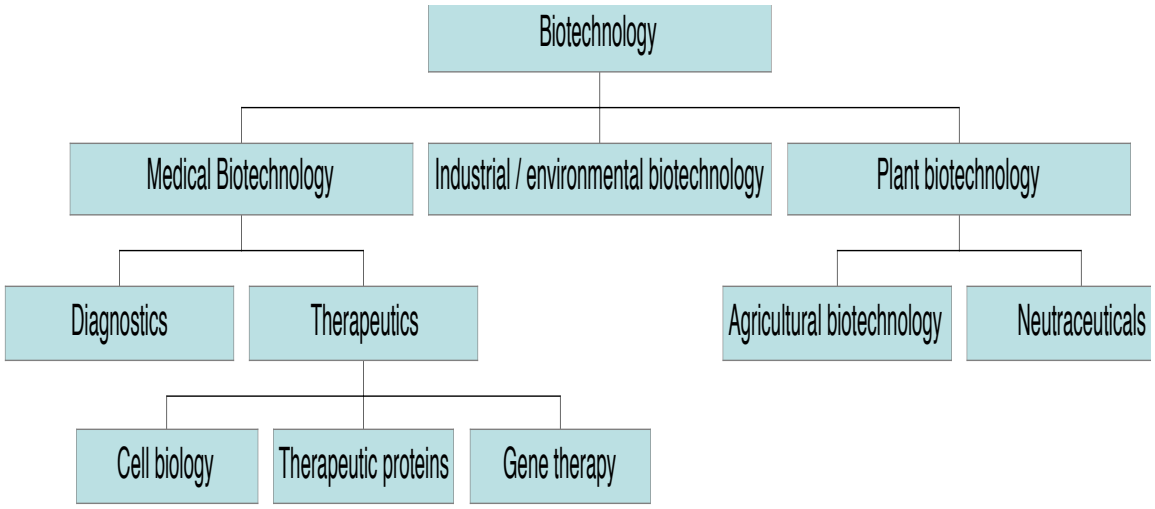
and "semiconductor and related device manufacture" to "waste management and remediation services." Given the astounding variety of industries that apply cellular and molecular processes to solve problems, conduct research, and create goods and services, it is clear that the application of new biotechnologies is an integral part of the national and international economic fabric and thus a critical component of economic competitiveness, social well-being, and security.

Table 1. Brief History of Biotech

Period	Developments
Pre-science	Robust technologies developed and applied without understanding of scientific principles. *Examples:* Alcoholic beverages, bread, cheese, fermented foods (yogurt), tanning, purification of sewage.
Mid 1800s–1940	Medical operations dependent on near-sterility; manipulation of media to increase product yields; specific processes of strain selection; use of pure cultures. *Examples:* Acetone and butanol, glycerol, citric acid, lactic acid, yeast in pure culture for food, fodder, baking, alcoholic fermentations, crude enzyme preparations, first microbial (fungal) insecticide.
1940–1970s	Microbial processes leading to pharmaceutical (pharma) products; high standards of sterility; pure cultures and extensive strain development essential. This era also witnessed sophisticated process control and quality control techniques. *Examples:* Antibiotics, single-cell protein, vaccines.
Late 1970s–present	Identification, isolation, controlled alteration, and generation of specific gene products. *Examples:* Production of drugs by gene transfer (human growth hormone, insulin); prenatal screening for genetic disease (sickle cell anemia); identification of individuals for forensic purposes from blood or semen samples; gene manipulation strain improvement.

Based on current biotechnological applications and the industry's near-term potential, biotech can be segmented according to Figure 1.

Figure 1. Biotech Industry Segmentation



Each of the segments can be further divided into more specialized biotech applications. However, in the common parlance, the term "biotech" refers to medical biotech, as illustrated in Figure 1.

Medical Biotech

DNA Makes RNA Makes Protein Makes Money

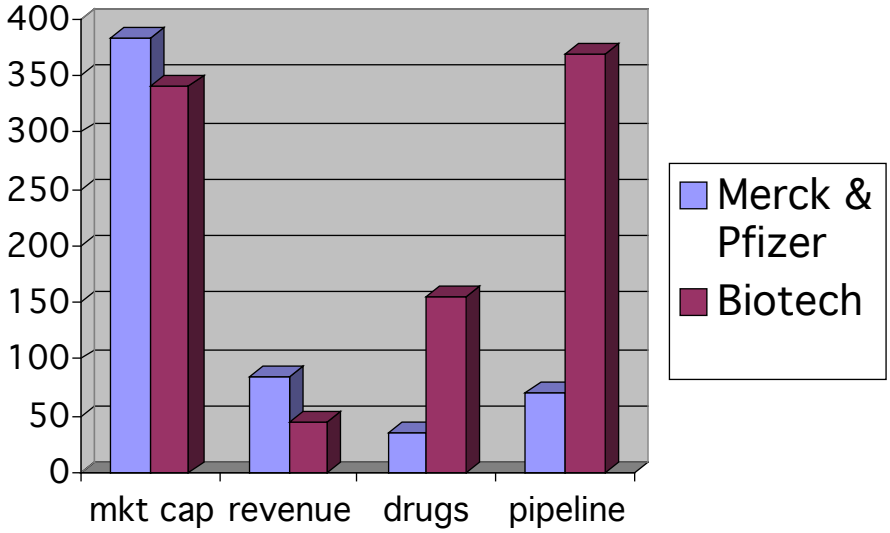
Medical biotech has been by far the most influential, beneficial, and controversial field of biotech. It has not only generated superlative discoveries to improve the quantity and quality of life, but also the greatest amount of wealth for all the players involved, and the greatest volume of public debate. Rapid advances in molecular biology—recombinant DNA (rDNA) technology, or genetic engineering, in particular—are giving bioscientists a remarkable understanding and control over biological processes. This rDNA technology will be the most revolutionary technology of the first part of the twenty-first century. It will have a profound impact on medicine, the diagnosis and cure of hereditary defects and serious diseases, and drugs and vaccines for human and animal use.

The biotech and traditional pharma industries overlap in many ways and thus need to be evaluated together, though they differ in many respects. The basic difference between the two industries is that the traditional pharma industry makes drugs and medicines based on chemistry, whereas medical biotech uses biology to make drugs and therapies. The most compelling reason to study their relative positions and strengths

is that they aim for the same end result: improving the lives of their customers, the public. In the future, however, we shall see these industries converge—in business control rather than process. This convergence has already begun through alliances, partnerships, and mergers and acquisitions (M&A).

Today there is a great mismatch between the two industries in terms of their potential and reflected market valuation. Figure 2 compares the two biggest firms of the pharma industry, Merck and Pfizer, vis-à-vis the biotech industry as a whole.[2]

Figure 2. Pharma versus Biotech



Source. Burrill & Co. presentations, November 14, 2003 and April 17, 2004.

Figure 2 illustrates the future potential of the biotech industry in financial terms. However, the pharma industry's potential exceeds that of the biotech industry on three counts:

- Expertise to take products from bench to market. Pharma players are well equipped to conduct clinical trials and work with the FDA to obtain product approval. The biotech industry lacks this experience and capability, and in many cases has depended on the pharma industry for it.
- Marketing and distribution. The biotech industry has neither the necessary sales and marketing expertise nor the reach to physicians and patients to make a product a "blockbuster"—that is, one with sales of more than $1 billion.
- The pharma industry has the tremendous financial muscle needed to take a potential product through all the phases of laboratory and clinical development through to market launch.

In these key respects, the biotech industry has a long way to go to catch up with the pharma industry. But there are indications that the pharma industry is willing to share a larger slice of the profits with the biotech industry, as the latter shows signs of moving up the value chain.

Medical Biotech Industry Statistics

The medical biotech industry has achieved rapid success in recent times, as the following facts show:[3]

- More than 155 biotech drugs and vaccines approved by the FDA have treated more than 325 million people worldwide.
- Seventy out of 155 biotech products were approved in the last six years.
- There are more than 370 biotech products currently in clinical trials targeting more than 200 diseases including various cancers, Alzheimer's disease, heart disease, diabetes, AIDS, multiple sclerosis, and arthritis.
- Biotech is responsible for many medical diagnostic tests that detect diseases early enough to treat them successfully.

Table 2. Biotech Industry Statistics for Major World Markets (2002)

Particulars	Unit	U.S.	Europe	Canada	Australia
Revenue	$ B	45.2	8.3	1.5	0.9
R&D	$ B	13.3	5.0	0.6	0.1
Market cap	$ B	342	25	8.8	4.1
No. of companies	Nos.	1,455	1878	417	214
No. of employees	Nos.	143,000	33,300	7,800	6,500

Source. Burrill & Co. presentations, November 14, 2003 and April 17, 2004.

Medical Biotech in the United States

The first in-depth government assessment of the development and adoption of biotech in industry was accomplished by a survey of more than 3,000 U.S. firms, conducted by the U.S. Department of Commerce in October 2003.[4] Its findings were:

The industry is diverse.

- Firms vary greatly in size and scope, from small, dedicated biotech companies that are research and development (R&D) intensive and operate primarily on venture capital, grants, initial public offerings (IPOs), and collaborative agreements to large, diversified companies that have greater in-house resources and well-established production and distribution systems.

Most companies are at a nascent stage.

- Ninety percent of respondents had 500 or fewer employees.
- Fourteen percent were established prior to 1980, 70 percent were founded after 1986, and 29 percent emerged during 1993–2001.

Biotech is the core business and healthcare the major focus.

- For 90 percent of the firms, biotech-related business lines accounted for more than 75 percent of net sales, employment, and operating income.
- Seventy-two percent named human health applications their primary area of biotech-related activity.
- Sixty-five percent fit into one of two broad categories: "medical substances and devices" and "scientific R&D services."

Biotech is characterized by rapid advancements.

- Patent data underscore the dynamic and rapidly evolving nature of biotech. In the last quarter of 2002, companies reported 33,131 pending applications for biotech products or processes, compared with 23,992 current portfolio patents.

Before addressing trends in the industry, I will discuss intellectual property rights and the financing of biotech ventures.

Intellectual Property Rights (IPR)

Broadly, intellectual property consists of design rights protecting aesthetic creations, trademarks, copyright, confidential information, patents, and other special rights, including Plant Breeders' Rights.

A patent is a negative right, which permits the inventor to stop third parties from using the invention. It is not a positive right in that it does not give the inventor the right to do something that he would otherwise not be able to do. A patent is not obtainable on demand by the inventor, nor does it act as an all-powerful talisman permitting the inventor to have the market for his invention all to himself. Patents involve considerable time and expense.

Patents can be obtained for most industrially applicable processes, devices, and products. Patents are not granted automatically, and in practice an inventor is not entitled to a patent as a right. Patent examiners normally conduct a search to find out what prior proposals in the same general area have been published. Frequently, the precise form of the patent is the subject of much argument with the examiner.

A patent specification usually contains an abstract, followed by a detailed description of the invention, and finally some numbered statements, which are called

the claims. The claims define the boundaries of the monopoly that the applicant is claiming. Once the patent is granted, any third party can look at the claims and—in theory at least—understand the forbidden territory of the patent. It takes one to five years to obtain a patent, depending on the country. Generally speaking the inventor of a completely new technology will be able to obtain wide claims, but as a technology develops, the allowable scope of claims narrows considerably. Though as a general rule the words of the claims must be regarded as the absolute boundaries of what is protected, courts are occasionally prepared to bend the rules, and hold that something not literally within the scope of the claims is nevertheless an infringement. This can be done by the doctrine of equivalents, or what is known as the doctrine of "pith and marrow." The cardinal rule of patents is that whatever is claimed must be new and must not be obvious. A patent's age is judged by its date of application. The Paris Convention permits an inventor to claim as the priority date the date of first filing in his home country, provided that the filing in the foreign country has been made within one year of the first filing. In the United States, though, when there is a dispute between applicants as to who made the invention first, an inventor can obtain a date earlier than the date of filing if he can show that the invention was conceived and first reduced to practice at a date earlier than the filing date.

The law is a creature of the society that makes it. Labor laws are adapted to real-world labor-management disputes. Commercial laws generally are adapted to the norms and expectations of actual business practices. Technology has driven much of the change of the late twentieth century, and some of the most rapidly evolving areas of law are those relating to science and technology. Patent law is no exception. Patent law serves a public policy to stimulate innovation and promote the progress of science and the useful arts. Inventors and owners favor a broad scope to patents, whereas their competitors would prefer such claims to be narrow. The public interest lies in between, allowing sufficient scope to afford a meaningful commercial benefit for innovators but avoiding claims that block competitors from related areas, since full disclosure promotes progress in science by providing ideas to build upon. For biotech companies, the existence of pending applications can provide tangible evidence of a company's research progress and intellectual assets of the company. A granted patent will in turn influence the company's development and marketing strategies.

Patent Protection Strategies

With fewer innovative drugs emerging from pharma companies' pipelines to replace the loss in revenue that mass patent expiration represents, research-based companies will become increasingly reliant on patent protection strategies, at least for their short- to medium-term growth. In the United States alone, blockbusters with global sales of almost $82 billion will be exposed to generic competition by the end of 2007. The global generics market was worth US$27 billion in 2001 and is forecast to grow by a compound annual growth rate of 13.3 percent between 2001 and 2007.

Patent protection strategies include regulatory options and product-related options. Supplementary protection certificates, orphan drug privileges, and pediatric extensions fall into the former category; all extend the life of a patent through a variety of regulatory means.

Among the latter options, pharmaceutical companies initiate reformulation and line extension strategies, generally five to six years before a patent expires. Inevitably, as more companies market products for multiple indications from the outset, opportunities to develop and launch new indications for existing products as a means of extending patent protection will decline. Line extensions do not offer the same level of revenue protection as reformulations, due to the potential for off-label prescriptions of generic versions of the original drug. Companies also focus on additional revenues post-patent expiration by diversifying into the over-the-counter (OTC) and generics markets. That is, in order to optimize revenues, companies switch their product to OTC status before the patent expires, rather than afterward. Some companies even form alliances with generics companies prior to patent expiration.

Licensing and M&A

Defensive licensing/M&A is the last option when a company's R&D pipeline does not offer any promising new revenue generators and the potential for litigation, line extensions, and reformulations has already been maximized. Licensing agreement opportunities will substantially rise over the next decade.

Patent Protection in the United States

Major differences between the U.S. and other countries with respect to patent position include the following:

- In the United States only, an inventor's own disclosures will not invalidate his U.S. patent provided they are made no earlier than one year before the date of filing in the United States.
- Patent applications are not published at the 18-month stage but remain confidential until they are issued, refused, or withdrawn.
- Normally in other countries, it is not possible to add any further description to a patent application after the initial one-year priority period. In the United States, an addition can be done by filing a Continuation-in-Part Application.
- The United States Patent and Trademark Office has a completely different philosophy from other patent offices regarding the prosecution of patent applications. In the United States, the applicant must be scrupulously careful not to mislead the patent examiner; otherwise, this may have the effect of making a patent that appears perfectly good to be unenforceable.

Licensing of Rights and Exploitation of Technology

In the biotech field, exploiting a technology by putting it into practice and selling the resulting product or carrying out the patented process is not the most practical method. This is more so for a new venture, especially if it involves heavy capital expenditure or if it is not necessarily the most remunerative. Much depends on the size and financial strength of the investor. In deciding how to exploit a new technology, one of the major considerations is what protection is available. Cost determines whether an inventor chooses the trade-secret route or a patent. Obtaining a patent and policing and defending it are expensive.

Smaller biotech companies enter into two major types of agreements with larger companies. The first is outright sale of technology. In this case, the inventor loses his right over the property but, equally, sheds the responsibility for paying for it. A simple assigning document is executed that identifies the rights to be transferred and the price to be paid.

In the second agreement, licensing is allowed to make use of the technology. Licensing is much more complicated. The license agreement deals with the rights to be licensed, the exact nature of the license, how royalties are payable, and the conditions under which it can come to an end. Normally, certain competition constraints are imposed on license agreements but not on assignments. Sometimes, the existence of complementary technologies leads to a cross-license between the owners, so that each is authorized to use the other's technology. The type and terms of the license are primarily a commercial decision, which varies from country to country and from company to company.

Biotech companies rely on patents to protect their discoveries. Without patents, most, if not all, biotech companies would be unable to stay in business. As with previous waves of technological advancement, patents are fundamental to the industry and often are contested by competitors.

Financing

According to survey results published by the U.S. Department of Commerce, 53 percent of firms reported that the main impediment to the advancement of biotechnology research or product commercialization is access to startup capital.[5] This claim does not accurately represent the critical role that money matters play in biotechnology companies. Indeed, one of the most intriguing financial stories of the last quarter-century is the successful financing of independent biotechnology companies. Biotech ventures have been remarkably successful in raising capital on the basis of potential, rather than actual, operating results, primarily because they offer the possibility of huge returns. The main factors in this success, especially in the United States, include:

- Entrepreneurial spirit
- Availability of risk capital

- Extensive, sustained federal support of basic research
- Skilled and motivated workforce
- Accessible capital markets.

One of the principal determinants of a biotechnology venture's success is its ability to raise capital at a reasonable cost and in amounts sufficient to meet its business objectives. The main sources of financing of biotech companies are:

- Equity (including quasi-equity) purchases by venture capital and other private investors
- R&D and joint venture (including licensing) arrangements with and equity purchases by established companies
- Government-supported R&D
- Sales of equity in public equity markets
- Payments from research and development limited partnerships
- Equipment lease lines
- Debt financing

The major stages of financing are:

- Seed investment of no more than a few hundred thousand dollars;
- Six months to a year later, first-round venture capital funding with a lead investor, followed by subsequent rounds of funding;
- By year three or five, an additional requirement to pay for the facilities to commence production and clinical trials (i.e., second and third rounds of funding);
- Around year six or eight, the company may become a public corporation, form an alliance, or be acquired by a large pharma or biotech company.

Further, biotech companies confront unique problems and circumstances, including high cash-burn rates, lengthy product development cycles, and uncertain and often unreceptive capital market. All of these potential difficulties have led to the development of several innovative variations on traditional financing methods.

R&D Limited Partnerships

Federal income tax regulations formerly in effect liberally permitted favorable tax deductions by limited partners in a partnership engaged in passive loss-making activities. This led to the widespread use of R&D partnerships, which allowed biotechnology companies to report, for accounting purposes, payments received from a properly constructed R&D partnership as contract revenues and, at the same time, permitted limited partners to obtain favorable tax deductions. Once this tax

treatment was eliminated, the importance of R&D limited partnerships as a vehicle for funding research activities drastically declined.

SWORD—Stock and Warrant Offering for Research and Development

The SWORD arrangement allows companies to pursue promising but risky research activities in an off-balance-sheet manner. A typical SWORD transaction consists of the creation of a new special-purpose corporation, which is sold to the public through an offering of investment units, or SWORDs. Each SWORD consists of one share of a special-purpose corporation, subject to a call option in favor of the company, and a warrant to purchase one share of stock in the sponsoring company. SWORD becomes unbundled after a specified period, generally 3 to 30 months, at which time stock and company warrants start trading separately. The money raised is transferred to the sponsor company in exchange for an undertaking to perform certain research activities on behalf of a special-purpose corporation. The special-purpose corporation is given ownership rights to all products and technologies developed out of that research. However, the company's call option on the special-purpose corporation stock allows it to capitalize on such developments should they prove successful.

SWORD allows the company to account for R&D costs as income rather than losses, and the sponsor company is also able to protect itself against exposure to risk in the event of an unsuccessful research effort. Purchasers benefit in two ways: there is a significant upside if the company exercises its call option, and if it is not exercised there is a lesser benefit through exercise of warrants to purchase the company's stock, provided the stock continues to trade at a level above the warrant exercise price.

The Virtual Corporation

The search for sustainability has led to a variation on traditional top-down organizational structure. In a virtual corporation, employees are few and key company functions are contracted out to third parties. This helps to avoid many of the bricks-and-mortar costs associated with building laboratories and manufacturing facilities. However, it also leads to the loss of oversight and control that is inherent in depending upon a third party's performance. Many biotech startups have used this model only to build the bricks-and-mortar model after initial success.

Follow-on financing means subsequent public offerings. PIPES (private investment in public equity securities) was introduced in the early 1990s. This method of financing is a public-private hybrid that allows investors to buy stock in public companies at a discount, usually 5 to 15 percent off the market price, and eliminates the restrictions normally placed on private investors. The closing of such financing is contingent on the filing of a shelf registration statement.

Table 3. U.S. Biotech Industry Funding (in millions of dollars)

Year	IPO	Follow-on	PIPES	Debt	VCs	Others	Total
1997	688	1,601	1,283	1,288	569	184	5,613
1998	369	521	977	1,262	800	84	4,013
1999	670	5,805	1,433	1,520	1,084	184	10,696
2000	6490	12,651	4,061	5,728	2,872	203	32,005
2001	440	2,539	1,741	4,848	2,397	9	11,974
2002	445	979	907	5,251	2,688	178	10,448
2003	453	3,536	2,051	7,170	2,841	244	16,295

Source. Burrill & Co. presentations at industry events, November 14, 2003 and April 17, 2004.

Venture Capital (VC)

As is apparent in the above table, VC money has contributed significantly to biotech industry financing and, unlike other forms, has been steadily increasing. Recently, in fact, the biotech industry overtook the IT industry in terms of attracting VC money in the United States. VCs normally fund companies in the early stages of development, up to the first or second phase of clinical trials. It is interesting to note that VCs do not base their investment decisions on financial models or on numbers in the companies' business plans. Instead, they consider the people (i.e., the management team and the CEO), the market opportunity that the biotech company addresses, and the technology itself. VCs attach little importance to intellectual property rights (IPRs) unless they are a necessary condition for the company's success.

Industry Trends

Several important trends are shaping the future of the pharma and biotech industries. Some may be more applicable to one segment than the other, but studying them will help either industry to help prepare valuable strategies.

Clusters

An industrial cluster is a geographic concentration of interconnected companies, specialized suppliers, service providers, firms in related industries, and associated institutions that compete but also cooperate. As in the IT industry, the biotech industry is characterized by the presence of strong clusters in all countries. Examples of such clusters occur in the United States (e.g., Silicon Valley (San Francisco), Boston, San Diego, Seattle, Maryland), and especially California; the United Kingdom (e.g., Cambridgeshire and Oxfordshire); Germany (e.g., Munich and the Rhineland); Canada (e.g., Toronto, Montreal, and Vancouver), and India (e.g., Bangalore and Hyderabad).

Many factors play a critical role in the development of these clusters. While it is understood that such clusters cannot be created, support and incentives certainly encourage their growth. The main contributors include a strong science base, an entrepreneurial culture, availability of talent, infrastructure, research institutions, financing options, and a supportive policy environment.

Outsourcing

Like the IT industry, the pharma and biotech industries are experiencing an outsourcing phenomenon. This is due to a lack of in-house expertise and efficiencies. The pharma industry's profitable heritage did not provide the impetus to address internal company efficiencies properly, as other sectors have. Investment decisions have not necessarily been explicitly linked to shareholder value. From an economic perspective, past decisions have not necessarily been based on efficiencies, due to the industry's high profitability, protection of perceived core competencies, and lack of faith in the capability of outside vendors.

As erosion in prices and margins challenges the industry's profitability, outsourcing will increase. In the United States, R&D outsourcing is expected to increase from $10 billion today to $36 billion by 2010.[6] Unlike the pharma industry, which currently contracts out and will continue to increase outsourcing purely for cost savings, the biotech industry is forced to outsource because it lacks all the expertise of the value chain. R&D and sales and marketing functions suffer from declining productivity. It is estimated that—compared to the 80 percent of activities performed in-house today—only 40 percent will eventually be performed in-house, and 60 percent of those through a risk-managed portfolio of straight outsourcing arrangements and strategic alliances. In the short and medium term, however, outsourcing is likely to remain internal or domestic, rather than offshored to low-cost developing countries, due to FDA regulations and intellectual property concerns. Further, e-technologies in R&D will have a positive effect on the outsourcing sector. They have the potential to improve outsourcing effectiveness through superior knowledge management and communication between vendors and sponsors. Thus outsourcing will help reduce both the time and the cost of drug development.

Theranostics and Personalized Medicine

The term "theranostics" has arisen from a combination of diagnostics and therapeutics. Diagnostics and therapeutics are increasingly converging, a trend that will lead to predictive and precise diagnostics and personalized and preventive medicine. Many scientists believe that personalized medicine will be the dominant trend of the future due to the sensitivity and specificity to individual patients, and the compliance benefits that it provides.

The new frontier of the post-genomic era is preventive medicine, initiated by predictive diagnostics. Most genomic technologies are enabled to discover molecular signatures produced by cells in the early stages of disease that lead to early and correct diagnostics.

Another trend is the development of theranostic tests that predict drug response in individual patients. The pre-genomic era has successfully developed drugs to treat the symptoms of disease. In the post-genomic era, molecular diagnostics and therapeutics will allow preventive steps to be taken to stop disease from developing in the first place, or to prevent disease from progressing by treating its cause, not just its symptoms. In addition to theranostic tests, according to industry experts, predictive tests for approximately twenty-five conditions are likely to become available by 2010.

Partnering/Alliances

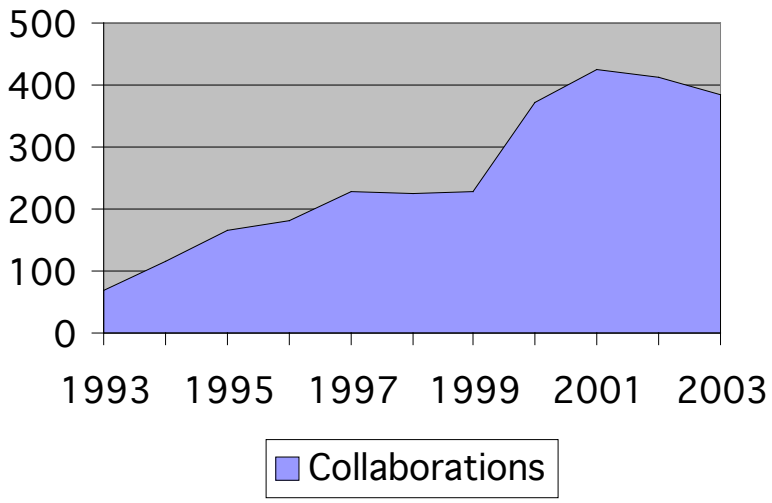
The Commerce Department survey points out the growing importance in biotech of partnerships, alliances, and collaborations. The near-term strategies of 53 percent of the firms surveyed focus primarily on developing technologies that can be licensed to other customers. Forty-seven percent of firms are focused on acquiring technologies from other companies through licensing arrangements, and 23 percent of firms are intending to develop joint-venture agreements for technology development.[7] Since the early 1990s, research and discovery collaborations between biotech and pharma companies have increased to the point that they now provide more than half the total capital invested in the biotech sector. Although smaller biotech companies may be engaged in only a few alliances at a time, some of the most active pharma players may be engaged in anywhere from thirty to forty alliances at once. Not only are these partnerships of long duration, but the agreement process itself is lengthy. In one case study, Novartis screened about one thousand alliance proposals, of which six hundred were shortlisted. Due diligence was carried out on forty companies and finally only ten to fifteen agreements were finalized. This gives an indication of the time and resources the big companies devote to this purpose.

According to the conclusions of another report,[8] the first two years of the twenty-first century have witnessed significant changes in the pharma/biotech alliance landscape. These changes concern the number of alliances announced, the value of alliance agreements, the split between relationship- and transaction-based alliances, and the profiles of the partnering companies. This study revealed the following trends and outcomes:

- There has been major growth in relationship-based alliances, whereas the number of transaction-based alliances has remained constant.
- There has been an overall increase in the average deal value.
- More than one-half of the companies covered under the study are categorized as biotech companies.
- Alliances are divided equally between deals involving technology and therapeutic areas, those involving only therapeutic areas, and those involving technology only.

- Well over one-half of alliances—65.8 percent—happened in the discovery/preclinical stage, 24.1 percent in the clinical development stage, and 10.2 percent in the registration, approval, or marketing stages.
- Relationship licensing agreements were the most widely employed, co-commercialization agreements were the highest value type, and co-development agreements are experiencing the greatest growth.
- Oncology was the most popular subject area and also has the highest-value alliances, but cardiovascular medicine is experiencing the greatest growth rates.
- Genomics is the most popular subject area, bioinformatics has the greatest value, and drug-delivery agreements are experiencing the highest growth rates.
- Agreements between two or more biotech companies are the most popular, bio-pharma offers the highest-value alliances, and alliances involving equipment and device companies have the highest growth rate.

Figure 3. Alliances between Biotech and Pharma since 1993



Source. Burrill & Co. presentations at industry events, November 14, 2003 and April 17, 2004.

In their simplest form, these alliances consist of a contractual arrangement under which the biotech company performs specified research funded by the established company and licenses the sponsor to develop, manufacture, and market products that incorporate the research results in return for a royalty on net product sales. A joint venture between two companies is formed with the biotech company contributing its research results and capability and the established company contributing its financial, manufacturing, distribution, or marketing resources. As the biotech company gains strength, it negotiates to retain the right to develop its other products and manufacture a portion of the licensee's needs for commercial products. It also seeks to preserve one

or more countries as its exclusive territory for marketing and sales. If a company is judicious in its selection of venture partners, the venture can be a creative vehicle to accelerate the commercial introduction of the company's technology in a defined area, or to build a foundation for the company's efforts in other areas. The relationship must be structured to ensure mutual interest and an equitable sharing of control and returns based on the value of the respective contributions of the partners.

The major terms of the alliance agreement are:

- *Technology rights*: Distinction between basic technology and product technology.
- Field: Product, application, and territory. The most difficult element is determining what product is being licensed. It is relatively easier to express specific permitted uses, such as therapeutic vs. diagnostic, human vs. animal healthcare, health vs. agriculture, etc.
- *License grant*: Grant of right describes the primary subject matter of the license in connection with product's commercialization.
- *Diligence*: It is extremely important that the licensor be protected against the possibility that the license will put the technology "on the shelf." Two solutions can be worked out: termination of the license or payment of minimum royalties.
- *Termination*: Agreements commonly contain a termination right for the licensee in the event that the alliance becomes technically or commercially infeasible. Another safeguard is a non-compete clause.
- *Patents*: Licensor should retain the right to prosecute patent applications and enforce patent rights if a multiple licensing strategy is its objective.
- *General term*s: Licensor should obtain product liability indemnity and should disclaim warranties.

A typical deal might involve a small biotech company collaborating with a big pharma or biotech company for joint development of its product. In such a case, both companies agree to take the product through clinical trials, with the bigger company having the exclusive right to market the product in the U.S. market. The bigger company makes some upfront payment to the smaller company and agrees to fund clinical development. The bigger company also agrees to pay certain royalties on net sales to the biotech company once the product is launched. We are also witnessing a growing trend toward nonexclusive deals wherein biotech companies retain the right of co-promotion or co-marketing.

Research alliances with small, close-to-the-science companies are the source of many innovative ideas, but they present formidable challenges. Successful collaboration depends not only on solving scientific and technical problems, but also on successfully resolving many leadership and organizational problems. Effective alliances must resolve the following issues in order to succeed:

- Power differences and other asymmetries between partner firms, with implications for alliance dynamics.

- Sector history and evolution as a basis for understanding the cultural divide that characterizes many biotech-pharma relationships.
- The need for leaders on the biotech side to assume greater leadership responsibility in these alliances.
- Different—and predictable—challenges over the alliance's life cycle, from start to completion/termination.
- Leadership roles needed for productive and effective collaboration across groups, locations, and companies.[9]

A single alliance may be the lifeblood for a small biotech company; the same relationship may be just one of many for the pharma partner. Management and leadership of these alliances should rest squarely on the shoulders of those on the biotech side. Alliances should be led and managed by the biotech companies, even though it is the big pharma companies that experience the innovation gap, who need biotech expertise beyond their own in-house R&D, and who are the paying parties. Strategic biotechnology alliances are not relationships among equals. Smaller companies invariably have less say in the alliance yet still have to do more to keep the alliance on track. Yet responsibility for the relationship should fall on the shoulders of the leadership of the biotech company for two reasons. First, knowledge frontiers are moving quickly, and biotech companies with competent scientists are better able to master this dynamic field. Second, a biotech firm's survival depends, to a large extent, on alliance revenues.

Contrasting cultures, along with differences between pharma and biotech companies, contribute to complicated alliance dynamics. Big pharma companies evolved from the chemical industry, and biotech evolved from academia. The pharma industry culture is a rigorous culture of precision and objectivity, but also of hierarchical dependency, discipline, and subservience. The biotech industry, on the other hand, stems from a primarily democratic, liberal culture in which formal hierarchies play a much smaller role. Personal development and freedom are more important. Challenges also arise due to differences in scale of operations. For the alliance to be effective, alliance team members must:

- Discuss the asymmetry between partners in order to appreciate and manage its implications.
- Perform due diligence on the organization and its people to get a good sense of the partner's strategy and the perspectives of its scientists.
- Prepare each person involved in the alliance, paying special attention to interpersonal skills.
- Avoid surprises by staying in touch with one another to monitor productivity and morale through effective and efficient communication.
- Be disciplined and careful in their science.
- Not guard information.

- Be willing to work collegially with one another and with scientists of the partner organization.
- Have well-defined milestones and exit clauses in the alliance agreement.
- Form a joint governing group of scientists.[10]

Alliances may be ineffective if team members (1) do not consider the impact of a change in the senior management of the larger partner on the priority of the alliance; (2) fail to be upfront about difficulties with a set of experiments; (3) do not trust the partner enough to hand over data efficiently; (4) assume interpersonal problems will solve themselves; (5) do not manage the "difficult scientist" effectively; (6) feel they have to fight for attention and commitment from senior leaders.[11]

Evolving Technologies and Their Convergence

Today we are seeing the "omic"-ization of the biotech industry: most of the emerging technologies are genomics, proteomics, cellomics, pharmacogenomics, and so forth. These technologies promise more rational drug discovery, faster drug development, targeted patient populations, greater chances of clinical success, faster time to market, and reduced marketing costs. It is also anticipated that new technologies, such as arrays of genes and proteins, will permit analysis of multiple gene and protein expression that will more accurately detect and profile a patient's disease. The drive for traditional drug discovery research has shifted from chemistry to genomics. Previously, researchers made chemical compounds first and then tried to identify compounds' use for a disease target. Now, researchers first identify and understand a disease target, and then develop a chemical compound that can be used to counter that target. The drug development process has become more focused and, thereby, effective. Next, the drug discovery process will transition from structural genomics to functional genomics to structural proteomics and finally to functional proteomics.

In this new era, it will not be any single technology but the integration of many technologies and the collaborative efforts of scientists that will allow drug discovery to reach its fullest potential. This will lead to improved efficiency and productivity in the drug discovery process. According to the Pharmaceutical Research and Manufacturers of America, the R&D expenditures of U.S.-based pharmaceutical companies have more than tripled in the last decade.[12] Pharmaceutical companies are integrating entirely new discovery technologies into their drug development programs, through alliances with biotechnology companies and universities as well as their own in-house initiatives. From the pharmaco-genomics perspective, three main trends are emerging:

- Target validation will take precedence over other niche technologies.
- Increasing usage of information technology hardware and software tools will drive DNA-related data recording and analysis in drug discovery, which in turn will enhance the speed and accuracy of drug discovery process.

- Diagnostics is the next area of expansion but will continue to be dominated by a few companies with established expertise.

Pharmaco-genomics will increasingly be driven by marketing. The incorporation of pharmaco-genomics into clinical trials will likely increase over the next decade but will remain in either early-stage testing or post-launch in phase IV trials. Pharmaco-genomic tests can be employed throughout the drug life cycle, including in preclinical development, clinical trials, regulatory approvals, and marketing.

Through the use of predictive modeling tools, molecular informatics, and ultra-high-throughput screening technologies, in addition to parallel and integrated drug-discovery approaches, the traditional sequential process of drug target discovery will become shorter. There is also an increasing trend toward convergence of different technologies, both within and outside of biotech, all aimed at reducing the time and cost of drug development, and achieving breakthroughs. This convergence involves diverse streams of sciences and technologies, including wet biology (meaning the actual laboratory experiments carried out), digital biology (involving IT, including bioinformatics), and extension of nanotechnology applications. Such a fusion of sciences will not only accelerate the process but will also help scientists to explore untouched areas of research.

Ethical Issues

Ethical values include belief in the promotion of patient welfare and the social good, scientific freedom and responsibility, self-determination, encouragement of civic discourse, public accountability of scientists and research institutions, and respect for diverse religious, philosophical, and secular belief systems. It is important to realize that technologies, like the tools by which they are manifested, can be used for better or for worse. The biotech industry faces uphill ethical issues and challenges, some of which are discussed below.

A. Excessive Marketing

Today, companies have huge budgets for promoting drugs. Marketing costs have skyrocketed and raised the price of products, thereby increasing healthcare costs and reducing the reach of drug benefits.

Possibly a more important development is that companies today are reinventing normal health conditions as diseases, either to boost their new drugs, or to convert their ordinary drugs into blockbusters. The best example of this phenomenon is drugs for male erectile dysfunction. Until a variety of products designed to overcome it hit the market, this was considered a normal condition. Now even people without this condition use these drugs, causing overuse of the product and increased sales and profitability for pharma companies.

Finally, pharma advertising has reached new peaks, which again has the potential to result in drug overuse or misuse. The claims and attractive promises made by companies in their campaigns induce patients to self-prescribe medicines and sometimes even to override their doctors. Restrictions on the costs, as well as guidelines on the authenticity and quality of drug marketing campaigns are needed.

B. Third-World Drug Availability

Developed countries represent nearly 90 percent of global pharma sales. However, of the 14 million annual deaths caused by infectious diseases worldwide, 90 percent occur in developing countries. The WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) is flexible, and to make full use of that flexibility, member states need to adapt national patent legislation. The current patent protection system restricts the access that people in developing countries have to medicines, due to their prohibitive cost. Trade-related aspects of intellectual property rights (TRIPS) should not prevent WTO member countries from endeavoring to protect public health and, in particular, to promote access to medicines for all. To tackle new public health problems with international impact, such as SARS, access to new medicines and health innovations should be universally available without discrimination.

C. The 10/90 Gap

There is little R&D being carried out on diseases that primarily afflict the poor. According to a report by the Global Forum for Health Research,[13] the public and private sectors spend more than US$70 billion on health R&D a year, yet only about 10 percent of this money is targeted at the diseases that account for 90 percent of the global disease burden. Of the 1,400 new products developed by the pharma industry between 1975 and 1999, only thirteen were for tropical diseases and three were for tuberculosis.[14] R&D in the pharma sector must address public-health needs and not only potential market gains. This 10/90 gap has arisen due to the following:

- Communicable diseases not prevalent in the high-income countries continue to account for a large share of the disease burden in lower-income countries.
- Vaccines developed for industrialized country markets may not be effective against the different types of viruses and bacteria prevalent in poorer countries.
- Determinants of ill health can vary greatly between regions.
- Performance of health systems and services varies greatly between countries.
- Access to treatment and medicines differs between and within countries.
- Interventions for noncommunicable diseases available in more advanced countries may not be directly adaptable, appropriate, or cost-effective in lower-income countries due to costs and infrastructure requirements.

These high costs provoke the question: Are we over-investing in this type of research? Is it possible to spend more to reduce poverty and improve education and infrastructure, thereby improving people's health? Society must consider reevaluating its investment portfolio.

D. Genetic Engineering, Stem Cells, and Cloning

Decisions about the immensely complicated subject of genetic engineering should not remain solely in the hands of scientists. Public attitudes will influence its evolution and marketplace applications. The genetic engineering debate could prove to be a critical testing ground for efforts to insert socioeconomic and sociocultural measures—the so-called fourth criterion—into governmental policies. Measures of efficacy, quality, and safety alone are insufficient to judge the potential risk associated with these new techniques. Social and moral considerations also play a role. Though biomedical applications have progressed rapidly, these factors will have a major impact on agricultural and environmental applications.

Stem cell research raises ethical and policy concerns, but such issues are not unique to this field. The recommendations of the American Association for the Advancement of Science and the Civil Society Institute provide a good overview of key points to consider about stem cell research:

- It is essential that the public be educated and informed about the ethical and policy issues raised by stem cell research and its applications. Informed public discussion of these issues should be based on an understanding of the science associated with stem cell research, and it should involve a broad cross-section of society.
- Existing federal regulatory and professional control mechanisms, combined with informed public dialogue, provide a sufficient framework for oversight of human stem cell research.
- Federal funding for stem cell research is necessary in order to promote investment in this promising line of research, to encourage sound public policy, and to foster public confidence in the conduct of such research.
- Public and private research on human stem cells derived from all sources (embryonic, fetal, and adult) should be conducted in order to contribute to the rapidly advancing and changing scientific understanding of the potential of human stem cells from these various sources.
- Public funding should be provided for embryonic stem cell and embryonic germ cell research, but not at this time for activities involved in the isolation of embryonic stem cells, about which there remains continuing debate. This approach will allow publicly funded researchers to move more quickly toward discoveries that will lead to alleviating the suffering caused by human disease.

- Embryonic stem cells should be obtained from embryos remaining from infertility procedures after the embryo's progenitors have made a decision that they do not wish to preserve them. This decision should be explicitly renewed prior to securing the progenitor's consent to use the embryos in embryonic stem cell research.
- Persons considering donating their excess embryos for research purposes should be afforded the highest standards of protection for the informed consent and voluntary action of their decision.
- Where appropriate, guidelines that can attract professional and public support for conducting stem cell research should be developed.
- In order to allow persons who hold diverse moral positions on the status of the early participation of the embryo to participate in stem cell research to the greatest degree possible without compromising their principles, and also to foster sound science, stem cells (and stem cell lines) should be identified with respect to their original source.
- Special efforts should be made to promote equitable access to the benefits of stem cell research.
- Intellectual property regimes for stem cell research should set conditions that do not restrict basic research or encumber future product development.
- The formation of company-based, independent ethics advisory boards should be encouraged in the private sector.[15]

Challenges of the Medical Biotech Industry

There are about nine hundred known human diseases, of which 70–80 percent have no cure. With the completion of the sequencing of the human genome, scientists have discovered thirty thousand genes and forty pathways to work with. The healthcare needs of the world population are so vast that in spite of achieving great success in the last decade or so, the biotech industry still faces stiff challenges. First, science, the human body, and disease are, essentially, complex. Second, unlike other high-technology industries, the biotech product development cycle is very long even after proof of concept. In most other industries, especially information technology, the development period is short and a new technology or product rarely fails after the concept is proven. Such projects also achieve profitability or viability quite early. Biotech projects take between ten and twenty years to become successful and cost over $200–300 million before a product reaches the market. Third, delivery of most biotech products and therapies is complex and often painful due to intravenous delivery. There has been increasing interest in developing easier delivery mechanisms, which sometimes also prove more efficacious. Inhalable insulin is the best example of what the future might hold. Fourth, R&D financing poses a challenge.

R&D investments are encouraged through the incentives of the patent regime, whereby a company obtains exclusive rights to its product for twenty years from the patent application filing date. On average, companies receive eight to ten years of

market exclusivity to sell their product and recoup R&D costs. Critics have suggested that this regime leads to high drug prices and high profitability for the industry. Indeed, there is great inequality in worldwide drug availability and affordability. Only 10 percent of R&D expenditure is invested to research 90 percent of the disease burden of the world. In this ongoing debate, there have been many suggestions for changing the framework of R&D financing. Some of the alternative approaches include:

- Prize model (researcher/research organization entitled to a cash prize based on the value of the discovery or novel drug)
- Direct funding through government or public-sector agencies
- Open collaborative models such as the Human Genome Project
- Competitive intermediaries to manage R&D
- Combination of the above approaches.[16]

In the case of drugs for critical diseases such as AIDS, companies are especially challenged to address the tension between their interest and the public good.

Outside Determinants

Regulation

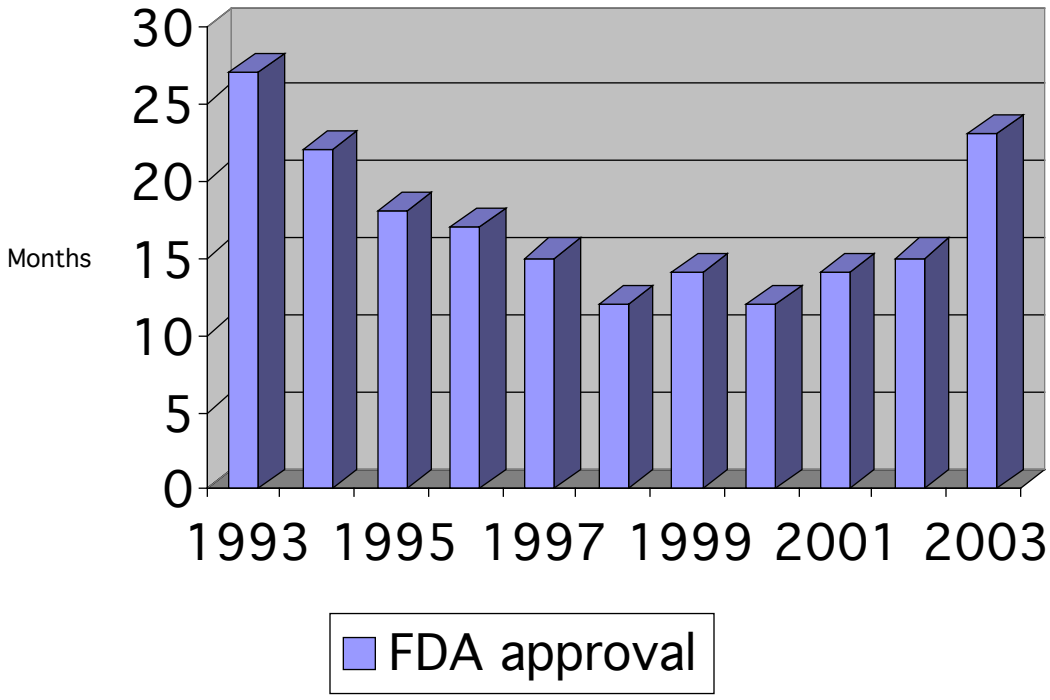
The FDA wants to exclude reasonably unsafe products from the marketplace and industry wants to bring reasonably safe products in. This clash of interests and attitudes between the food and drug authorities and industry has a major impact on the latter. In a Commerce Department survey, 59 percent of firms indicated that the main impediment to the advancement of their biotech research or product commercialization was the regulatory approval process and associated costs. FDA drug approval has been delayed in the recent past.

When the FDA declined in December 2001 to approve ImClone's cancer drug Erbitux, the market valuation of both the company and the biotech industry fell by about 40 percent. As it turned out, the FDA approved the drug two years later completing its full scrutiny, whereupon the company's valuation bounced back to its original level. In the interim, however, the industry was severely challenged, especially during the drug approval process. In short, the FDA's guidelines regarding clinical trials and the generic drug approval process can have a pronounced financial cost.

Aging Population

In most of the developed countries baby boomers are a significant portion of the population. As life spans increase, healthcare costs place a greater burden on developed nations' economies. This affects the biotech industry in two ways: first, there is pressure to develop cures for diseases related to old age, and second, there is a need to improve drugs and therapies to reduce the cost of treatment.

Figure 4. FDA Approval Time (months)



Source. Burrill & Co. presentations, November 14, 2003 and April 17, 2004 at industry events.

Reimbursement Climate

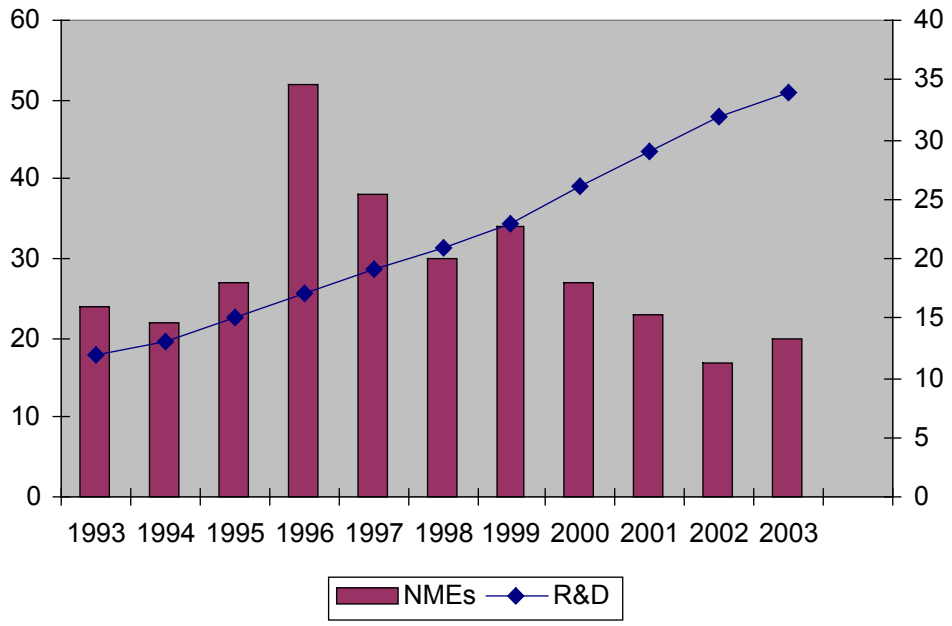
Healthcare costs are an increasing burden on government budgets, and the United States and Europe offer ample evidence to support this statement. In 2003, the United States spent about 15 percent of GDP on healthcare. Because of this mounting pressure to spend, restrictions have been put in place to limit reimbursement of medical expenses. As these expenses are curtailed, company profits will in turn come under pressure, which might act as a deterrent to investments in R&D. Critics of the pharma industry believe that prices and rates of return in the prescription drug market are abnormally high. The industry counters that rates of return in the industry, when R&D costs are appropriately accounted for, are fair.

Big Pharma

Big pharmaceutical companies are investing more in R&D, but their product pipelines—also known as new molecule entities, or NMEs—are drying out, as Figure 5 shows. Of forty-four products generating blockbuster sales in 2000, thirty-three will lose patent protections in the United States before 2007.[17] That is, about $82 billion of blockbuster sales worldwide will be under threat from generic competition by 2007. Moreover, existing product pipelines are too small to match the market expectations

and continue to generate similar numbers in the future. Major consolidation has already taken place and big pharmaceutical companies are looking to the biotech industry to fill their product pipeline gap, as Figure 5 also illustrates.

Figure 5. R&D Investment and New Drug Discovery



Source. Burrill & Co. presentations, November 14, 2003 and April 17, 2004, at industry events.

Stem Cells

Stem cell research is one of the most fascinating areas of biology today. But like many expanding fields of scientific inquiry, research on stem cells raises questions as rapidly as it generates new discoveries. The greatest potential application of this research is the generation of cells and tissues that can be used for cell-based therapies. Human stem cell research holds enormous potential for contributing to our understanding of fundamental human biology. Although it is not possible to predict the outcomes of basic research, such studies offer the possibility of treatments, and ultimately, of cures for many diseases for which adequate therapies do not now exist.

Stem cells are the cells from which all 210 different kinds of tissue in the human body originate. Stem cells occur from the earliest stages of human development and provide the starting material for every kind of tissue and organ in the human body. A stem cell is a special kind of cell that has a unique capacity to renew itself and to give rise to specialized cell types. To put it simply, stem cells, through the process of differentiation, form various tissues and organs; the combination of these differentiated materials develops into the whole human body.

Stem cells have three important properties. First they are capable of dividing and renewing themselves for long periods through cell division. Second, they are unspecialized. Third, they can give rise to specialized cell types with special functions under certain physiological or experimental conditions. The possibility that stem cells from one tissue may be able to give rise to cell types of a completely different tissue is a phenomenon known as plasticity. This within the category of stem cells, there are two kinds: embryonic and adult.

Embryonic Stem Cells

Embryonic stem (ES) cells are found at the blastocyst stage, four to five days after the union of the sperm and the egg, before the embryo implants into the uterus. The blastocyst consists of a hollow ball of cells containing about twenty undifferentiated stem cells clustered in an inner cell mass. These cells are believed to be "pluripotent"—that is, capable of forming all embryonic tissues, but unable to form a complete organism without placental support. By culturing the cells derived from the inner cell mass, researchers can obtain embryonic stem cell lines that can grow and divide indefinitely. These cell lines can be frozen in small batches for future experiments. Unlike most other types of cells, embryonic stem cells can reproduce themselves repeatedly and mature into a wide range of different cell types. This provides a potential source of new cells to repair damaged tissue in, say, diabetes or Parkinson's disease. These embryonic stem cells dislike solitude and refuse to thrive unless they are in contact with so-called feeder cells. Mouse cells are normally used as feeders. But there are fears that such stem cells may have picked up nasty viruses from their mouse feeders. A number of groups are working on alternatives—to use human feeder cells or simply dispense with feeder cells altogether. The National Institutes of Health has approved sixty embryonic stem cell lines developed all over the world as eligible for federal funding for further research.

There are five ways to obtain embryonic stem cells:

- Somatic cell nuclear transfer, or "cloning" as it is more popularly known, is a way to create embryos without the conventional meeting of egg and sperm that is needed to provide a full complement of the genetic material to make a new individual.
- Embryos can also be created by parthenogenesis, a biological trick in which an unfertilized egg cell is coaxed into providing all the genetic material required for embryonic development.
- Taking one of the existing embryonic stem cell lines and forming another cell type to create new lines.
- Culling fetal stem cells from aborted fetuses.
- Removing embryonic stem cells from unused embryos taken from in vitro fertilization clinics.

Adult Stem Cells

The other groups of stem cells, called adult stem cells, are found in tissue or organs. Adult tissue reportedly containing stem cells includes brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, and liver. Bone marrow contains at least two kinds of stem cells—hematopoietic stem cells and stromal cells. Adult stem cells are responsible for repair and regeneration in the body. In the body, adult stem cells can proliferate without differentiating for a long period. Evidence to date indicates that umbilical cord blood is an abundant source of hematopoietic stem cells. Current methods for characterizing adult stem cells depend on determining cell-surface markers.

The differences between adult and embryonic stem cells are as follows:

- The most distinguishing feature is their source.
- They have a capacity to specialize into various cell and tissue types.
- Large numbers of embryonic stem cells can be relatively easily grown in culture, while adult stem cells are rare in mature tissues and methods for expanding their numbers in cell culture have not yet been worked out.
- The potential advantage of using stem cells from an adult is that such cells would not be rejected by the immune system.
- Embryonic stem cells may form clumps of cells that can differentiate spontaneously to generate many cell types.
- Adult stem cells do not seem to have the same capacity to differentiate.

Developments and Scientific Evidence

Research on stem cells is rapidly advancing knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat disease, which is often referred to as regenerative or reparative medicine. In 1998, for the first time, investigators were able to isolate this class of pluripotent stem cell from early human embryos and grow them in a culture. Thus, this class of human stem cell holds the promise of being able to repair or replace cells or tissues that are damaged or destroyed by many of our most devastating diseases and disabilities.

It is now possible to grow these cells for up to two years in a chemically defined medium. Four types of cells have been successfully grown in the lab: pancreatic islet-cell like cells, cardiac muscle cells, blood cells, and nerve cells. Some of the uses of stem cell research include new windows on human developmental biology, new models of human disease that go beyond current animal and cell culture models, transplantation, and gene therapy. Human stem cells could also be used to test new therapeutic drug candidates.

The opportunity to utilize small samples of adult tissue avoids ethical or legal issues surrounding stem cell research. However, production of a large numbers of these cells is much more difficult.

Chronologically speaking, embryonic stem cell research has experienced ups and downs. In 1979, Congress approved a moratorium on experiments using human embryos fertilized in labs. In 1996, the first "Dickey amendment" banned federal funds for experiments that destroyed human embryos. The amendment was renewed in 1998 and 2000. In 1998, researchers at the University of Wisconsin and at Johns Hopkins University extracted and grew stem cells from human embryos. In July 2001, a Virginia lab announced that it had created embryos for research using private funds.[18] On February 14, 2004, news broke out that researchers in South Korea, for the first time, had cloned a human embryo and then culled stem cells from it.[19]

While many believe that embryonic stem cells offer the greatest promise for developing new medical treatments, others feel that adult and alternative sources of stem cells have demonstrated much brighter prospects. The jury is still out with regard to the validity of either claim, but the public's perception will have significant societal consequences, and may even affect levels of public and private research funding of embryonic and adult stem cell therapies. So far, adult stem cell research is leading the race.

Sweden's Potential

Sweden is a leader in stem cell research. Compared to the United States, where only handful of the initial fifty companies engaged in stem cell research remain viable, Sweden has forty private stem cell companies. Sweden's research institutes have 32 percent of the world's stem cell inventory, close on the heels of the U.S.' 35 percent. Sweden consistently leads the race in per capita output of patents and peer-reviewed scholarly articles. Sweden has well-established stem cell research programs, thanks to government-backed funding incentives.

Challenges

Despite these promising new approaches, many regulatory, ethical, and scientific hurdles lie in the path ahead. Some key questions include:

- Is there a universal stem cell?
- What are the sources of adult stem cells in the body?
- How will specialized cells derived from embryonic stem cells behave in the human body?
- How can we control the differentiation of stem cells into specific cell types?
- What factors in living organisms normally regulate stem cell proliferation and self-renewal?
- What stage of differentiation of stem cells will be best for transplantation?
- What differentiation stages of stem cells would be best for screening drugs or toxins?

Table 4. Recent Regenerative Research Successes Using Adult Stem Cells

Parkinson's Disease	Brain function in five patients with advanced Parkinson's disease was partially restored using a natural body chemical known as glial-derived neurotrophic factor (GDNF). Phase II studies are now being considered.[i]
	A Parkinson's patient treated with his own brain cells appears to have experienced substantial remission with no adverse side effects. Human trials in this technique are now being considered.[i]
Heart disease	Bone marrow stem cell, blood stem cells, and immature thigh muscle cells have been used to grow new heart tissue in both animal subjects and human patients. Human trials using adult stem cells have commenced in Europe and other nations.[i]
Diabetes	Harvard medical school researchers reversed juvenile onset diabetes in mice using precursor cells taken from spleens of healthy mice and injecting them into diabetic animals.[i]
	In the U.S. and Canada, more than 250 human patients with type I diabetes were treated with pancreatic tissue (islet) transplantations taken from human cadavers. Eighty percent of those who completed the treatment protocol have achieved insulin independence for over a year.[i]
	Blindness is one symptom of diabetes. Human umbilical cord blood stem cells have been injected into the eyes of mice and led to the growth of new human blood vessels.[i]
Cancer	The British company Tristem is claiming to have developed a process to convert easily isolated white blood cells into stem cells. If confirmed, the technique alone could revolutionize bone marrow transplants and leukemia therapy. The key to Tristem's transgeneration technique is a special antibody manufactured by DakoCytomation of Denmark that is normally used to detect abnormal brain cells.[ii]
Alzheimer's Disease, muscular dystrophy, and other neurological dysfunction	Sweden announced that one of its biotechnology companies is the first in the world to enter clinical trials with a new drug that could cure Alzheimer's disease.[iii]
	Bone marrow stem cells have partially helped regenerate muscle tissue in mice with muscular dystrophy.[i]
	Several spinal cords in rats were regenerated using gene therapy to prevent growth of scar tissue that inhibits nerve regeneration.[i]
	After more than a decade of human neural transplantation studies, our knowledge of the basic immunological properties of conventional embryonic and fetal donor tissue remains inadequate. In most cases, immunological concerns are not specifically addressed. The results of experiments are encouraging with respect to the ultimate immunological success of neural progenitor cell transplantation.[iv]

[i] See Wesley J. Smith, "Stem Cell News That Isn't Fit for Print," *Weekly Standard*, December 3, 2003 <http://www.weeklystandard.com/Utilities/printer_preview.asp?idArtic> Accessed February 6, 2004.

[ii] See Sciscoop.com Science News Forum, "Major Breakthrough in Disease Treatment Via Stem Cells Claimed," November 29, 2003.

[iii] See *Red Herring*, "The Hard Cell," *Red Herring* no. 97 (February 13, 2003) <http://www.redherring.com/PrintArticle.aspx?f+Articles/Archive/inve> Accessed February 6, 2004.

[iv] Junko Hori, Tat Fong Ng, Marie Shatos, Henry Klassen, J. Wayne Streilein, and Michael J. Young, "Neural Progenitor Cells Lack Immunogenicity and Resist Destruction as Allografts," *Stem Cells* 21, no. 4 (2003), 405–16.

Some misconceptions persist about both adult and embryonic stem cells. First, the lines of unaltered human embryonic stem cells that exist will not be suitable for direct use in patients. Second, adult stem cells are ready to use as therapies. Recommendations of the committee formed by the National Research Council and the Institute of Medicine provide guidance about how to proceed in this new scientific frontier.[20] Of note are the committee's contentions that experiments in mice and other animals are necessary, but not sufficient, for realizing the potential of stem cells to develop tissue-replacement therapies. It asserts that studies with human stem cells are essential and such research should continue, and finally, that high-quality, publicly funded research is the wellspring of medical breakthroughs. Public funding offers greater opportunities for regulatory oversight and public scrutiny of stem cell research.

Diabetes

Diabetes mellitus is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. Diabetes mellitus is a chronic metabolic disorder. It results from the body's failure to produce insulin and/or the body's inability to respond adequately to insulin secreted. Insulin is a hormone produced in the pancreas that enables the glucose released during digestion to enter the body's cells as a source of energy. A consequence of diabetes is a build-up of glucose in the blood, which passes out of the body as urine, thereby depriving the body of its main source of fuel.

Type I diabetes, also called juvenile-onset diabetes or insulin-dependent diabetes, develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the insulin that regulates blood glucose. This form normally strikes children and young adults, although disease onset can occur at any age. Risk factors for type I diabetes may include autoimmune, genetic, and environmental factors. Type I accounts for 5–10 percent of the diagnosed patient population.

Type II diabetes, also called adult-onset diabetes or non-insulin-dependent diabetes, may account for 90–95 percent of all diagnosed cases of diabetes. It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin. This is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. Type II diabetes usually develops in adults over the age of forty. In the late stage of type II diabetes the pancreas fails and insulin can no longer be produced. At this point, patients become insulin-dependent.

Gestational diabetes is a form of glucose intolerance that is diagnosed in some women during pregnancy. It is more common in obese women. Other specific types of diabetes result from specific genetic conditions, surgery, drugs, malnutrition, infections, and other illnesses. Such types of diabetes may account for 1–5 percent of all diagnosed cases of diabetes.

Factors that contribute to the growing number of diabetics include:

- Increased prevalence of obesity
- Sedentary lifestyle
- Poor dietary habits
- Aging populations
- Evolving diagnostic criteria

Over time, all diabetics experience some or all of the co-morbidities including nephropathy, retinopathy, neuropathy, hypertension, and hyperglycemia.

The Epidemic Global Scenario

The following facts about diabetes indicate the alarming proportion of the population it is affecting and the threat it presents in the years to come. In 2003, the International Diabetes Foundation (IDF) reported that:

- There are more than 194 million diabetics worldwide, with this number expected to exceed 333 million by 2025.
- The five countries with the largest patient populations are India (35.5 million), China (23.8 million), the United States (16 million), Russia (9.7 million), and Japan (6.7 million).
- The five countries with the highest diabetes prevalence in the adult population are Nauru (30.2 percent), United Arab Emirates (20.1 percent), Qatar (16 percent), Bahrain (14.9 percent), and Kuwait (12.8 percent).
- At least one-half of all people with diabetes are unaware of their condition.
- Diabetes is the fourth main cause of death in most developed countries.
- Diabetes is the leading cause of blindness and visual impairment in adults in developed countries.
- Diabetes is the most common cause of amputation that is not the result of an accident.
- People with diabetes are 15 to 40 times more likely to require a lower-limb amputation compared to the general population.
- Cardiovascular disease is the number one cause of death in industrialized countries. People with diabetes are two to four times more likely to develop cardiovascular disease than people without diabetes.
- People with type II diabetes have the same risk of heart attack as people without diabetes who have already had a heart attack.
- By 2025, the prevalence of diabetes is expected to more than double in Africa, the Eastern Mediterranean, the Middle East, and Southeast Asia; to rise by 20 percent in Europe; 50 percent in North America; 85 percent in South and Central America; and 75 percent in the Western Pacific.

- For developing countries, there will be a 170 percent increase in diabetes For developed countries; there is a projected rise of 42 percent.
- Diabetes accounts for between 5 and 10 percent of national health budgets.
- Of the seventy-four countries that participated in the IDF study, thirty admitted that they could not ensure a continuous supply of insulin to people with type I diabetes.
- A person with diabetes incurs medical costs that are two to five times higher than those of a person without diabetes.
- As another source points out, India's diabetic population, about twenty-five million in 1998, is expected to double in the next decade. Less than half of all the diabetics in India currently receive treatment. Among those who do receive treatment, under 3 percent use insulin.[21]
- About 90 percent of the world's diabetics have type II diabetes, which is associated with obesity and lack of exercise.[22]

U.S. Incidence of Diabetes

Today, diabetes affects more people and causes more deaths in the United States than breast cancer and AIDS combined. It is the sixth leading cause of death in the United States with nearly 200,000 deaths reported each year.[23] About 18.2 million Americans (or 6 percent) have diabetes, of which 13 million are diagnosed.[24] In addition, at least 20 million other Americans have a precursor condition called pre-diabetes.[25] In 2002, the average healthcare cost for a person with diabetes in the United States was $13,243, compared with $2,560 for a person without diabetes.[26] Direct medical and indirect expenditures attributable to diabetes were estimated at $132 billion in 2002. Direct costs were $91.8 billion, of which $23.2 billion was for diabetes care; $24.6 billion was spent on chronic complications; and $44.1 billion was for increasing prevalence of coexisting medical conditions. Of that direct medical expenditure, 51.8 percent was incurred by people over the age of sixty-five.[27] Indirect expenditures resulting from lost workdays, restricted activity days, mortality, and permanent disability totaled $39.8 billion.[28]

These cost estimates exclude undiagnosed cases of diabetes. Most of the healthcare use attributable to diabetes is for the treatment of general medical conditions. Diabetes accounts for a sizable increase in the use of healthcare services.[29]

Eliminating or reducing the health problems caused by diabetes—through factors such as better access to preventive care, more widespread diagnosis, more intensive disease management, and the development of new medical technologies—could significantly improve the quality of life for people with diabetes and their families. At the same time, they could potentially reduce national expenditures for healthcare services and increase productivity in the U.S. economy.

Current Drugs and Therapies

Management of type II diabetes involves a variety of drug classes:

- *Sulfonylureas* stimulate the pancreas to make more insulin
- *Biguanides* decrease the amount of glucose made by the liver
- *Alpha-glucosidase inhibitors* slow the absorption of starches consumed
- *Thiazolidiones/Glitazones* make the body more sensitive to insulin
- *Meglitinides* stimulate the pancreas to make more insulin
- *D-phenylalanine* derivatives help the pancreas make more insulin quickly
- *Combination therapy* involving multiple oral medications
- *Insulins*

Insulin is currently the most effective drug for controlling hyperglycemia and is widely accepted as the gold standard for treating type I diabetes and even late-stage type II diabetes. However, there is significant reluctance among physicians and patients to use insulin until other less effective drugs have been attempted. This is mainly because insulin therapy is invasive: patients must take insulin intravenously, making it a painful therapy.

The NIH reports that scientists have achieved significant milestones in the management of diabetes. Researchers are now able to identify those at highest risk for type I diabetes years before symptoms appear. Survival rates for people with type I diabetes are improving. Scientists have identified several genes that contribute to diabetes susceptibility. A major clinical trial, the Diabetes Prevention Program, has clearly shown that type II diabetes can be prevented through modest changes in diet and exercise, which lead to a 5–7 percent weight loss in overweight people with pre-diabetes.[30] Worldwide diabetes market figures (in millions of dollars) are described in Table 5. Table 6 outlines Sales of various classes of products and different brands available in the United States in each class, notably the $4 billion insulin market. Figure 6 shows the distribution of various types of diabetes treatments in the United States.

Table 5. Worldwide Diabetes Market

Particulars	2000	2001	2002
Diabetes drugs	9,694	11,714	12,482
Glucose monitors	3,276	3,743	4,735
Insulin pumps	543	637	749
Total	13,513	16,094	17,966

Source: BCC Research, *Diabetes Therapies and Diagnostics: Markets, Technologies, Players*, October 1, 2002 <http://www.marketresearch.com/product/display.asp?productid=821988&g=1> Accessed July 18, 2007.

Table 6. Diabetes Product Class and Brand Sales

Brand	Marketer	2001	2002
Sulfonylureas			
Amaryl	Aventis	450	545
Glucotrol XL	Pfizer	283	297
Biguanides			
Glucophage XR	BMS	230	297
Thiazolidinediones			
Avandia	GSK	1061	1214
Actos	Takeda/Lilly	361	392
Prandial glucose regulators			
NovoNorm/Prandin	Novo Nordisk	178	206
Starlix	Novartis	53	89
Insulin			
Novolin	Novo Nordisk	1872	1881
Humulin	Lilly	1061	1004
Humalog	Lilly	628	834
Lantus	Aventis	84	299

Source: Business Insights, "Commercial Opportunities from an Aging Population: Epidemiology, Market, and Pipeline Analysis across Seven Major Indications," February 2004 <http://www.globalbusinessinsights.com/report.asp?id=rbhc0113> Accessed July 18, 2007.

Diabetes disease management is on the brink of a revolution with the arrival of inhaled and oral insulins, which will offer greater flexibility for physicians and patients, improve compliance, and help to slow disease progression. Two phase III products in this category are currently under development: Exubera (made by Nektar in collaboration with Pfizer), and AERx iDMS (made by Aradigm in collaboration with Novo Nordisk).

Stem Cell Therapy as Regenerative Medicine: From Research to Clinic

One of the most promising ways to cure diabetes is to restore the function of islet cells biologically, either through islet cell transplantation or through engineering of cells to restore the insulin secreting function. Islet transplantation, a procedure that can restore insulin production in patients, is a highly promising area of research. As we know from experience, organ transplants do not always succeed, and one the biggest

obstacles is the availability of fresh islet cells. New studies indicate that it may be possible to direct the differentiation of human stem cells to form insulin-producing cells that eventually could be used in transplantation therapy for diabetes. Researchers have turned their attention to adult stem cells that appear to be precursors to islet cells and embryonic stem cells that produce insulin. Many researchers seek to develop a system in which stem or precursor cell types can be cultured to produce all the cells of the islet cluster, in order to generate a population of cells that can coordinate the appropriate release of insulin.

Several companies are pursuing a more permanent therapeutic solution for type I diabetes via the transplantation or regeneration of pancreatic islet cells. Stem cell researchers at the University of Florida appear to have successfully treated diabetes in mice by chemically coaxing bone marrow stem cells to produce insulin. But crucial questions about the treatment's potential may take another decade to answer. This preliminary study conducted on animals with diabetes shows that adult stem cell plasticity exists. The Florida researchers took bone marrow stem cells from adult rats and used a unique chemical process to induce laboratory cultures of the cells to form clusters that produced insulin and three other hormones usually made only in the pancreas. These clusters were implanted in nine diabetic mice, and the animals' blood sugar levels dropped from about 550 milligrams per deciliter to 200 and remained stable for three months.[31]

There are several concerns about applying stem cells. First, whether human stem cells differentiate into islet cells in a manner similar to the human body is a matter for further research. Second, a more efficient way is required to drive differentiation toward islet cells from the total population of differentiated stem cells. Third, researchers need to test the safety of this cell therapy in long-term implantation studies. Fourth, better ways to conquer rejection of transplanted cells must be developed.

While stem cell research is at a very early stage, it offers great promise to quicken the pace of discovery for a cure for diabetes. Federal funding will allow many more scientists to conduct clinical research and will ensure public oversight and accountability. In the words of Philip Noguchi, M.D., the director of the FDA's division of cellular and gene therapy, "From the biologics perspective, emphasis on products for diabetes is clearly experimental at this time, but potentially very promising."[32]

Valuation Models

Based on this analysis of stem cell research, diabetes market opportunities, and the development of stem cell therapies, it is possible to place a value on a company in the early (preclinical) development stage of a stem cell therapy for diabetes. Such a valuation is an art—not a science. To carry out the valuation, we need to make some assumptions about the technology. Before financial valuation is feasible, we have to assume that we have overcome certain technological barriers. In this case, I assume that the company in question has discovered an efficient process for differentiating

and cultivating stem cells into pancreatic islet cells. Using a proprietary technology, the company is able to isolate and cultivate enough islet cells for use in patients. To attain an optimal range of valuation, I have adopted three approaches that provide good guidance on the value of the company.

Discounted Cashflow (DCF): The Net Present Value (NPV) Model

First, the universal approach of DCF/NPV considers net cashflows over a period of time and discounts it with the cost of capital or expected rate of return. The discount rate in the traditional DCF models covers the risks of production to market. In the case of biotechnology companies, however, there is an additional risk factor of R&D and regulatory approval. This process is both expensive and time-consuming. There are no set parameters or benchmarks for including this factor in valuation by adjusting the discount factor. Hence, many stakeholders, including entrepreneurs and investors, incorrectly estimate the value of their technology by failing to account adequately for the cost, risk, and time associated with product development. The improved model considers this aspect and might be called a risk-adjusted model, rDCF or rNPV. In the underlying model, different probabilities of success at different stages of product development are considered and cashflows at these stages are adjusted accordingly.[33]

Various risks are associated with the development cycle of a stem cell therapy for diabetes. Technical and scientific risks include all unanswered questions about stem cells and how they will develop into a feasible cure for diabetes. Regulatory risks include clinical trials and other FDA requirements. Although the FDA has developed a protocol for reviewing human autologous tissue and cell therapy products, companies must conduct some confirmatory post-marketing studies. This means a prolonged clinical trial even after commercial launch. Finally, ethical and community risks are associated with the difficulty in recruiting patients for trials and the public debate over stem cell research. I address these additional risk factors in Table 7 by quantifying probabilities of the success of stem cell therapy vis-à-vis probabilities of success of other drugs. Table 8 addresses the time and costs associated with development.

A. Market Size and Penetration

My research indicates that there are approximately 17.5 million diabetes patients in the United States.[34] Under current treatments, 19 percent of the patients use insulin,[35] hence the target population for stem cell therapy is assumed to be 3,326,330 (or 19 percent of all diabetics). I have assumed that the target patient population will increase by 1.5 percent per annum, as against projected growth of 1.4 percent for the diabetes population in the United States.[36] Further, comparing the rate of adoption of other innovative technologies, I assumed that 1.5 percent of the overall target population would be willing to undertake the stem cell therapy treatment in year one. The rate of adoption is expected to increase by 5 percent per annum as the technology proves its benefits and more payers cover its use.

Table 7. Stem Cell Therapy Success Probability

Development Stage	Stem Cell Therapy—Success Probability	Other Drugs—Success Probability[i]
Phase I clinical trial	20%	20%
Phase II clinical trial	30%	30%
Phase III clinical trial	45%	67%
FDA approval	50%	81%

[i] See Jeffrey J. Stewart, Peter N. Allison, and Ronald S. Johnson, "Putting a Price on Biotechnology," *Nature Biotechnology* 19, no 9 (September 2001), 5–8.

Table 8. Time and Cost of Product Development

Development Stage	Time (years)	Number of Patients	Cost ($)
Phase I clinical trial	1	20	200,000
Phase II clinical trial	2	50	500,000
Phase III clinical trial	4	200	2,400,000
FDA approval	1	-	2,000,000
Total	8	290	5,100,000

B. Price

Benchmarking with other innovative technologies that cure chronic diseases, and taking into account the current average cost per patient per year, I assumed a price of $12,000 for the therapy. As a matter of fact, most of the stem cell therapy companies are targeting a final price of $15,000 to $20,000 for their therapy, depending on the disease area. Even though this price appears to be much higher than the average cost of other diabetes drug therapies, taking into account the nature of the technology (it cures a long-lasting disease), the savings on medical expenses for other diseases that develop out of diabetes, and the pricing of other similar technologies, I believe that the $12,000 price tag is reasonable and feasible.

C. Patent Protection

I assumed the patent for this technology was filed in 2002. Hence, the development of the therapy would be completed in 2011; about ten years from the date of patent filing. As a result, the company will receive patent protection of ten years from the date of market launch.

D. Discount Rate

Since the cashflow projections in the model already adjust for the risks associated with R&D of the technology, we assume a discount rate of only 20 percent for business

risks associated with production, marketing, and distribution. However, the following table indicates the benchmark of a 20 percent discount rate from perspectives of equity cost and expected return. Of course, each reflects the other.

Table 9. Cost of Equity and Risk-Return Profile

Cost of Equity	%	Expected Return	%
Risk-free return	5	Debt	4–6
Equity risk premium	8	Mutual funds	6–8
Small-company premium	3	Public equity	8–10
Company-specific risk premium	3	Private equity	12–15
Total	19	Venture capital	> 20

E. Other Costs

Based on research on the financial models of other companies, I have determined both the human resources necessary to run this company and the expected costs. Other sales promotion costs are assumed to be 2.5 percent of sales. I have also assumed other costs of R&D, equipment and supplies, travel, professional fees, and facilities expenses.

F. Payment/Reimbursement Risk

Currently the major insurance companies consider stem cell therapy to be experimental and do not pay for it. But many insurance companies pay for bone marrow transplantation. Therefore it is reasonable to assume that insurance companies and other payers will pay for stem cell treatment of diabetes.

G. Net Present Value / Internal Rate of Return

Utilizing the aforementioned assumptions, my model values this technology company at approximately $16.6 million. The internal rate of return (IRR) works out to 40.27 percent.

Royalty or Licensing Model

The second approach assumes that the stem cell technology company licenses out its technology to a bigger company (either a biotechnology or a pharmaceutical company) for clinical development, manufacturing, and marketing. As we have seen, in a typical deal of this nature a smaller technology company receives milestone payments based on successes at various stages of development, and then receives royalty payments on sales after commercial launch. The deal terms considered in this model are mapped out in Table 10.

Table 10. Licensing Deal Terms

Licensing Deal	Revenues ($)	Costs ($)
Milestone payments		
Phase I clinical trial	2,000,000	1,866,000
Phase II clinical trial	4,500,000	4,312,000
Phase III clinical trial	14,500,000	14,200,000
FDA approval	9,000,000	8,142,000
Royalty payment on launch	10% or 1,200	

All the other assumptions of the DCF model have been retained except that under this scenario the company will not incur any production or sales costs. Based on the above assumptions, my licensing model values this technology company at approximately $6.6 million. The internal rate of return (IRR) works out to 35.50 percent.

Comparables

The third and last approach involves analysis of comparables. In this exercise, three types of biotech/pharma companies are included: stem cell technology companies, technology companies developing products for the diabetes market, and other technology companies in the early stages of product development. Ideally, such an analysis should include a set of listed (publicly traded) and unlisted (privately held) companies. However, information is not available for most unlisted companies. This exercise is therefore restricted to listed companies, but even with these entities, information is limited because they are in the early stages of technology development. Moreover, since the companies have not yet posted significant revenues or profits (most have negligible revenues and are incurring losses), it is difficult to carry out the usual comparative analysis. In my analysis, I considered parameters such as market opportunity, market capitalization, status of product development, and technology type. For instance, Table 11 shows the market sizes of certain therapeutic areas and the market caps of companies in these spaces. There is no perfect correlation between these parameters, but Table 11 provides an outline of similar companies, their future path, the nature of their financing, and their stock market valuation. A better indication of the last is provided by the company's average market capitalization over six months to one year.

Table 11. Early Stage Technology Companies

Company	Technology	Disease Area	R&D Status	Market Capitalization
StemCells	Cell therapy	Diabetes, Parkinson's	Preclinicals	$55 million
Transition Therapeutics	Biopharma	Diabetes	Phase I	$78 million
Alteon	Biopharma	Diabetes, Aging	Phase II, Preclinicals	$69 million
Aradigm	Medical devices	Diabetes	Phase II, III	$134 million
Aastrom Biosciences	Cell therapy	Oncology, Dermatology	Phase I	$83 million
Emisphere Technologies	Medical devices	Diabetes, Blood system	Phase I, II, III	$109 million
NeoPharm	Biopharma	Oncology	Phase I, II	$476 million
ConjuChem	Biopharma	Diabetes, AIDS, CHF	Phase II	$589 million
Spectrum Pharma	Biopharma	Oncology, Neurology	Preclinicals	$79 million
Ergo Sciences	Biopharma	Diabetes	Technology sold	$15 million

According to Table 11, valuation of a given stem cell therapy company addressing diabetes appears to be very low. This could be due to conservative assumptions; a market premium for track record and proven capability of the listed companies; key collaborative alliances; and positive news during the product development stage. Given these factors, valuation assumptions also depend on the purpose of the valuation and who is represented in the exercise.

Sensitivity Analysis

To evaluate the impact of lower or higher estimates on the value of a company, a series of sensitivity analyses is required. The variables that should be considered in such an analysis are:

- Market size and growth
- Market penetration and growth
- Price of the product or therapy
- Cost of goods sold
- Discount rate

- Research and development cost and period
- Risk profile, i.e., probability of success

Valuation Drivers

For biotechnology companies, the following drivers play a critical role in company valuation.

A. People—Management Team and Chief Executive Officer (CEO)

The most important factor in building a company's valuation is the people behind that company. This universal factor in company valuation is especially important in the biotechnology space, since it is a knowledge-driven industry. Simply put, experienced people add to the value of the company. This may be the only industry in which the experience of failure is highly valued, due to the industry's inherently high-risk profile.

B. Alliances and Partnerships

As we have already noted, this is an industry that thrives on collaborations. Smaller biotechnology companies depend on alliances for all aspects of business, from R&D to marketing. Such relationships also validate the company's potential. The mere fact that a company's product is being jointly developed pushes the value of the company upwards.

C. Intellectual Property Rights

Patents play an important role in helping companies gain exclusive rights to their products, thereby enhancing pricing and profitability. There is also less likelihood of an issued patent being circumvented in biotechnology compared to other industries. On the other hand, patent infringement leads to huge legal expenses, which deter the filing of suits. Hence, valid patents contribute to higher company valuation.

D. R&D and Technology

These are by far the most valuable factors for a biotechnology company. Proven technology acts as a foundation for any biotechnology company, but at the same time, if a company has a diversified portfolio of technologies or products; it creates more value than a single platform.

E. Funding/Financing—Cash is King

The availability of funds, the long-term pattern of funding, and the timing of funding have a huge impact on the valuation of a company. If a company is running low on cash at the time of valuation, it will bring a lower value. Also, if the company has issued equity at a lower value in any of the subsequent rounds of financing, it will bring a lower value. Conservative utilization of funds over the life of the company also helps to increase value.

F. Market Opportunity and Therapeutic Area

A company's research focus also decides the value of the company. A company engaged in cancer research will attract a better valuation than a company focusing on dermatology research, even though the stage of development may be the same.

Conclusion

My research on the biotechnology industry and the valuation of early-stage technology companies produced several findings:

- Some deals are made out of fear—fear that another party will hijack a given product or therapy. Given this impetus, such deals may not add value in the immediate future and may not fit into the company's value chain.
- Equity plays an important role in deals. It brings more commitment from both parties to the deal agenda. For the bigger company, equity is not an expense, so approval is easier to obtain. The smaller company receives the money upfront, which directly helps to increase its valuation.
- Margins in biotechnology products vary between 40 percent and 70 percent of the selling price. In joint development projects, this is split between the partners, from 20 percent to 50 percent, depending on the product development stage and expected time to market.
- Biotechnology company valuations make a quantum jump on successful completion of the second phase of clinical trials.
- Ethical issues influence biotechnology companies' core strategies and decisions. More than most industries, public relations are an integral part of the decision-making process.
- Contrary to the populist view that there have recently been no funds available for biotechnology entrepreneurial ventures, venture capitalists (VCs) have had abundant money. In fact, the VC industry suffers from a phenomenon called "capital overhang," meaning an excess of capital overinvestment opportunities. To be sure, VCs are investing more cautiously, but such overhang leads to two results: first, valuation of good projects is driven up since there is more competition among VCs, and second, VCs promote competition for biotechnology companies by creating promising new ventures.
- The market values sales more than mere profits.
- Projections are usually wrong, so it pays to be prepared. There are no perfect answers when valuing a company, but solid analysis of the company's total profile is the best preparation for negotiating a given deal.
- Wall Street rewards forward integration. Biotechnology companies that are expanding into areas such as clinical development or marketing command higher multiples.

- Matching the interests of both parties is critical in order to arrive at an acceptable valuation. If prospective partners do not believe in the value of the technology at stake, then any alliance will only waste time and resources.

Notes

1. See U.S. Department of Commerce Technology Administration and the Bureau of Industry and Security, "A Survey of the Use of Biotechnology in U.S. Industry," October 2003 <www.technology.gov/reports/Biotechnology/CD120a_0310.pdf> Accessed February 21, 2007, ix.

2. Burrill & Co. presentations at industry events, November 14, 2003, and April 17, 2004.

3. Guide to Biotechnology, Biotechnology Industry Statistics <http://www.bio.org/er/statistics.asp> Accessed October 11, 2003.

4. See U.S. Department of Commerce Technology Administration and the Bureau of Industry and Security, "A Survey of the Use of Biotechnology in U.S. Industry," ix–x.

5. See U.S. Department of Commerce Technology Administration and the Bureau of Industry and Security, "A Survey of the Use of Biotechnology in U.S. Industry," xiii.

6. See Reuters Business Insight,"The Future of Pharmaceutical Outsourcing," *Pharmaceutical R&D Outsourcing Strategies Report* (September 2002), 120.

7. See U.S. Department of Commerce Technology Administration and the Bureau of Industry and Security, "A Survey of the Use of Biotechnology in U.S. Industry," 94.

8. See Reuters Business Insight,"Twenty-first Century Alliances," *Pharmaceutical Strategic Alliances Report* (November 2002), 16.

9. See Alice M. Sapienza and Diana Stork with Joseph G. Lombardino, *Leading Biotechnology Alliances: Right from the Start* (New York: Wiley-Liss, 2001).

10. See Sapienza and Stork, *Leading Biotechnology Alliances: Right from the Start*.

11. See Sapienza and Stork, *Leading Biotechnology Alliances: Right from the Start*.

12. See Sapienza and Stork, *Leading Biotechnology Alliances: Right from the Start*.

13. See Global Forum for Health Research, *The 10/90 Report on Health Research 2001–2002* < http://www.globalforumhealth.org/Site/002__What%20we%20do/005__Publications/001__10%2090%20reports.php> Accessed February 21, 2007.

14. See Secretariat of the World Health Organization, "Intellectual Property Rights, Innovation and Public Health," Fifty-Sixth World Health Assembly, agenda item 14.9 (May 12, 2003) <www.who.int/entity/phi/A5617.pdf> Accessed February 21, 2007.

15. See Audrey R. Chapman, Mark S. Frankel, and Michele S. Garfinkel, "Stem Cell Research and Applications: Monitoring the Frontiers of Biomedical Research,"

Report for the American Association for the Advancement of Science and Institute for Civil Society (November 1999) <http://www.aaas.org/spp/sfrl/projects/stem/index.shtml> Accessed February 21, 2007.

16. See Tim Hubbard and James Love, "A New Trade Framework for Global Healthcare R&D," Columbia University *PloS Bio* 2, no. 2 (February 17, 2004) <http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.pbio.0020052> Accessed February 21, 2007.

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