



# THE FUTURE OF THE BIOMEDICAL INDUSTRY IN AN ERA OF GLOBALIZATION

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**About the Authors**

*This report was prepared by the Kellogg Center for Biotechnology at the Kellogg School of Management under the direction of Prof. Alicia Löffler and Scott Stern. Special contributors from the Kellogg Center for Biotechnology include: Steve Bull, for serving as the project manager and contributing with the science section; Michael Sullivan for contributing with the policy data; Alfonso Yanez for his contributions with the social drivers section; Sudhir Malhotra for contributing with the financial data, Gregory Dicreze for editing the report and finally, Julia Trosman and Christine Weldon, two Kellogg graduates, currently Principals at Executive Frameworks, for contributing with the personalized medicine section.*

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# THE FUTURE OF THE BIOMEDICAL INDUSTRY IN AN ERA OF GLOBALIZATION

## Executive Summary

The biomedical industry -- composed of pharmaceutical, biotech, medical device and diagnostics segments -- is shaped by a variety of distinctive forces. Among these are the need for specialized human capital, a formidable regulatory approval process, high sunk costs, a complex financing structure, science risks, and a range of ethical and political issues.

**The outlook for the industry in the next 10 years is very positive.** It will experience explosive growth in markets for the treatment of both chronic and acute illnesses. These markets will be driven by a confluence of political and demographic trends -- most notably globalization and population growth and aging -- as well as by new products resulting from the genomic discoveries of the late 1990s and early 2000s and a generally favorable policy environment.

**This report makes the case for fundamental changes in the biomedical industry** in the coming years. **It anticipates the ascendance of personalized medicine and suggests ways in which industry players will have to adapt** to profound demographic, political and technological shifts in order to compete successfully in a world transformed by forces of globalization.

This executive summary highlights three principal aspects of the case presented fully in the larger paper, which will be made available in its entirety at the end of April:

1. Background: Basic Characteristics of the Biomedical Industry
2. Adapting to a "Flat" World: Implications of Globalization and Opportunities for the Industry
3. Business Models: How Successful Industry Players Can Adapt to Changing Conditions

## Basic Characteristics of the Biomedical Industry

- *The biomedical industry is composed of four primary segments, long regarded separate and distinct, but which in the 21st Century should be considered as fundamentally convergent and increasingly interrelated.* The **pharmaceutical segment** is the industry's mainstay and is composed of large, fully integrated, global players. The **biotechnology segment** is an upstart, having emerged commercially only 30 years ago, but is increasingly the engine of innovation in biomedicine. The **medical device segment** is much older than biotech, but is composed of many fewer players, and owing to the nature of its products, exemplifies the life-saving power of "convergence": a marriage of engineering know-how and biomedical science. The **diagnostics segment** has grown up

along mainstream pharmaceuticals, and has acquired a new dynamism and centrality since the advent of the genomics revolution.

- *In all of its segments, the biomedical industry is science-driven and highly regulated.*
- *The biotechnology segment has been and will continue to be a fundamentally entrepreneurial industry.* Since its origins in the development of recombinant DNA technology in the late 1970s, biotechnology has generated and commercialized a wealth of innovations emerging from basic scientific research conducted in leading research universities. It is therefore a compelling instance of successful technology transfer.
- *Biotechnology has shifted the paradigm by which innovation and knowledge are created.* Innovation in the sector emerges at the intersection of research disciplines and private/public institutions. It is characterized by its “duality,” simultaneously making contributions to both basic and applied research. Within the industry, traditional disciplinary and institutional lines are blurred. This loose structure has unleashed enormous productivity and creativity, and increasingly has become a model for other biomedical segments, enabling us to characterize the entire biomedical industry as “convergent.”
- *Specifically, biomedical innovators stand at the confluence of biology, computer science, engineering and material sciences.* These disciplines will continue to blend, making it difficult to differentiate one from another and increasingly bringing together personnel, and to some extent, business practices, in the industry’s pharmaceutical, medical device, diagnostics and biotechnology segments.
- *The biomedical industry is constantly generating and adapting to new technologies* [Exhibit 4]. Pharma and biotech have experienced four technology shifts over the last three decades alone. From the medicinal chemistry and pharmacology paradigms of the 1970’s (which yielded a plethora of antibiotics and small molecule drugs), cutting-edge drug developers came to focus on biochemistry and molecular biology in the 1980’s (resulting in recombinant DNA technology, genetically engineered organisms, and therapeutic biologics) and genomics in the 1990s -- *a shift that will soon make possible personalized medicine.* Each of these overlapping shifts has produced increasingly valuable therapies.

**The constant flow of new innovations in biomedicine has several important implications:**

- *Despite a converge of methodologies, the industry is highly fragmented and is likely to remain so.*
- *The biomedical supply chain is fulfilled by specialized players, particularly in the highly innovative biotech segment.* Firms often do not integrate vertically and continue to play within specific and limited stages of the biotechnology value chain.

- *Business models are constantly evolving.* While the pharmaceutical and medical device sectors have operated with fairly consistent business models, biotechnology models have been evolving constantly, as companies search for the best way to capture the most value from their innovations. Companies have experimented to compete in different spaces within the value chain, from producers of research and tools to full vertical integration.
- *Because innovation is at a premium in the industry, intellectual property right protection is key for the growth of all industry segments and tends to define the revenue life cycle of their products.* In pharma and biotech, patent expirations and generics cause portfolio erosions. Biologics -- a product of the biotech industry -- have been protected so far from this threat and enjoy extended revenue cycles. This trend will continue at least for the next few years.
- *The availability of continuous funding -- from the basic research stage through product development and commercialization -- is essential to keep the biomedical industry's engines of innovation running at maximum efficiency.* A diversity of funding sources, both public and private, contribute at different stages to the "flow." This diversity provides the industry with a measure of stability as it nurtures innovation, but allows market forces to determine the ultimate value of innovations.
- *Biomedical companies grow in three stages, defined by their funding mechanisms.* These stages, in sequential order, are: (i) **trial-and-error**, funded mostly by federal sources and angel investors; (ii) **focus**, funded by venture capital; and, (iii) **diversification**, funded by the public markets. Full continuous funding, with no gaps, is key for the success of the industry
- The commercialization process is distinctive across the industry. *Biomedical products navigate through a complex value chain of institutional interests and issues before finding commercial success.* Characteristic of the industry's products is the fact that end-users or customers (patients) do not directly pay for products they use, nor do those who provide the product (doctors and hospitals) [Exhibit 2]. The ultimate payers -- insurers and governments -- interact with industry participants, and will do so increasingly owing to the current cost crisis in U.S. healthcare. This report argues that personalized medicine solutions -- the next great wave of industry innovations -- potentially provide a way out of the crisis [Exhibit 34].
- *Public response to industry innovations follows a steep indifference curve* [Exhibit 5]. Payers in the biomedical sector traditionally have been willing to pay high prices for a small increase in quality; increasingly, consumers demand it -- a trend favoring the emergence of personalized medicine. Some current indicators, however, suggest that "indifference" to cost for marginal improvements in outcome may not be feasible in the long run for all health products.

## The Biomedical Industry Must Adapt to a “Flattened” World

- *Profound demographic, political, and technological changes are precipitating fundamental shifts within the biomedical industry. As the process of globalization proceeds, the world is becoming “flat,” changing the dynamics of innovation and commercialization as well as the distribution of wealth and the incidence of disease.*
- *The sources of biomedical innovation will become more diverse in a globalized marketplace. The U.S. has the largest global output of biomedical knowledge, but China and India are narrowing the gap.*
- *Developments in science and technology, many of them byproducts of the “genomics revolution” and “the biotech age,” point to *the emergence of preventive, predictive, and personalized treatments*. These are likely to be mainstream in the U.S. as early as 2025 [Exhibit 37].*
- *There are three primary, or “macro” drivers of the trend toward personalized medicine:*
  1. **The unrelenting force of technological and scientific discovery and innovation**, sourced in leading research universities and in emerging biotechnology companies, which will make a personalized approach to medicine technologically possible;
  2. **The aging of a growing, affluent, and comparatively knowledgeable population** in developed nations, which will increasingly demand personalized treatments;
  3. **Withering pricing pressures**, which will only intensify in the increasingly globalized market for healthcare. Rising world population and a shift in prevalence of chronic diseases, combined with escalating research costs, global competition, and the increasing complexity of distribution systems is placing unprecedented cost pressure on all industry segments.

### **New Opportunities for Biomedical Companies:**

- *These factors will provide an opportunity for developers of innovative health solutions. Cost pressures paired with increasing pressures from governments, employers, and consumers to reduce pricing will lead to increasing global distribution of drugs and medical devices and spur the development of novel, innovative health solutions for curing and preventing disease. Reimbursement will increasingly require pharmacoeconomic evidence, beyond efficacy and safety. This will create a powerful incentive for developers of innovative, high-value health solutions (products-service combinations).*
- *These pressures will force players in the biomedical industry to adapt their business models and, in concert with healthcare providers and insurers, adopt*

personalized medicine as a systemic curative, thus overcoming longstanding institutional obstacles and impediments to change [see Section 3, below].

**Specific implications for industry participants and consumers:**

- *The biomedical industry will experience an explosive growth in the chronic disease market.* This will be driven by population growth, increased longevity, the economic and political ascent of highly populous nations including China and India, and attendant global redistributions of wealth. As the people of China and India become more affluent, they will increasingly come to suffer from maladies associated with affluence. This development will provide great opportunities across the biomedical industry, from makers of drugs to diagnostics to medical devices.
- *There will also be tremendous needs and opportunities in the acute-care and anti-infective markets.* This is another effect of globalization: highly porous international borders, increased urbanization, and uneven distribution of wealth, particularly in emerging nations, will create pockets of highly vulnerable populations and an ominous threat for new infectious disease transmissions and outbreaks.
- *Two types of radically different biomedical markets and consumers will emerge in response to these trends.* The **chronic disease market** will serve the “me” consumer. The **acute disease market** will serve the “desperate” consumer.
- *Markets serving “me” consumers will grow consistently.* In the U.S., this consumer is typically a highly educated, aging baby boomer afflicted with chronic disease or willing to pay to preserve his lifestyle. The “me” consumer will be served by niche, specialized, lifestyle, and cosmetic medicines and treatments, and in the future will be the mainstay of the three “Ps” market (*predictive, preventative and personalized medicine*).
- *Markets serving the “desperate” consumer will fluctuate markedly, by definition.* The “desperate” consumer is either a vulnerable and underprivileged patient or is a victim of an infectious disease pandemic or terrorist attack. Demand waxes and wanes with the arrival and passing of specific health threats. Markets are high-volume, lower-margin.
- *In the absence of acute health threats, generics will prevail in large markets.* Governments will favor generics as a means of reducing healthcare costs. Biologics and niche pharmaceuticals, however, will most likely be protected in the short term, continuing to enjoy extended revenue life cycles in developed-nation markets.

### 3. How Business Models Will Change

- *Biomedical firms will need to reinvent their business models to compete in this changing world.*
- *Two models will emerge.* Successful biomedical firms will divide among those that can forcefully compete in *global markets* through robust infrastructure, and those in *niche markets* that will specialize in predictive, preventive and personalized treatments.
- *While in the past, the main source of competitive advantage for firms throughout the industry has been technology, in the future it will be the supply chain.* Global companies will need to partner/form networks with firms outside the U.S. Emerging companies in the personalized medicine space will need to partner/form networks with firms in the healthcare delivery sector.
- *The winners in the global market will be pharmaceutical and medical device companies.* These companies will be capable of creating innovative and robust supply chains to increase efficiencies. They will also reduce development costs and increase flexibility to adapt to accordion-type markets that will serve “desperate” medical consumers.
- *The number of global alliances will grow within and between all segments of the industry; these will include novel cross-fertilizations such as medical device makers joining forces with biotech companies. At the same time, the number of acquisitions by global players will diminish.* Growth through alliances, not acquisitions, will be the modus operandi for firms competing in the global marketplace, as firms will need to increase their flexibility both at the technical and supply-chain levels.
- One consequence of this trend is that *early-stage biotech companies will increasingly be driven to the IPO market rather than seek to be acquired* by pharma or other biotech companies.
- *Biotech companies will remain the engine of innovation in biomedicine. They will be the winners in the predictive, preventative and personalized market.* Specifically, successful companies will be highly profitable, highly specialized small and medium-size companies that focus on research and health delivery innovation. These companies will have highly integrated and deep knowledge of specific disease groups. They will develop creative alliances, financing the commercialization of new personalized, predictive, and preventive medicine tools in alliances with healthcare delivery organizations and payers. Successful companies will create a network organization that will offer complete health solutions and services to the patient.
- *The number of alliances between biomedical players and service, health delivery organizations, and employer groups will grow.* Companies in the personalized medicine space will grow through innovative alliances with health delivery service organizations, rather than with traditional pharmaceutical companies.

- *Product-service models dealing with predictive, preventative and personalized markets will attract non-traditional private investors to the biomedical sector.*

Part III of the full report provides a more detailed discussion of future business models.

## PART I

### Introduction: Basic Characteristics of the Biomedical Industry

The biomedical industry develops innovative products for the prevention, treatment, and cure of human diseases. It is composed of four primary segments, long regarded separate and distinct, but which in the 21st Century should be considered as fundamentally convergent and increasingly interrelated. The **pharmaceutical segment** is the industry's mainstay and is composed of large, fully integrated, global players. The **biotechnology segment** is a comparative upstart, having emerged commercially only 30 years ago, but it is increasingly the engine of innovation in biomedicine. The **medical device segment** is much older than biotech, but is composed of many fewer players, and owing to the nature of its products, exemplifies the life-saving power of "convergence": a marriage of engineering know-how and biomedical science. The **diagnostics segment** has grown up along mainstream pharmaceuticals, and has acquired a new dynamism and centrality since the advent of the genomics revolution.

### Industry Dynamics

The biomedical industry employs more than 734,000 people in the U.S. The medical device segment accounts for 40% of industry employment, drugs and pharmaceuticals, 44%, and research and testing, 16% (Exhibit 1). The average annual industry wage in 2003 was 85% higher than that for the entire U.S. private sector.<sup>1</sup>

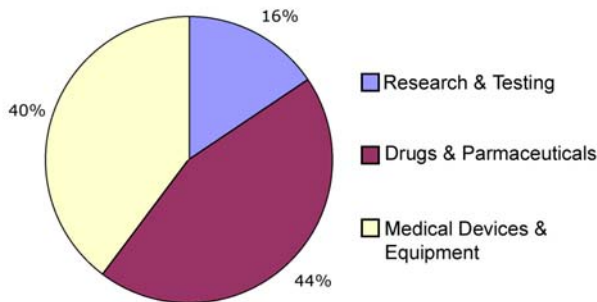
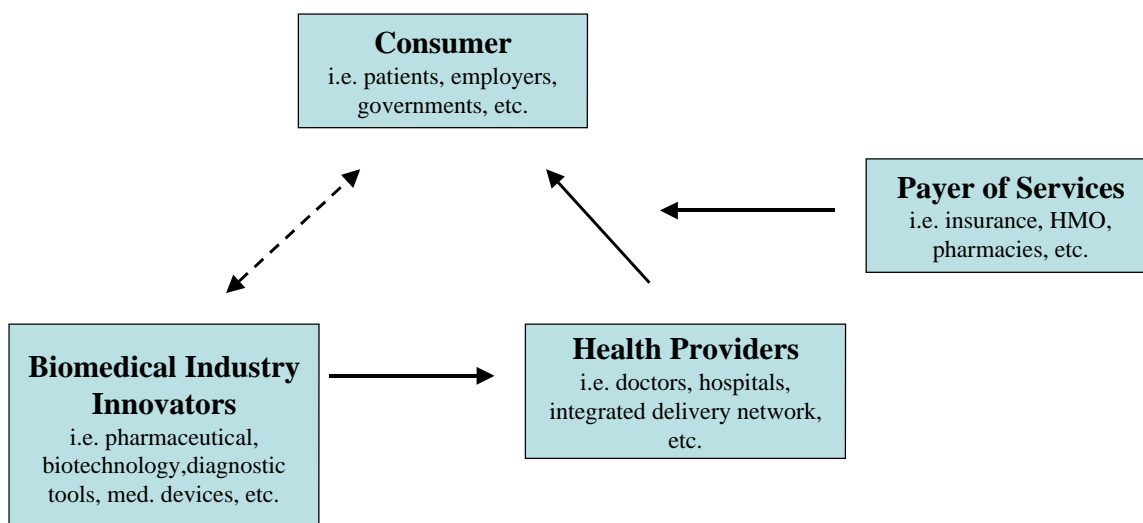


Exhibit 1. Employment in the U.S. biomedical industry

The industry is shaped by a variety of distinctive forces. Among these are the need for specialized human capital, a formidable regulatory approval process, high sunk costs, diverse financing mechanisms, science risks, and a range of ethical and political issues. Interaction among industry players, academic labs, governments, end-users, and healthcare providers and payers is complex (Exhibit 2).

<sup>1</sup> Laboratories of Innovation: State Bioscience Initiatives 2004.



**Exhibit 2. Interaction among players in the biomedical and healthcare industries.** End-users (patients) do not directly pay for products they use, nor do those who provide the product (doctors and hospitals). The ultimate payers -- insurers and governments -- interact with industry participants, and will do so increasingly owing to the current cost crisis in U.S. healthcare. The dotted arrow indicates the advent of direct-to-consumer advertising, in which global pharma players communicate directly with end-users.

## Science and Entrepreneurialism Drive Biomedical Innovation

Perhaps the most distinctive characteristic of the biomedical industry is its prodigious capacity for innovation. All segments of the industry are propelled forward by new discoveries in science and technology.

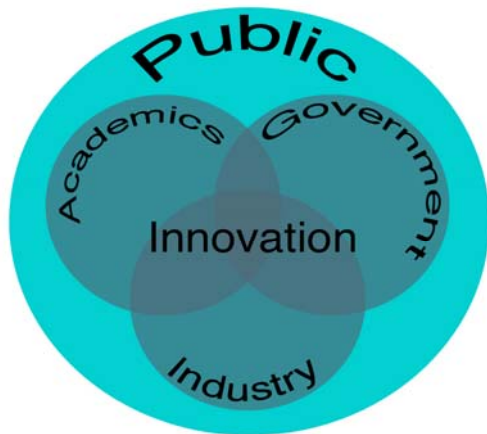
This is especially true in the biotechnology sector, which, for good reason, has been called “**perpetually entrepreneurial.**” Since its origins in the development of recombinant DNA technology in the late 1970s, biotech has generated and commercialized a continuous stream of innovations sourced in scientific research that forces the industry to be constantly adapting to new processes and models.

## Public/private partnerships

Biotech has shifted the paradigm by which innovation and knowledge are created. Innovation in the sector emerges at the intersection of research disciplines and private/public institutions (Exhibit 3). It is characterized by its “**duality,**” simultaneously making contributions to both basic and applied research, academic and industrial pursuits.<sup>2</sup> The biomedical industry has components of both, simultaneously pursuing

<sup>2</sup> Stokes, D. *Pasterur's Quadrant: Basic Science and Technological Innovation*. Brookings Institute Press, Washington DC., 1997

basic understanding and commercialization. This duality has a profound impact on the management, policy and economics of the industry.

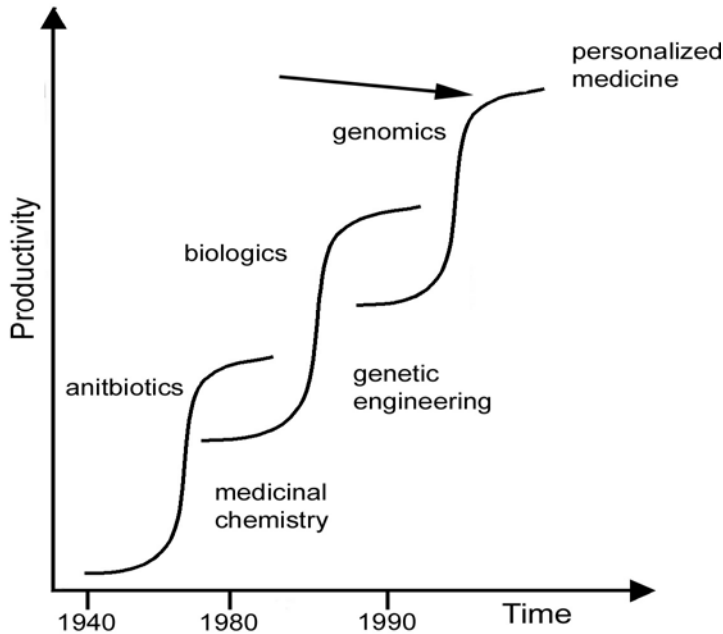


**Exhibit 3. Innovation in biomedicine emerges at the intersection of research disciplines and public/private institutions.**

Until recently, norms and institutions supporting basic versus applied research were clearly separable and distinct. But institutional lines today are blurred in the biomedical sector. **Innovation thrives primarily at the intersection of governmental (policy), educational (academia) and commercial (industry) institutions.**

Interdisciplinarity within scientific and technological fields has unleashed enormous productivity and creativity in biomedical research, and increasingly has become a model for industry. In disciplinary terms, biomedical innovators stand at the confluence of biology, computer science, engineering and material sciences. These disciplines will continue to blend, making it difficult to differentiate one from another and increasingly bringing together personnel, and to some extent, business practices, in the industry's pharmaceutical, medical device, diagnostics and biotechnology segments.

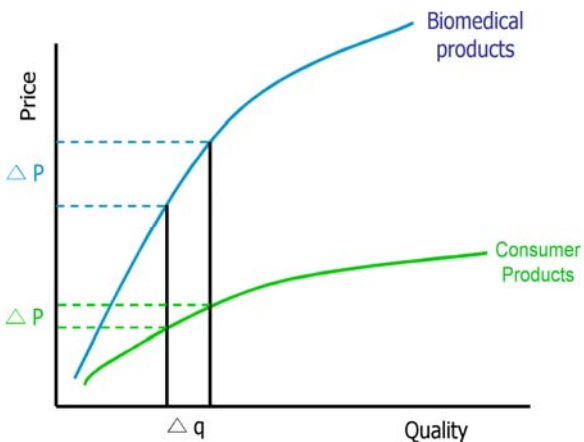
As shown in Exhibit 4, pharma and biotech have experienced four important technology shifts over the last three decades. These technologies have yielded increasingly valuable therapies. The medicinal chemistry paradigm of the 1960s and 1970s resulted in what is known as the "golden age" of antibiotics. Hundreds of new antibiotics were launched, including top sellers like Lilly's Keflin and Ceclor, and Pfizer's Vibramycin. The genetic engineering curve of the 1980s first gave us products such as Genentech's TPA and Amgen's EPO and later gave rise to monoclonal antibody therapeutics, which have flourished in the early 2000s (e.g., Genentech's Herceptin, Avastin, and Rituxan). The completion of the first draft of the Human Genome Project in 2000 signaled the start of the industry's genomic phase. It also set the stage for a rapid acceleration of genomic applications and products, which in the coming decades will make possible a profound change in medical practice and healthcare delivery -- a paradigm shift away from acute-care medicine and toward predictive, preventive, and personalized medicine.



**Exhibit 4. Rapid innovation in the biomedical industry is driven by a continuous flow of scientific and technological advances.** After a lag period marking the development phase of a new technology or scientific paradigm, a period of exponential commercial growth typically follows. As the technology is perfected, it moves into a plateau period and slower growth, at which point it is superseded by a new technology. The transition between shifts inevitably results in a loss of efficiency. We are in such a phase today (indicated by the arrow); personalized medicine is the curve of the future.

**No price too high for extending life**

Public response to industry innovations follows a steep indifference curve. This means that affluent consumers are willing to pay higher prices ( $\Delta p$ ) for incremental increases in quality ( $\Delta q$ ). Put another way, the explosive demand for innovative biomedical products is essentially independent of pricing, and is driven instead mainly by demographics.



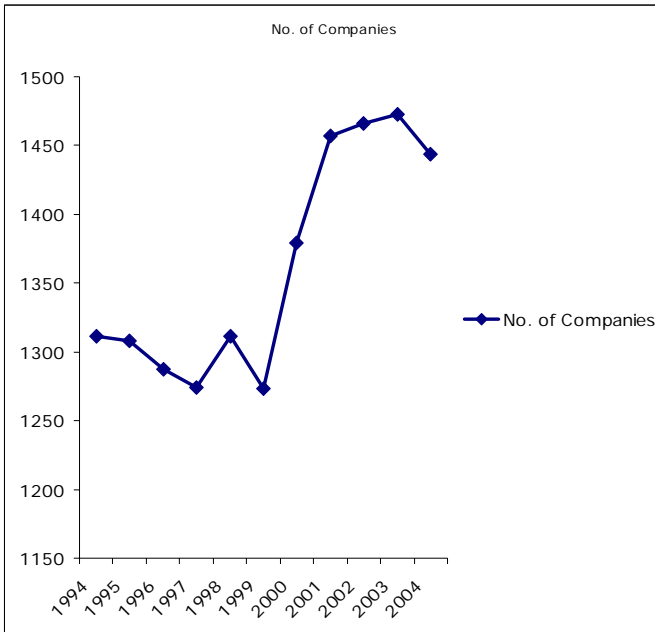
**Exhibit 5. Indifference to cost** for incremental improvements in outcome may not be feasible in the long run for all health products, but it does suggest high future consumer demand among affluent populations for predictive, preventive and personalized medicine products and treatments.

## Industry Fragmentation, R&D, Capital Markets

The continuous flow of scientific innovations forces participants in the biotech sector to experiment constantly with new business models. Although successful individual biotech companies grow large and mature -- Genentech and Amgen being the prime examples, each with a market cap in excess of \$80 billion -- the sector as a whole is a study in dynamism, with new entrants appearing on the scene every year, attracting capital from both public and private sources. Once companies in the biotech sector establish a proven commercial path, they often consolidate or partner with others to maximize value. These partners are in biotech and pharma, primarily, but increasingly in medical devices and diagnostics.

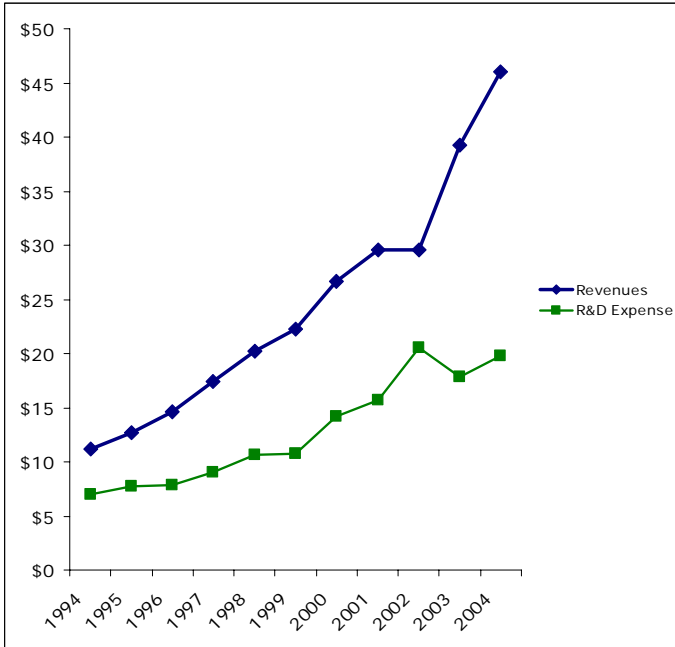
In view of methodological convergence, one would expect consolidation to result in a gradual winnowing of companies; but the innovation-driven rate of company formation keeps the biotech sector highly fragmented. The biomedical supply chain is fulfilled by specialized players. Firms often do not integrate vertically and continue to play within specific and limited stages of the biotechnology value chain.

Currently there over 6,000 biotech companies worldwide and about 1,500 in the U.S. (Exhibit 6). About 350 biotech firms are publicly traded in the U.S. (recent market capitalization = \$311 billion). There is no reason to believe that the number of companies will shrink in the next decade. In fact, if anything, *the number of biotech companies will grow* in response to continuing innovation. Global expansion of the research enterprise and society's growing expectations of improved quality and length of life bolster this trend.



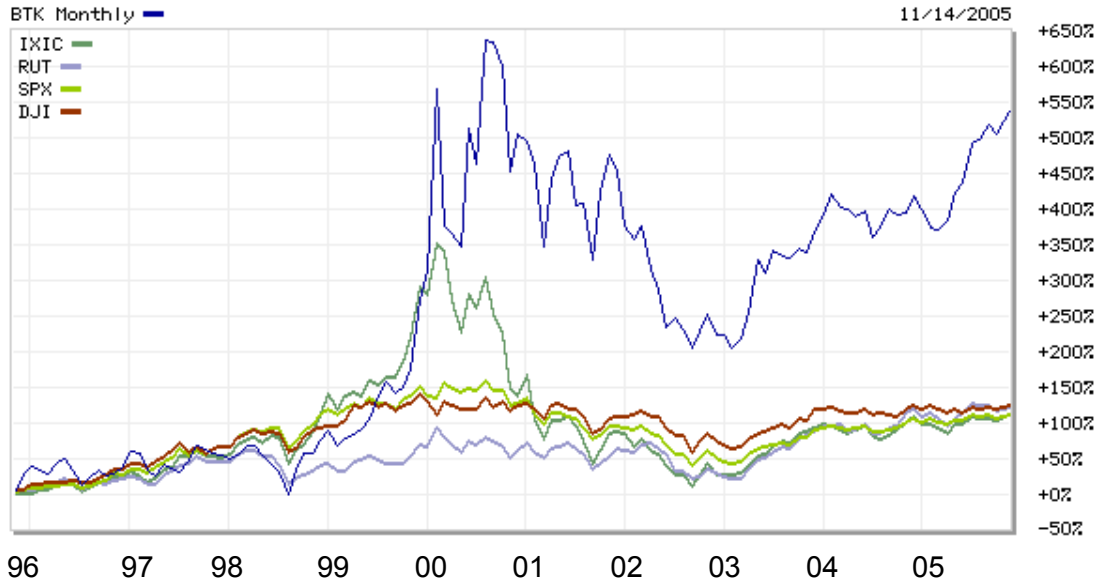
**Exhibit 6. Number of biotechnology companies in the U.S., 1994-2004** Source: www.bio.org

R&D is the lifeblood of the biotech enterprise. Not surprisingly, sector R&D expenses have risen steadily since the early 1990s, and reached \$20B in 2005. But revenues have accelerated at an even faster rate, especially in the last several years, reaching \$46B in 2005 (Exhibit 7).



**Exhibit 7. Biotech R&D expenses plotted against revenues, 1994-2005.**

These data suggest that after a period of gestation, investments in R&D have paid off handsomely for the sector’s most successful players. This fact, in turn, is reflected in long-term stock price movements. Exhibit 8 reveals that the AMEX Biotech Index has outperformed major market indices over the last decade, in some time frames by enormous margins. This, despite a “crash” in prices following a hype-induced boom associated with completion of the effort to map the human genome. Biotech stock prices -- and industry financing -- have recovered steadily since bottoming at the end of 2002 and are not far now from historic “boom”-period levels.



Index Performance to Nov. 11, 2005 *since*

INDEX	1/98	1/99	1/00	1/01	1/02	1/03	1/04	1/05
BTK	328.0%	243%	55.2%	7.5%	34.4%	98.9%	30.5%	28.0%
S&P 500	26.0%	-3.5%	-11.4%	-9.6%	9.3%	44.2%	9.2%	4.6%
NASDAQ	36.0%	-12.1%	-44.1%	-11.0%	13.9%	66.7%	6.6%	6.8%
DOW	35.2%	14.2%	-2.3%	-1.8%	7.7%	32.7%	1.9%	1.9%
RUS 2000	55.1%	56.2%	34.4%	31.2%	38.1%	79.3%	14.8%	6.9%

**Exhibit 8. BTK vs. Dow Jones Industrials, S&P 500, Nasdaq Composite, Russell 2000, 1996-2005**

### Clustering

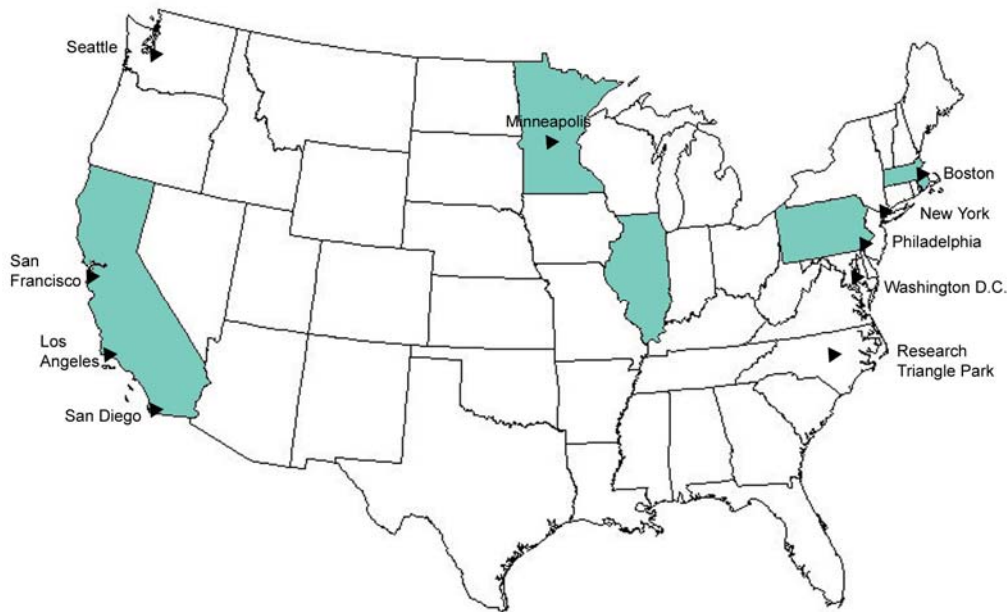
The need for inter-institutional relationships within the biomedical sector, particularly in biotech and medical devices, has stimulated the formation of biomedical clusters -- geographical regions of intense biomedical activity. Today, start-ups are concentrated in San Diego, Boston, Research Triangle Park (North Carolina), Seattle, Washington D.C., Philadelphia, San Francisco, New York, and Los Angeles (Exhibit 9).<sup>3</sup>

Clusters are autocatalytic -- innovations generate more innovations -- helping them to become stronger with time. These clusters are expected to continue to dominate. Certain states control a large portion ( $\geq 5\%$ ) of total U.S. biotech employment, and are specialized in particular subsectors within the industry.

California and Massachusetts specialize in platform technologies (e.g., high-throughput analysis, physical diagnostics, surgical equipment) and medical devices & equipment. Illinois specializes in platform technologies as well as drugs & pharmaceuticals, Minnesota specializes in medical devices, and Pennsylvania in both drugs &

<sup>3</sup> Brookings Institution, "Signs of Life: The Growth of Biotechnology Centers in the U.S."

pharmaceuticals and medical devices & equipment.



**Exhibit 9. Biotech and medical device clusters in the United States.**<sup>4</sup>

The colored states indicate areas of high biomedical employment and specialization.

### **Regulation, Intellectual Property Rights, Reimbursement**

Three additional factors profoundly affect the dynamics of companies across the biomedical industry. They are the 3 “Rs”: government regulation, rights governing intellectual property, and policies and practices affecting reimbursement. We will take them up in that order.

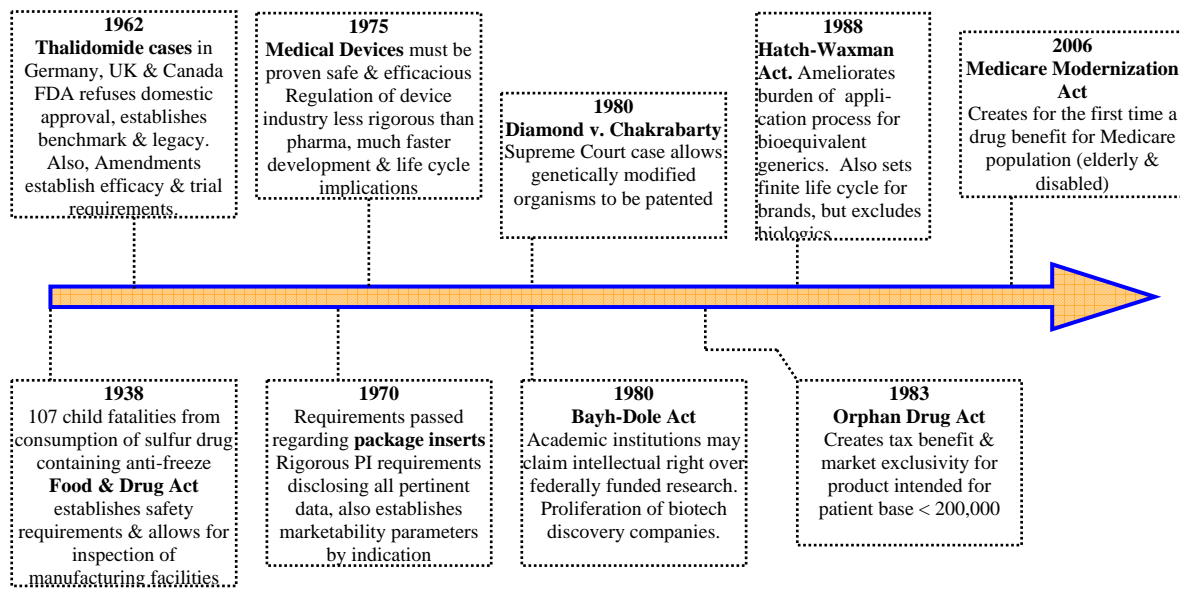
#### **Regulation**

Biomedical businesses are highly regulated. Pharmaceutical, biotechnology, and medical device products must be approved before marketing can begin. In the U.S., the Food and Drug Administration (FDA) is responsible for foods and drugs and their manufacturing, while recombinant DNA experiments are overseen by the Recombinant DNA Advisory Committee (RAC).

It is tempting to view regulation as an impediment. But it can fairly be said that U.S. regulatory laws and several pivotal legal decisions are the foundation upon which the

<sup>4</sup> Based on data from the Brookings Institute

modern biomedical industry has been built. The lead that American companies enjoy in the industry globally is a direct consequence of clear, strong, and highly responsive government regulation (Exhibit 10).



**Exhibit 10. Highlights of the legal and regulatory history of the modern U.S. biomedical industry**

Two key drivers of the industry -- and especially the biotech industry -- were the 1980 U.S. Supreme Court decision in *Diamond v. Chakrabarty*, which allowed genetically modified organisms to be patented; and the Bayh-Dole Act, enacted by Congress in the same year. Bayh-Dole has fulfilled the intentions of its framers to promote the transfer of government-sponsored research from universities to the private sector. Congress acted because the vast majority of technologies developed with federal funding were not being commercially exploited.

Prior to Bayh-Dole, federal agencies would rarely relinquish ownership of federally funded inventions, even when private-sector scientists and engineers contributed to the inventions. This left valuable technology to languish on the shelves of research institutions. For example, in the 1960s, the U.S. government claimed it owned the rights to 5-fluorouracil (an important anti-cancer drug) even though it had provided merely a fraction of the funding that had supported its discovery. As a result, market entry of this

product was unnecessarily delayed and industry distanced itself from federally funded university research.

Bayh-Dole authorized universities, non-profits and small businesses to elect title to inventions made under federal funding agreements. The Act also authorized federal agencies to grant exclusive licenses for their technologies to private companies.

Since the enactment of Bayh-Dole, technology partnerships have led to the founding of more than 1,100 biotechnology companies based directly on NIH and university research. These technology partnerships and the patents on which they are based are particularly important to small biotech companies, which focus their research on breakthrough technologies that arise from basic biomedical research.

### **Intellectual property rights**

Protection of intellectual property is key for the growth of the biomedical industry. A biotechnology company typically spends more than \$600 million over the 10- to 14-year period leading to its first dollar of product revenue. Patents allow companies to attract the funding necessary to develop their products. Company valuations are closely linked to IP news.

Strong IP protection has arguably its downside. Exclusivity is claimed to inhibit the dissemination of research knowledge within academia. In the absence of an efficient mechanism for gaining access to knowledge (e.g., through efficient licensing), patents can be used to erect barriers that hinder the effective exploitation of the scientific commons. Some argue that these restrictions can hurt the biotech sector since the restriction on shared knowledge can lower overall research productivity (the so-called “anti-commons” effect).<sup>5</sup> The strong historical linkage between basic research spillovers and long-term economic growth has undergirded the federal government’s support for basic research; it is in fact the largest source of funding for such work. Because of this, the anti-commons effect has become a central concern of policymakers.

However, it can be also argued that IP protection actually facilitates a “market for ideas” by increasing incentives for disclosure (rather than secrecy) and encouraging the exchange and trade of knowledge.<sup>6</sup> The ability to use intellectual property rights to contract over knowledge potentially ameliorates the anti-commons effect. Undoubtedly, Few would take issue with the contention that patent protection and clear contracting have helped the U.S. to become the global leader in the biomedical industry.

### **Biologics have an extra measure of IP protection**

After the patent on an innovative drug has expired, others may produce copies of that drug. Generics profoundly affect the pharmaceutical sector and have pushed it toward maturity and commoditization. Competitors still require approval before placing generics on the market. To avoid the costly and lengthy clinical trials process, they must demonstrate equivalency -- show that the generic copy is identical in chemical composition, purity, and concentration to the original compound.

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<sup>5</sup> “Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge? Evidence from Patent-Paper Pairs,” paper by Fiona Murray, Scott Stern.

<sup>6</sup> Merges and Nelson, 1994; Arora et al, 2001; Gans and Stern, 2000; Gambardella, 1995

Patent protection is expiring for some of the biologic drugs developed by the pioneering biotechnology companies. But there is no established process to prove equivalency in biologics. Biologics are more complex and difficult to characterize than small-molecule compounds, making it virtually impossible to show “equivalency.” Even slight variation in biologics could have a significant impact on humans. Those who would reproduce them therefore face the prospect of having to go through the full FDA clinical trials process. Thus developers of biologics so far have enjoyed a kind of immunity to the threat of generic competition.

### **Reimbursement**

Even after a biotechnology firm succeeds in getting its product approved by the FDA, there is no guarantee the product will be successful in the market, or that the government will cover the cost of the drug for patients. Securing coverage by Medicare is the single highest priority in the payment strategy for a drug. Since the government accounts for over 40% of U.S. healthcare spending and Medicare is the most significant part of the federal program, Medicare is the market driver when it comes to determining healthcare reimbursement. Medicare reimbursement decisions tend to set the standard for all payers in both the public and private sectors.

An effective reimbursement strategy is critical in achieving maximum sales for new biomedical products. They may be more efficacious than competing products; they may be safer; they may be ‘first-in-class.’ But who is most likely to pay for the patient to use new products? This is the question physicians ask. Physicians use products they know will be paid for by some type of medical insurance. Access to reimbursement through Medicare depends on whether the new drug or medication meets a host of criteria, which change, stage-by-stage, throughout the drug’s development cycle. Reimbursement, therefore, adds a layer of risk and uncertainty to product development and to the larger fortunes of firms that develop them.

### **Socially charged**

The biotechnology industry differs from other industries in that many biotech decisions are driven by direct public consensus or, at least, influenced by public opinion and input. This is usually achieved by advocacy groups raising concerns about biotechnology products or firms, or by indicating a preference toward promoting a certain type of biotechnology product.

The industry develops technologies that could change the way we understand life. Several activists and advocacy groups question the power that these technologies and the business models of the biomedical sector. Embryonic stem cell research, for example, has created deep controversies among diverse public groups that question its long-term impact on society.

The growing number of disease advocacy groups, private lobbies, and not-for profit organizations dedicated to promoting medical research is staggering. In many cases, a disease advocacy group will dedicate its effort to the study of a specific health condition that affects many of its members or their relatives, or a patient’s narrow interest. Notable examples include the supporters of diabetes and cancer research. These groups not only fund the research, they may directly hire researchers to undertake studies related to their specific disease.



## Industry processes and structures

The value of a biomedical company's tangible assets is minimal in comparison to its intangible assets, which its returns primarily depend upon. This difficulty is magnified in the biotech sector, where a company's ability to convert intellectual property into a revenue stream is subject to strict government regulations, a lengthy approval process, and public scrutiny.

A biotech company's product pipeline -- which is defined by both the number of products that a company is developing and their stage in the development cycle -- is a very important determinant of the company's risk profile.<sup>7</sup> A company whose success or failure is entirely dependent upon one product is clearly riskier than a company that is developing several products. This risk is somewhat mitigated in big pharma, although extensive pharma pipelines have not translated in recent years into a stream of approved products sufficient to maintain rates of profit growth expected by many investors.

Owing to the effect of compounding across multiple stages, a great deal of investment is required upstream (in the product discovery phase) to account for each phase of the product life-cycle, with very few products making it to approval. Even more daunting, development costs are fully recovered in only 30% of approved products. But one or two products of high value can effectively finance many unsuccessful projects, as well as generate substantial profits. A single promising development-stage product may serve to attract a suitor or corporate partner, another outcome that potentially can serve to defray high sunk costs.

### **Drug Development: A Long and Costly Road**

Therapeutics are the most expensive biomedical products developed today. It now takes 12-15 years and anywhere from \$800 million to \$1.7 billion to bring most new drugs to market.<sup>8</sup> The development process consists of the following stages:

- (i) Discovery Stage, which involves the discovery and validation of a drug candidate. This stage involves mostly biological, chemical, and computational processes.
- (ii) Development Stage, when the drug is tested for safety and efficacy in humans. This is the most expensive and lengthy stage, as well as the most highly regulated. Drugs must pass through three clinical phases before they can be brought to market.
- (iii) Commercialization Stage, which involves manufacturing and marketing of the drug.

The process of drug development is notoriously "leaky." On average, one drug emerges from 10,000 drug targets, and the FDA only approves 15% of compounds that make it to the pre-clinical phase of testing (Exhibit 11).

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<sup>7</sup> "Navigating through a product valuation," Bratic, Tilton, Balakrishnan, PwC report

<sup>8</sup> As reported in FDA White Paper, "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products," March 2004; see executive summary and fig. 3.

## Compound Success Rates by Stages

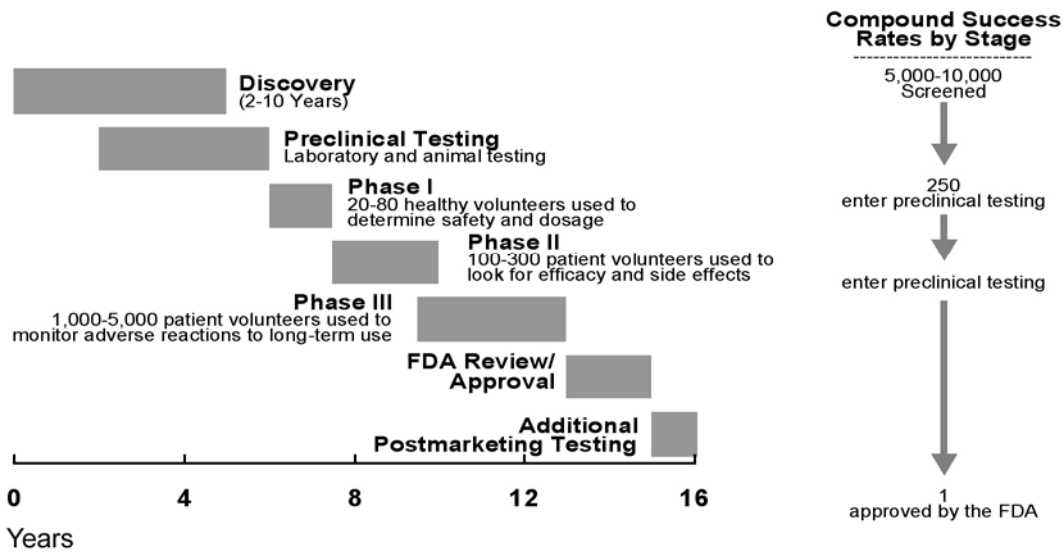


Exhibit 11. The long road to FDA approval

### Current biomedical business models

Firms in the pharmaceutical and medical device sectors have operated for years with stable and predictable business models, although, as we will suggest, these models have begun to change in significant ways in response to changing conditions. As noted, business models in the biotechnology sector have been evolving constantly, as firms search for the best way to capture the greatest value from their innovations. Biotech companies have experimented to compete at different spaces in the value chain; some produce research, some produce tools, and others produce therapeutic products, with a few making the leap to full vertical integration.

### Fully Integrated Companies (FICOs: FIPCOs, FIBCOs, FICOPs)

FICOs produce, develop, and market innovative therapeutic products, and broadly divide into two categories: FIPCOs (fully integrated pharmaceutical companies) and FIBCOs (fully integrated biotechnology companies).

FIPCOs such as Abbott, Novartis, and Pfizer include all the large pharmaceutical companies that produce, develop, manufacture and market therapeutics. These companies, increasingly, license or acquire innovations from biotechnology companies. The core competency of FIPCOs is scale -- the ability to reach markets effectively through strong global channels.

FIBCOs include fully integrated biotech companies focused on a lead product with no unique underlying technology platform, and fully integrated companies with unique platforms (the latter are called FICOPs). The core competency of both types of firms is usually innovation.

Some FIBCOS are considered “one pony shows.” These companies are focused on a single product or very few products and are built to be acquired by pharmaceutical or medical device companies. This is particularly true if the company’s capabilities are not unique or innovative and can be easily duplicated and enhanced by a pharmaceutical company.

FICOPs, in contrast, often have platforms and/or products that do not “fit” the mainstream capabilities of pharma. In the early 1980s, for example, when pharmaceutical companies were slow in incorporating specialized processes for the commercialization of therapeutic proteins, the field was left open for new companies that were able to do so. These companies defined commercial biotechnology: Genentech, Amgen and Genzyme. These new entrants integrated vertically and successfully developed commercialization capabilities for innovative protein-based drugs. Therefore they provided value to the industry not only as product innovators but also as process innovators.

A similar situation seems to exist today in the stem cell space (see Part II of this report). Companies involved in the discovery process are finding themselves responsible for creating commercial scale. This is illustrated by ViaCell, of Boston, which is engaged not only in the discovery of stem cell-based therapeutics but is also spearheading scale-up efforts.

### **Non Research Development Only (NRDOs)**

NRDOs are biotechnology companies that focus only on development; they do not have a discovery capability. This model provides a way to reduce the risks of development. Instead of building the company around a technical innovation, many NRDOs focus on developing commercialization capabilities first, with the hope that by in-licensing innovations or acquiring companies, they will eventually build a deep and continuous pipeline.

The question to consider is what is the *unique* value that NRDOs provide to the industry and society? One could argue that a start-up can never have the manufacturing scale and marketing reach that big pharma has, unless the products involved include specialized processes or small niches that do not fit pharma’s capabilities. If that is the case, the barriers to entry for performing development are low. But, if the barriers are low for NRDOs, they should also be low for the inventors of the innovation. This raises the question of why inventors are willing to out-license to NRDOs.

### **Platform Model**

Platform companies produce research, tools or services. They capture value by licensing early-stage products, tools or services to mature companies, which in turn develop them into therapeutics, diagnostics, or devices.

By licensing their discoveries to seasoned pharmaceutical companies, platform companies expect to mitigate costs as well as the risks of product discovery and development. By selling services and tools, platform companies avoid the burdensome regulatory approval process and can reach profitability faster than fully integrated companies. Some platform companies are able to boost profitability by negotiating royalties on therapeutics or devices developed by others who use their tools or services.

But platform companies face important challenges. These include the constant threat of commoditization, the complexity of dealing with multiple customers, and the need to achieve significant scale rapidly in order to remain competitive. If the value proposition of a new platform technologies is sufficiently compelling, it can be out-licensed. But by out-licensing inventions at the early stages of development, platform companies relinquish much of their value to pharmaceutical or biotech companies. Moreover, new platform technologies face the major hurdle of adoption: their technologies must be integrated within the already existing pharmaceutical value chain.

### **Mixed Models**

There is no clear formula to build a profitable and sustainable biomedical firm. Platform models work in some cases, vertical integration works in others. An alternative common approach for biotech firms is to use a mixed model, where companies do both (outsourcing and integrating), either in sequence or in parallel. The mixed company is comparatively complex; strategic decisions about when and how to out-license need to be choreographed carefully.

Mixed-model companies run two businesses at once. Alnylam Pharmaceuticals (Cambridge, MA), for instance, uses a sequential mixed model. Founded in 2002, it has a rich RNA-interference platform for developing therapeutics. Alnylam has licensed its technology to leading biotechnology, pharmaceutical, and medical device partners that have provided it with about \$100M in funding. The company is attempting to develop its own therapeutic pipeline with these funds.

Sangamo Bioscience (Richmond, CA) is searching for sustainability through a parallel mixed model. Founded in 1996, it licenses to other biotechnology and pharmaceutical companies its ZFT (zinc finger transcription factors) technology for the screening of small molecules, monoclonal antibodies, and protein drug leads. ZFT are transcription factors that can be used to activate or repress gene expression. Sangamo uses the revenues generated by the licenses to advance its own therapeutics.

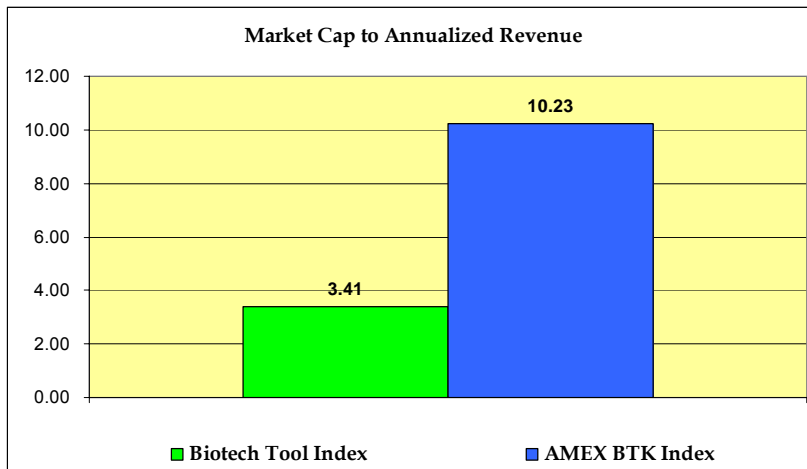
### **Medical Device Model**

Companies that develop, manufacture, and market innovative medical devices often acquire innovations from smaller device companies. The largest and most successful medical device companies cultivate highly specialized and efficient channels of distributions by developing close relationships with providers.

## The Relation Between Business Models and Valuation

Company valuations are highly dependent on business models. High sunk costs of product development companies are linked to the high clinical attrition rate of candidate drug compounds. Drug discovery takes years of research and heavy investment with no guarantee of success. This makes valuation difficult. Investments remain sunk until pipeline products are approved and brought to market. In the interim, valuations are often linked to the attainment of development milestones.

On a comparative basis, platform companies, though their businesses are not as risky, are not valued as highly as product companies in the marketplace. Exhibit 12 illustrates the ratio of market cap to annualized revenue for platform-based companies in comparison with the universe of companies in the AMEX Biotech Index.



### Exhibit 12. Platform company valuation.

Source: Mike Blastick and Sheldon Ng with data obtained from yahoo finance, Kellogg Center for Biotechnology, Kellogg School of Management.

Our research demonstrates, too, that valuations of platform companies are more vulnerable to capital market fluctuations than those of product development companies. While valuations of product companies usually correlate closely with clinical success, those of platform companies tend to reflect movements in the biotech index.<sup>9</sup>

## The Relation of Business Models to Corporate Growth Patterns and Industry Finance

Because of high capital requirements, time commitment, and development risks, biotechnology financing rarely comes from a single source. Government sources are essential at the early stages of product discovery, while private sources are essential in

<sup>9</sup> Source: research on valuation of Nerogen (1994-2004) and ArQule (1995-2004) done by Justin Busarakamwong, Mike Joo, Paul Seamon, Kellogg Graduate School of Management.

the commercialization stage. An emerging company must have both to ensure that all stages of early development are adequately supported.

Biotechnology companies grow in three stages (Exhibit 13): (i) *trial-and-error* (early-stage discovery); (ii) *focus on lead product* (transition to commercialization); and (iii) *pipeline diversification* (maturation). Each of these stages is characterized by distinctive funding mechanisms.

Growth Stages	Characteristics
<p><b>Trial-and-error Stage</b> Approximately 900 of these “early stage” companies in the U.S.</p>	<ul style="list-style-type: none"> <li>• University spin-offs transitioning between academic laboratories and commercial culture</li> <li>• 1-100 employees</li> <li>• Most supported by government and corporate alliances</li> <li>• Main goal is to provide biomedical product concept</li> <li>• Highly dependent on regional and state incubation infrastructure</li> </ul>
<p><b>Focus Stage</b> Approximately 500 companies in the U.S.</p>	<ul style="list-style-type: none"> <li>• Private and Public companies</li> <li>• Funded mostly by VCs, some go public</li> <li>• 50-200 employees</li> <li>• Development costs increase</li> <li>• Clinical Trials</li> <li>• High failure rate</li> </ul>
<p><b>Diversification Stage</b> Approximately 140 companies in the U.S.</p>	<ul style="list-style-type: none"> <li>• Public companies</li> <li>• Increased costs for product (&gt;\$600 million over &gt; a decade)</li> <li>• 500-5,000 employees, including scientists and sales force</li> <li>• Recovery of development costs before patent expiration</li> </ul>

**Exhibit 13. Three stages in the life of a growing biomedical firm.**

**Government grants are crucial in the “trial-and-error” period**

This is an experimental stage when the capabilities of a new technology or drug candidate are explored by a young company, often formed by an academic researcher or lab with promising intellectual property. It is inherently chaotic, unfocused, and highly innovative. Scientists are the decision makers and the CEO is often both a scientist and a manager. Processes are crafted “on the go.” Marketing and manufacturing have yet to enter the picture. *At this point, the company is funded by angel investors, government grants and, sometimes, early-stage venture capital (VC).*

Government sources such as the National Science Foundation (NSF), National Institute of Health (NIH), Small Business Innovation Research Programs (SBIR/STTR) and the Advanced Technology Program (ATP) are among the most important sources of federal funding for early-stage discoveries.

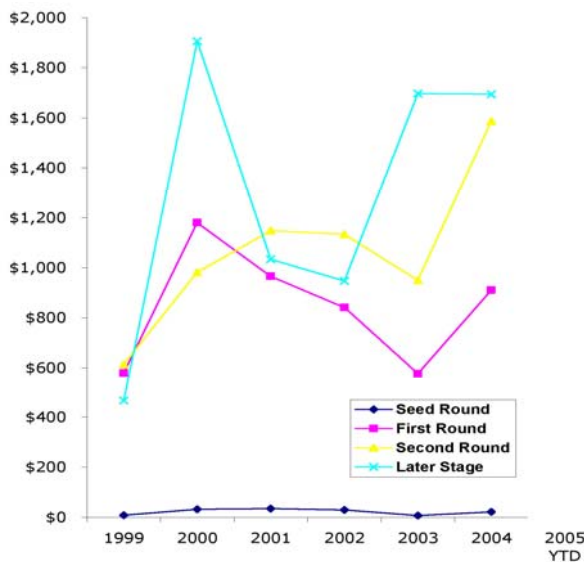
The SBIR program is a competitive, three-phase, government-funded program designed to encourage commercialization of promising technologies. Federal funds are used for

the critical startup and early development stages, i.e., those that seek to demonstrate proof of concept, which is usually necessary to attract private equity. Because the private sector is expected to take over 100% of funding by the third phase of the SBIR process, companies are incentivized to expedite commercialization. SBIR grants play a particularly useful role when private equity is plentiful but directed to late-stage private and public companies in which investors' exit strategies are clear and risks are lower.

The ATP program, instituted in 1990, does not fund product development. Instead, it supports *enabling* technologies essential to the development of new products, processes, and services across diverse application areas. ATP provides cost-share funding in the critical early stages of R&D, when research risks discourage other funders. The program can pay up to \$2 million in direct costs over a period not to exceed three years for a single company and up to half of the total project costs for a maximum of five years for a joint venture involving more than one company. Twenty percent of ATP funding has gone to biotechnology applications.

**The focus stage is usually shepherded by VCs**

Focusing the fledgling company usually involves a change of management and the establishment of commercial functions. The company prepares to go public or seeks an exit by being acquired. This is the most traumatic period for the organization, when scientists must become business managers or hand over the reins to seasoned managers capable of guiding the technology through the developmental process. Commercial functions need to be integrated without disrupting scientific innovation. Private seed funding (including venture capital and angel funding) seeks company ownership and is highly volatile, responding to market trends (Exhibit 14).



**Exhibit 14. Venture capital awarded to biopharmaceutical companies**

1999-2004 (\$ millions). After a precipitous drop in the year 2000, VC investments in biotechnology have rebounded. Angel investors are especially important in the earliest stages of company life, funding

approximately 40,000 deals a year. Though these average less than \$500,000, they give life to more than half of university-based start-ups.<sup>10</sup>

**The IPO window opens and closes in response to broad market conditions**

The IPO market is traditionally a cyclical market. Typical IPO valuations in the biotech sector were around \$100 million in the 1990s, soared to around \$800 million in 2000, and have since fallen back to the \$100-400 million range (Exhibit 15).

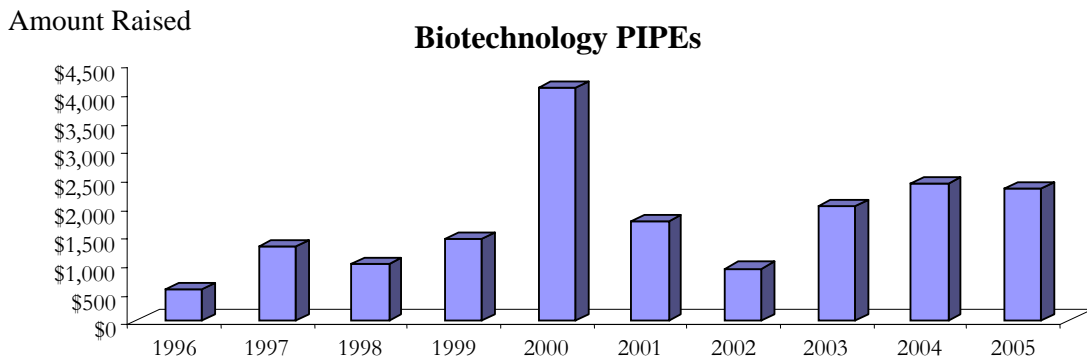
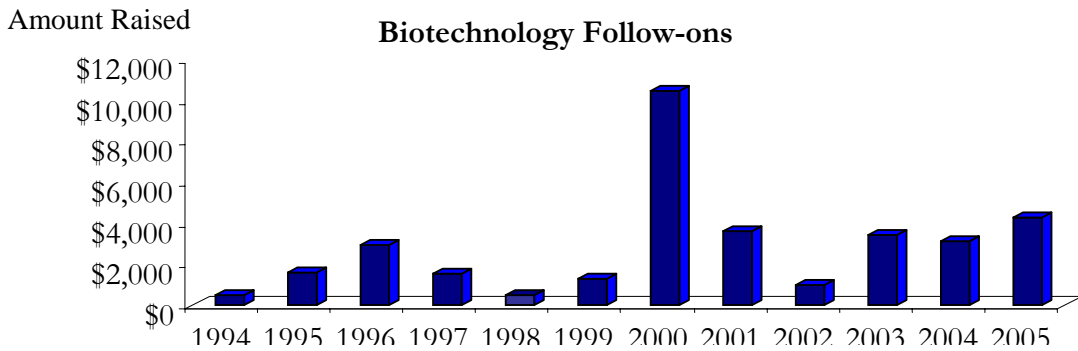
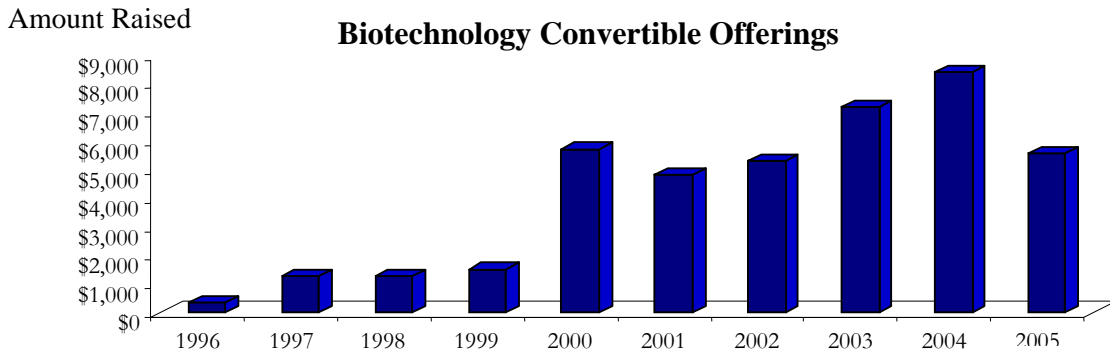


**Exhibit 15. Biotech IPO valuations, 1994-2006, plotted against the Nasdaq Biotechnology Index (NBI).** Data obtained from BioCentury.

**Multiple funding mechanisms are available to maturing public companies**

The “product diversification” period usually marks the transition out of a period of singular focus, and once again often results in a change of management. During this period, a product company will seek forcefully to deepen or broaden its pipeline. Because the company is now public, its major concern is meeting high growth rates expected by shareholders. Funding mechanisms used at this stage include follow-ons, PIPES (private placement of public companies) convertibles, etc. Investments in these vehicles have followed similar trends (Exhibit 16).

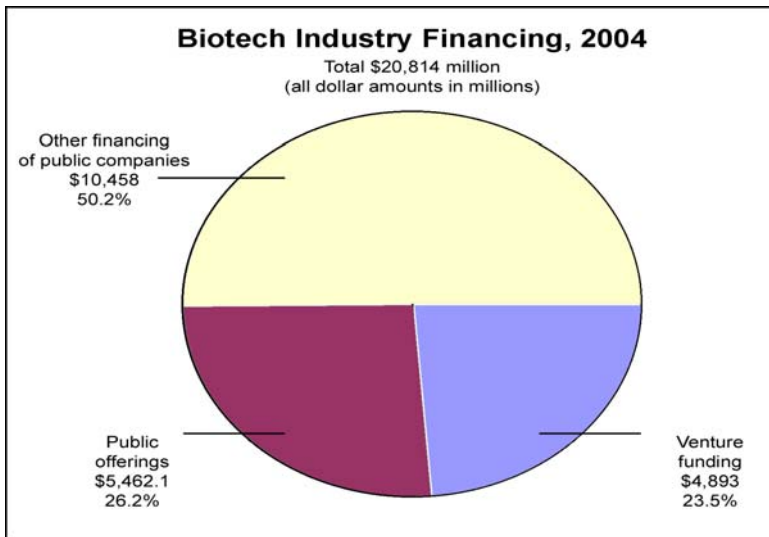
<sup>10</sup> *Bioentrepreneur*, Dec 22, 2005: “Venture capitalists and angels are pulling back from seed rounds, just as biotech startups need more money than ever to get off the ground.”



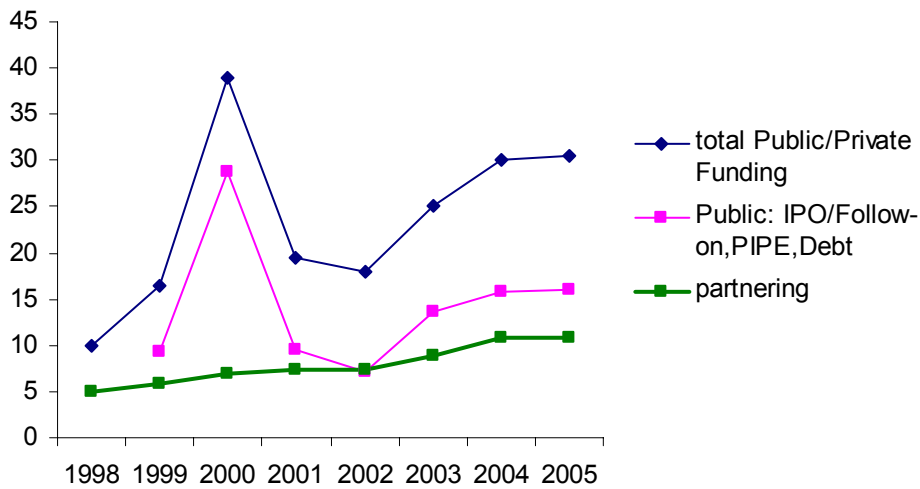
**Exhibit 16. Post-IPO funding (Follow-ons, convertibles, PIPES) (\$MM).**  
Data obtained from BioCentury.

### A Diversity of Funding Sources Is Key

Availability of continuous funding from diverse sources, public and private, is key to the success of the biomedical sector in the U.S. (Exhibit 17). Countries that lack this continuous stream of resources or have funding gaps have not been able to compete in biotechnology. The value of diversity was recently demonstrated: while capital market funding dropped precipitously after the “bursting of the bubble” in the year 2000, a combination of government funding and partnering revenue provided the sector with alternative sources of sustenance that allowed it to continue to prosper (Exhibit 18).



**Exhibit 17. Diverse sources of biotech funding (\$B)**



**Exhibit 18. U.S. biotechnology industry fundraising, 1998-2005 (\$B).**  
Data obtained from BioCentury

## PART II

### The Biomedical Industry in Transformation: How Industry Sectors Can Meet the Challenge of a “Flat” World

In the U.S., population growth and age, as they have in the past, continue to exert a profound influence upon the biomedical market. Baby boomers, now driving the nation's social and political agenda, are determined to remain healthy and active well into their retirement, and are willing to pay for solutions that promise to extend their quality of life (see Exhibit 5 in Part I). These demographic changes are resulting in an explosive growth in the demand for the industry's products; yet the industry is facing increasing costs as well as vexing pricing and distribution issues. The healthcare system in the U.S. is widely perceived to be in “crisis.”

At the same time, the world is undergoing a quiet, but deep and powerful transformation that is fundamentally affecting all industries on a global basis, including the biomedical industry. The world is becoming “flat,” changing the dynamics of innovation and commercialization as well as the distribution of wealth and the global incidence of disease. How will transformation of the global biomedical marketplace affect the biomedical industry in the U.S.? Will the U.S. continue to be the leader in biomedical innovation in the century of the “flattened” world? How will global social, political, and economic shifts affect the dynamics of an industry whose center has traditionally been the United States and Western Europe?

#### Demographic Trends

The world's population, led by gains in developing countries, will expand from 6.5 billion in 2005 to 7.9 billion in 2025.<sup>11</sup> Population is not only growing, but, in aggregate, growing older. Persons aged 60 and over comprised 10.4% of the global population in 2005; by 2050 this component will amount to 21.7% of a much larger total population. By mid-century, the number of persons aged 60 and above will grow by 1 billion. The greatest advance is expected in the rising nations of China and India, whose populations will come to benefit from drug treatments and medical devices formerly available mainly to consumers in the U.S. and Europe. *As life expectancy increases commensurately with other key socioeconomic indicators, a chronic disease market of substantial size will emerge in China, India, and other dynamic and populous nations now entering the world marketplace.* In the U.S., a well-established trend will only accelerate; the over-65 population is expected to increase approximately 73% in the next 20 years, from about 37 million to over 63 million. This will spur a marked increase in demand for medicines and treatments. Today, America's over-65 population consumes 40% of the nation's pharmaceutical output. The average 75-year-old American has three chronic conditions and consumes 4.5 medicines. These numbers will surely grow by 2050, at which point there will be more than 1 million Americans over the age of 100.<sup>12</sup>

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<sup>11</sup> The United Nations, “World Population Prospects, The 2004 Revision.”

<sup>12</sup> Magee, M., 2005 *Health Politics*, Spencer Books.

### A demand explosion for chronic disease treatments

Communicable infectious diseases are the world's chief health threat, particularly in developing countries, and this will continue to be the case into the next decade. But *with the expected shift of wealth to emerging economies such as China and India, non-communicable chronic diseases, or, in other words, ailments afflicting the elderly, will eventually overtake communicable infectious diseases.*

With this shift in the demographics of disease, the business strategies of pharmaceutical and biotechnology companies will need to shift too. The top deadly diseases for people over age 65 are heart disease, cancer, stroke, emphysema, and pneumonia (Exhibit 19). The top five causes of disability are accidents, arthritis, high blood pressure, heart disease, hearing impairments, and cataracts. According to a survey of the Pharmaceutical Research and Manufacturers of America (PhRMA), more than 800 experimental medications are currently in development for diseases primarily affecting elderly people. The most significant drug types being developed for the aging population are listed in Exhibit 20.

Cause of Death	Number of Deaths Estimated for 2003	Death Rate per 100,000 People
1. Diseases of heart	684,462	235.4
2. Malignant neoplasms	554,643	190.7
3. Cerebrovascular diseases	157,803	54.3
4. Chronic lower respiratory diseases	126,128	43.4
5. Accidents	105,695	36.3
6. Diabetes mellitus	73,965	25.4
7. Influenza and pneumonia	64,847	22.3
8. Alzheimer's disease	63,343	21.8
9. Nephritis, nephrotic syndrome, and nephrosis	42,536	14.6
10. Septicemia	34,243	11.8
All causes	2,443,930	840.4

**Exhibit 19. Causes of death in the U.S. and age-adjusted death rates<sup>13</sup>**

In the U.S. there is an increasing focus on “life-style” diseases. The best way to treat chronic diseases such as diabetes and obesity is not necessarily by pharmaceuticals, but instead by exercise and proper nutrition. The National Center for Health Statistics's Division of Vital Statistics has estimated that more than 74,000 deaths were directly related to diabetes in 2003; indirectly, however, diabetes, by complicating heart disease, stroke, and kidney disease, led to many other deaths. Similarly, according to some studies,<sup>14</sup> there were approximately 112,000 excess deaths related to obesity in 2000.

With population growth, increased longevity, the re-distribution of wealth in the world, and the concomitant shift toward chronic diseases not only in the developed nations of

<sup>13</sup> National Vital Statistics Reports; National Center for Health Statistics

<sup>14</sup> “Excess Deaths Associated With Underweight, Overweight, and Obesity”, *The Journal of the American Medical Association*, April 2005.

the West but in emerging nations like China and India, *market growth for diagnostics, therapeutics, and medical devices will explode*. The life-sciences market in Asia is expected to expand faster than that same market in America and Europe.<sup>15</sup> Revenue for the life-sciences industry in the U.S. is expected to grow by no more than 10% a year, while Japan and Western Europe should experience even slower growth. Prospects seem brightest for this market in China and India.

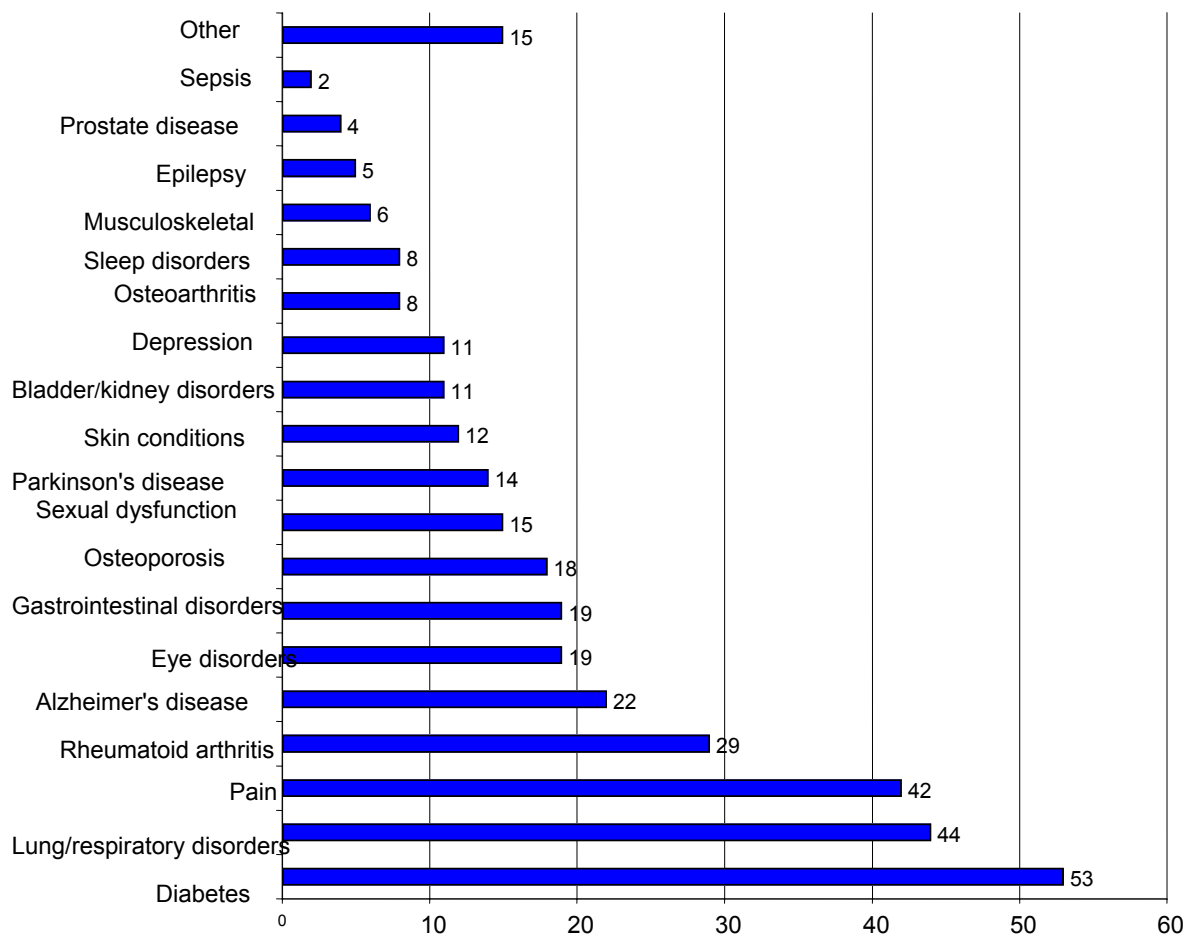


Exhibit 20. Drugs in development in the U.S. for the aging population<sup>16</sup>

### Globalization and disease: the rising demand for anti-infective treatments

While globalization is presenting unprecedented opportunities for the treatment of chronic diseases, especially those associated with aging, the economic and health benefits of globalization are not equally distributed. The flattened landscape of a globalized world is notable for its large pockets of highly vulnerable populations susceptible to large-scale infectious disease transmissions and outbreaks. Rising global

<sup>15</sup> "Future of Life Sciences Industries", Deloitte whitepaper, April 2005 ([www.deloitte.com/dtt/cda/doc/content/DTT\\_Lifesciences\\_survey.pdf](http://www.deloitte.com/dtt/cda/doc/content/DTT_Lifesciences_survey.pdf))

<sup>16</sup> Source: PhRMA

trade and travel, highly porous international borders, increased urbanization, and an uneven distribution of wealth all have helped to spread infectious diseases. Today, an infected person can carry a disease from almost any place on the planet to any other place in less than 36 hours, a disturbing fact made even more chilling when considering the threat of bioterrorism.

#### Two Kinds of Biomedical Consumer

Global demographic trends reveal two types of radically different biomedical markets and consumers. The chronic disease market is typified by the “me” consumer. The acute disease market is typified by the “desperate” consumer.

The “me” consumer is usually a highly educated, aging baby boomer consumer afflicted with chronic diseases or willing to pay to preserve his good health and affluent lifestyle. This consumer takes his health into his own hands and has the resources to look for highly personalized health solutions that will work when he wants and do what he wants. The “me” consumer wants options and is shifting the balance of power from the doctor to himself. Demand from this consumer segment favors developers of specialized, life-style medicines and cosmetic treatments. For the biomedical sector this is a predictable, high margin, growing market niche that will continue to expand as the population continues to grow.

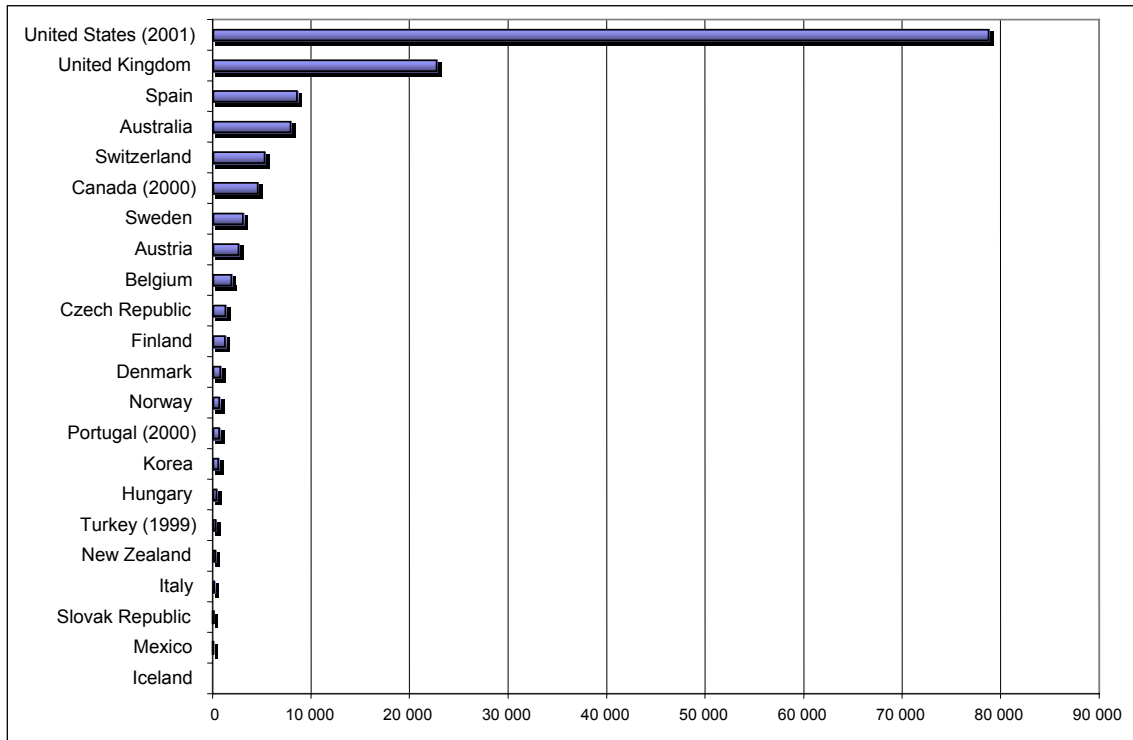
The “desperate” consumer, on the other hand, has no time and no resources to research health options. He is either a vulnerable and underprivileged patient or the victim of an infectious disease, pandemic, or terrorist attack. For the biomedical sector this profile suggests a sporadic, unpredictable, high-volume, low-margin market requiring robust scale and distribution channels.

#### **The U.S.’s lead in biomedical knowledge is dependent on foreign students and therefore vulnerable**

The U.S. is unquestionably the world’s leader in biomedical innovation. University research is the lifeblood that feeds the biomedical industry and keeps the U.S. ahead of the pack. Trends in the mobility of graduate researchers in the U.S. are therefore a good predictor of where future innovations will be sourced.

The cross-border mobility of doctoral students is an indicator of the internationalization of both higher education and innovation. During their doctoral studies and afterwards, young researchers in the sciences typically contribute to research carried out in the host country. But one of the byproducts of globalization is the growing tendency of foreign doctoral students in the U.S. to return home. These repatriated knowledge-workers bring back new competencies and links to international research networks, and thus help give rise to new centers of innovation around the globe.

The “production” of scientific researchers continues to be dominated by the U.S (Exhibit 21). In 2001, the U.S. hosted 79,000 foreign doctoral students in the sciences, by far the largest number in the OECD (almost 4 times that of the second major host, the UK).



**Exhibit 21. Where foreign doctoral students in the sciences study<sup>17</sup>**

Given the repatriation trend, determining where American-trained foreign scientists come from can provide insight into which countries may experience the greatest advancement in technology in the coming years and decades. The number of doctoral researchers in the U.S. from Asia has remained between 4,000-5,500 over the last 10 years, but is four times larger than the number coming from Europe. This suggests Asian countries will become the U.S.'s major competitor for high-quality science (Exhibit 22).

<sup>17</sup> OECD Science, Technology and Industry Scoreboard 2005

<b>TOTAL</b>	<b>9,486</b>	<b>100%</b>
China	2,501	26.4
West Asia (excl. Turkey)	1,291	13.6
Europe (excl. 3 biggest)	1,220	12.9
Korea	961	10.1
Chinese Taipei	442	4.7
3 biggest European (Germa	386	4.1
Africa	341	3.6
Turkey	374	3.9
Canada	325	3.4
South America (excl. Brazil)	352	3.7
Thailand	311	3.3
Mexico	219	2.3
Japan	202	2.1
Pacific / Australasia	145	1.5
Other East Asia	136	1.4
Brazil	107	1.1
Other countries	173	1.8

**Exhibit 22. U.S. Doctorates in the Sciences Awarded to Foreign Nationals**<sup>18</sup> There is anecdotal evidence that American-trained Indian and Chinese researchers are now more likely than previously to move back to their countries of origin, but government data does not yet support this claim. Indeed, two-thirds of all Indian and Chinese PhDs trained in the U.S. currently choose to remain in the U.S. Data also show that the number of students remaining in the U.S. from Japan, Korea, and Chinese Taipei — countries that have traditionally drawn many of their “exported” students back — has in fact increased. This suggests that U.S. dominance in biomedical and other scientific research will persist at least for the next decade -- until countries such as India and China improve their innovation infrastructure and thus induce more of their students abroad to return home.

<sup>18</sup> National Science Foundation/Division of Science Resources Statistics, Survey of Earned Doctorates, 2005 . Includes all European countries. OECD estimates based on NSF data. The ratio compares the number of new foreign citizens graduating at the doctoral level in S&E fields in the U.S. to the number of earned S&E doctoral degrees in the country of origin. New S&E doctorates refer to 1997 for India, 2001 for China, the UK, Chinese Taipei and Japan, and 200 for other countries.

## U.S. at forefront of global output of knowledge, but China and India are narrowing the gap

Most patents filed in the European Patent Office (EPO) in 2001 originated in the United States, which accounted for 41.5% of the total number. Germany was next with 12.8%, then Japan with 12.3% (Exhibit 23).

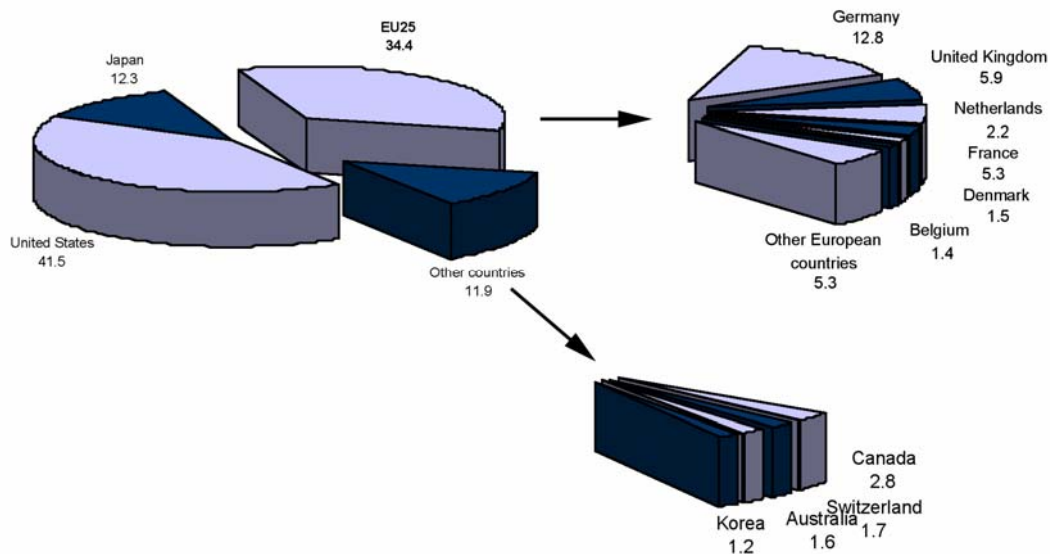


Exhibit 23: The EPO biotechnology patent pie, 2001.<sup>19</sup>

Clearly, citizens of developed countries led in the creation of biotech inventions. But the gap in the number of filed biotechnology patents between inventors of the developed “West” and Asia is expected to narrow dramatically in the next decade. This is reflected by the specialization index (SI) (Exhibit 24). The specialization index is the share of a given country in obtaining patents in a *specific* technology area (e.g., biotechnology) divided by the same country’s share in all technology areas (e.g., total European patents issued to the country’s nationals). An SI score of greater than 1 in biotechnology patents indicates that a given country tends to focus on biotechnology more than other technology areas.

<sup>19</sup> OECD Science, Technology and Industry Scoreboard 2005

Exhibit 24 gives the **biotech specialization index** for selected countries, using EPO-issued patents, 1996-2001, as a database. The U.S. is highly specialized in biotechnology patents, while Japan and most members of the European Union are not. Of particular note are the high indices for India and China.

Specialization Index	1996-2001	MEAN
Denmark	2.10	1
Canada	2.01	1
Australia	1.79	1
New Zealand	1.77	1
India	1.72	1
United States	1.67	1
China	1.48	1
Belgium	1.46	1
United Kingdom	1.30	1
Ireland	1.22	1
Russian Federation	1.06	1
MEAN	1.00	1
OECD	1.00	1
Netherlands	0.89	1
Norway	0.83	1
Korea	0.82	1
Spain	0.72	1
EU25	0.71	1
France	0.71	1
Austria	0.66	1
Switzerland	0.60	1
Japan	0.60	1
Sweden	0.57	1
Germany	0.54	1
Finland	0.44	1
Italy	0.31	1

**Exhibit 24: Specialization Index of biotechnology patents filed at the EPO, 1996-2001<sup>20</sup>**

## Policy Trends

### Cost Pressures and Their Impact on the Biomedical Industry

The increase in world population and shift in prevalence and distribution of chronic diseases, combined with escalating research costs, rising global competition, and the increasing complexity of distribution systems, are placing unprecedented cost pressures on the biomedical industry. These cost pressures are paired with increasing pressures from governments, employers, and consumers to reduce pricing and augment global distribution of drugs and devices. Spending on Medicare and Medicaid accounts for one-fifth (\$519 billion) of the 2005 U.S. federal budget. The Centers for Medicare and Medicaid Services (CMS) are changing the basis of Medicare to “defined contribution” to

<sup>20</sup> OECD, Patent Database, March 2005

help curb spending. In the private sector, GM and Ford have significant health-care liabilities and are negotiating with unions to reduce them.

Biomedical firms are more dependent than most business on the relationship between government and industry. The ability of biomedical firms to promote and sell product hinges upon legislation and the protection of intellectual property, as noted in Part I.

**Premium reimbursement will require benefit beyond efficacy and safety**

Managed health care firms, while experienced in governing the utilization of pharmaceuticals, have come to appreciate the costs associated with new therapies. According to Verispan’s Spring 2005 Formulary Drug Audit, the days of \$10-\$20-\$30 copay structures are long gone (Exhibit 25). The average third-tier copay now eclipses \$40. Just as significant as absolute copay is “copay delta,” or the difference between preferred and non-preferred brands. A copay delta (from tier two to tier three) greater than \$17 is no accident. Plans intentionally structure these benefits to open consumers’ eyes and drive behavior toward lower-cost alternatives, such as generics and non-innovative products. While governments are successfully influencing public demand for the output of the pharmaceutical sector, they have not yet been able to influence demand for the products of biotechnology and medical device companies.

Medco and ESI, leading pharmacy benefit managers (PBMs), have begun managing high-cost products by creating a fourth tier in which prior authorizations are a fact of life, and step-therapy is more common. They have also moved to reference-based pricing, which seeks to establish a baseline product that all competitors are reimbursed against. On the device side, “least-costly alternatives” are used to negotiate more affordable rates. Finally, in an attempt to rein in utilization of biologics, PBMs have tinkered with the concept of “functional equivalence,” seeking to equate the cost of therapies across multiple functions. These complex reimbursement schemes are designed to artificially flatten the competitive landscape. They are confusing to the patient and are so complex that only large pharmaceutical and device companies have the resources to navigate through the system.

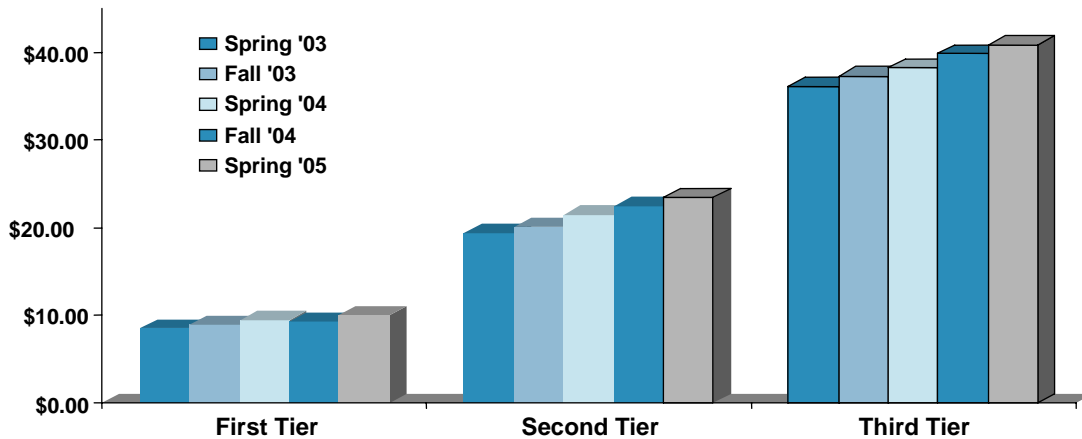


Exhibit 25. Copay amounts for biotech products

Increasingly the biomedical industry needs empirically to demonstrate product value. Though biologics often come at a higher cost, manufacturers need not only to establish endpoints, but also integrate Health Economics & Outcomes Research (HEOR) into basic discovery, research & development.

### **Generics, biologics and the cost of healthcare**

Payers in the U.S., both federal healthcare programs and employers, are trying to retard the rising prices of medical goods and services. This cost-containment strategy will squeeze future revenues and push the biomedical industry to come up with innovative products. Generic drugs are viewed as the catalyst for change in policy within the biomedical industry. As drugs become more expensive, governments are looking to generics as a way to cut costs. This cost-cutting drive requires generics companies to meet regulations that ensure their products are as efficacious as approved treatments. The emergence of new generic drugs is greeted by stock price swings in the pharmaceutical industry. As drugs come off of patent protection, investors in public markets make decisions based on how much the company will be hurt by the generic. For small molecule compounds, generic drugs are easily approved when the generic is shown to be the same compound as the parent drug. This is not the case with biologic drugs made by biotech companies, because the process by which they are made can influence efficacy (see Part I).

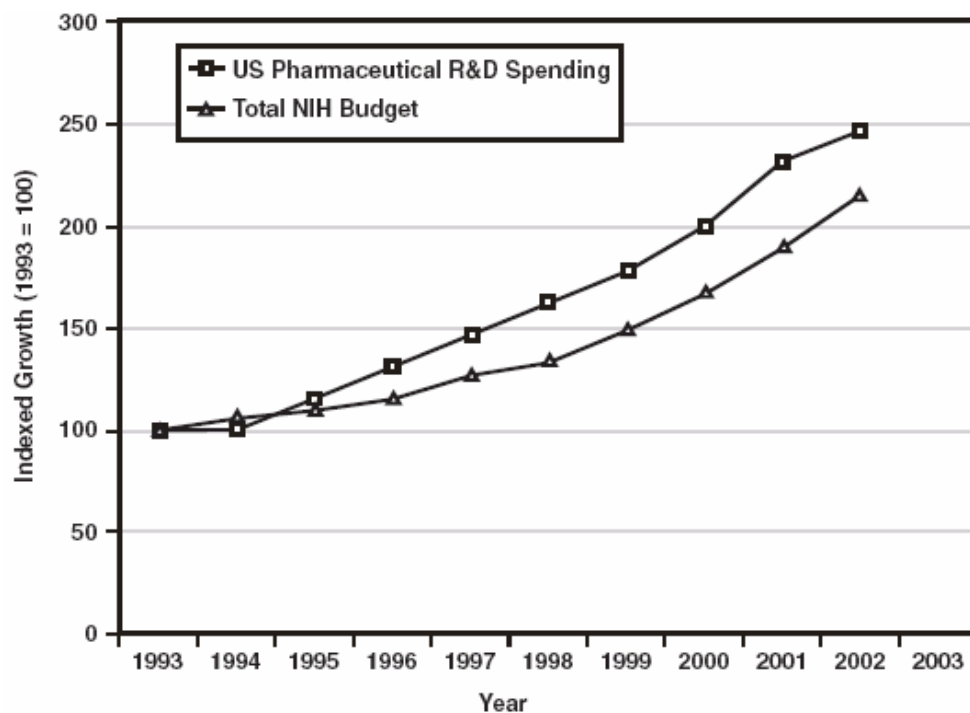
### **Global complications of patent law: a challenge for big pharma**

There are differing interpretations of The World Trade Organization's (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Among other regulations, the TRIPS Agreement provides flexibility for governments to make exceptions to patent holders' rights, for instance in national emergencies, or upon a determination of anti-competitive practices.

In light of the national emergency that HIV and TB present in low-income developing countries, governments of some of these countries have demanded the right to import inexpensive, generic versions of drugs from pharmaceutical manufacturers in countries such as Thailand, India, and Brazil. These IP pressures weigh heavily on the decisions of pharmaceutical companies to outsource fractions of R&D, especially when governments that believe prices are too high can disregard IP protection.

## **Technology Trends**

Innovation in the biomedical industry springs from scientific research. New scientific advances, which are becoming more and more difficult to achieve, have the greatest positive effect on revenue growth.<sup>21</sup> Academic and private investments in basic research escalated steadily for the period 1993-2003 (Exhibit 26), although U.S. government investment has leveled off during the last two years due to fiscal constraints.



**Exhibit 26. Ten-year trends in biomedical research spending.**

Source: "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." FDA whitepaper, March 2004.

Basic research, in theory, is pursued for its own sake, and not in direct response to needs of the marketplace. The science developed in conjunction with the Human Genome Project has taken a decade to migrate to the marketplace. New applications and products of the genomic revolution are pointing to better, more precise ways to determine and monitor disease predisposition, more precise ways to deliver treatments, and better ways to prevent disease from occurring in the first place. These advances are on the leading edge of what we expect to be a medical revolution in the U.S. and other highly developed nations, based on the concept of personalized medicine.

### ***Specific technological enablers of the coming shift to personalized medicine***

Some of the tools that are enabling these new capabilities include the commoditization of DNA sequencing, proteomic analysis, microarrays, and advances in optics and imaging technologies.

#### **DNA sequencing technology . . .**

. . . is becoming mainstream, faster and cheaper. According to Annelise E. Barron, Associate Professor of Chemical and Biological Engineering at Northwestern University, high-throughput DNA sequencing will grow exponentially in the next 15-20 years as the gathering of sequencing data becomes more important for the medical community. Advances in DNA sequencing technology will give rise to a \$1,000 human genome<sup>22</sup>,

<sup>22</sup> Source: <http://www.nih.gov/news/pr/aug2005/nhgri-08.htm>

enabling individuals to “own” their own genetic code on a CD. These sequences will be used to determine which medications will be the most efficacious for the individual and what side effects might arise. This is not feasible with current sequencing techniques (costing about \$10 million per human genome today) and will require a paradigm shift using a new technology.<sup>23</sup> Advances in microarrays and microfluidics are paving the road toward this goal.

### Microarrays . . .

. . . are the primary tool for gene expression and sequencing. The premise behind microarrays is to monitor the relationship between many genes simultaneously. Currently, microarrays can profile up to 100,000 single nucleotide polymorphisms (SNPs) per assay, a number expected to increase dramatically in the near future.<sup>24</sup> The major challenge today has to do with data analysis and interpretation.

*Uses of DNA microarrays:*

*Expression Profiling* — mRNA from relevant cell cultures of tissues

*Pathogen detection* — genomic DNA from microbes

*Genotyping* — genomic DNA from humans or animals

*Resequencing* — genomic DNA

Protein-DNA interactions — genomic DNA<sup>25</sup>

### DNA sequencing

- Rapid sequencing will provide the data for genotype-phenotype associations that will allow for future drug and therapy targets.<sup>1</sup>
- In cancer research, DNA sequencing will give us the ability to profile tumor sub-types for diagnosis and prognosis, and could give us a comprehensive database to help decipher the combinations of mutations that lead to cancer.<sup>1</sup>
- Sequencing will help find SNPs (single nucleotide polymorphisms), which can assist researchers in identifying the multiple genes associated with complex diseases like cancer and diabetes.
- Hypertension affects above 20 percent of the general population in industrialized nations. Investigations of rare mendelian forms of blood-pressure variation in which single gene mutations cause extremes in blood pressure has been informative in understanding molecular basis for hypertension. This basic understanding will determine targets for drugs and preventative treatment.<sup>3</sup>
- Type 1 diabetes is an autoimmune disease and should genetic variations be identified in patients, they will guide preventive and or replacement treatment. This research will also give comparisons to other autoimmune diseases and further treatment in those areas.<sup>1</sup>

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<sup>1</sup> Advanced Sequencing Technologies: Methods and Goals, Nature Reviews Genetics, 5, 2004, 335-344

<sup>2</sup> Source:

[www.ornl.gov/sci/techresources/Human\\_Genome/faq/snps.shtml](http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml)

<sup>3</sup> Cardiovascular Disease, The New England Journal of Medicine, 349, 2003, 60-72

### Microfluidic devices . . .

. . . are less than 1 mm in size and are used to study the properties of liquids in very small volumes as compared to the macroscopic properties one can see (i.e. surface

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<sup>23</sup> Advanced Sequencing Technologies: Methods and Goals, Nature Reviews Genetics, 5, 2004, 335-344

<sup>24</sup> Biotech 2004: Back on Track, Burrill & Company

<sup>25</sup> Annual Review in Biochemistry, 2005, 74:53-82

tension, mixing ability, energy dissipation, etc.). Advantages of microfluidics are in the small volume of material needed and their relatively inexpensive fabrication.<sup>26</sup>

Uses for microfluidics:

- Capillary electrophoresis<sup>27</sup>
- Immunoassays<sup>28</sup>
- Flow cytometry<sup>29</sup>
- PCR amplification

## Proteomics . . .

. . . offers a different way to look at the genome. Instead of analyzing the genetic code, it looks at the product of the genetic code in the form of proteins expressed by DNA.<sup>30</sup>

The old paradigm of “one gene – one function” has been superseded. Every individual’s complement of 25,000-30,000 genes produces approximately 1 million structurally distinct proteins.<sup>31</sup> Because proteins are dynamic in nature, they can be monitored to reveal changes in the state of an organism over time. Proteomics is thus fueling the biomarkers market. It promises the identification of markers for cancer and other conditions, in part by demonstrating the difference between healthy and diseased tissue.

Proteomics enables researchers to examine changes in numerous molecules at once. Drug researchers have

### Other applications for proteomics

- Proteomics has a broad benefit in the field of drug discovery. The majority of drug targets are proteins, but we exploit less than 1/6 of the predicted drugable proteins.
- Using proteomics to discover which proteins are up-regulated and down-regulated in cancer will give us greater insight into which cancers are related and how.<sup>1</sup> Knowing this relationship will give a clearer direction for both diagnosis and treatment.
- Study of the protein markers for cardiovascular disease has given an incomplete list of at least 177 different proteins.<sup>2</sup> It is hypothesized that a targeted proteomics approach would provide greater understanding of relationships among known markers.<sup>2</sup> This understanding would not rely on the behavior of just one protein but on a combination of different proteins, and would thus render diagnostics more efficient.
- Proteomic studies of Alzheimer’s disease have led to the potential identification of mechanisms in neurodegeneration that currently have no effective treatment or definitive diagnostic test.<sup>3</sup> These studies have provided clues as to the proteins involved in pathology as well as structural abnormalities of significant proteins.<sup>4</sup> Post-translational modifications of different proteins can also be probed with proteomics, providing insight into the mechanisms of disease.<sup>4</sup>

<sup>1</sup> The molecular make-up of a tumour: proteomics in cancer research, *Clinical Science*, 108, 2005, 369-383

<sup>2</sup> Candidate-based proteomics in the search for biomarkers of cardiovascular disease, *Journal of Physiology*, 2005, 23-60

<sup>3</sup> From proteomics to biomarker discovery in Alzheimer’s disease, *Brain Research Reviews*, 48, 2005, 360-369

<sup>4</sup> Proteomics in Alzheimer’s disease: insights into potential mechanisms of neurodegeneration, *Journal of Neurochemistry*, 86, 2003, 1313-1327

<sup>26</sup> <http://faculty.washington.edu/yagerp/microfluidicstutorial/basicconcepts/basicconcepts.htm>

<sup>27</sup> Kameoka, J., Craighead, H. G., Zhang, H. W. & Henion, J. A polymeric microfluidic chip for CE/MS determination of small molecules. *Analytical Chemistry* 73, 1935-1941 (2001).

<sup>28</sup> Hatch, A. et al. A rapid diffusion immunoassay in a T-sensor. *Nature Biotechnology* 19, 461-465 (2001).

<sup>29</sup> Sohn, L. L. et al. Capacitance cytometry: Measuring biological cells one by one. *Proceedings of the National Academy of Sciences of the United States of America* 97, 10687-10690 (2000)

<sup>30</sup> The clinical application of proteomics, *Clinica Chimica Acta*, 357, 2005, 151-158

<sup>31</sup> The molecular make-up of a tumour: proteomics in cancer research, *Clinical Science*, 108, 2005, 369-383

generated mountains of data and mined them to discover a host of new biomarker candidates, potentially useful in both pharmaceutical R&D and diagnostic applications.

This situation stands in stark contrast to that of the pre-genomic era when biomarker discovery was so difficult that adoption of a new marker was a relatively rare event. Biomarkers play an increasingly critical role in streamlining and accelerating disease detection and drug development programs by providing precise, evidence-based information (Exhibit 27). As firms continue to experience diseconomies of scale with research investments, the pharmaceutical industry has come to view the advancement of biomarker technology as a necessity.

Role	Description	Example
Disease Biomarkers	Indicates the presence or likelihood of a disease	Genotypes, gene profiling
Surrogate endpoints	Used to prove ongoing results in clinical studies	Tumor shrinkage, CD4 count for HIV AIDS
Mechanism biomarkers	Suggest a drug affects a particular pathway	Activation or deactivation of enzymes and receptors
Pharmacodynamic biomarker	Used to determine dosage levels for a particular drug	Blood or urine levels of proteins associated w/ disease
Target biomarker	Shows that a drug interacts with a particular target	PET imaging time to show residence time on a receptor
Toxicity biomarker	Indicates potentially harmful effects of a drug	Induction of cytochrome P-450

**Exhibit 27. Roles and uses for biomarkers**

## Nanotechnology . . .

. . . is an exciting new area that conjures up thoughts of small robots inside the body fighting disease.

Work with nanotechnology spans all areas of science, including biomaterials, fabrics, electronics, drug delivery and MRI contrast agents (Exhibit 28). The National Science Foundation estimates that this industry in its many applications will be worth \$1 trillion worldwide by 2015.<sup>32</sup> In its biological

<b>NANOSPHERE, INC</b>
<p>Nanosphere, Inc. is a venture-backed, privately-held life-sciences company outside of Chicago, Illinois. Chad Mirkin, Ph.D. and Robert Letsinger, Ph.D., two professors from Northwestern University, co-founded the company in 2000.</p> <p>The proprietary technology at Nanosphere uses the unique properties of nanoparticles with which the company has developed a nanoparticle-based DNA detection system with “10 times more sensitivity and 100,000 times more specificity than current genomic detection systems”. The technology is being positioned to complement and eventually eliminate the need for costly and time-consuming PCR/fluorophore-based approaches with the potential to dramatically simplify traditional analysis procedures. Nanoparticle probe detection systems will lower the cost, improve the quality, and dramatically decrease the time to market for hand-held molecular testing devices.</p> <p>The company envisions becoming the “global standard” of molecular diagnostics. The estimated market potential of the three major applications of this technology -- clinical research, in-vitro diagnostics, and animal/food/ environmental markets -- is approximately \$7.5 billion. Nanosphere has created a strategic partnership with IDEO Design and Development, headquartered in Palo Alto, to commercialize its first generation of detection systems</p>

<sup>32</sup> Biotech 2004: Back on Track, Burrill & Company

applications, nanotechnology enables the detection of a lower concentration of biological analytes in a cheaper, faster, and more selective fashion, ultimately facilitating the diagnosis of disease. Chad Mirkin Ph.D., Morrison Professor of Chemistry at Northwestern University, believes that nanotechnology will be used in the biomedical industry -- “nano-bio” -- in treatments for cancer and Alzheimer’s. More immediate applications are in the diagnostics arena. Professor Merkin sees nanotechnology tools as key to revolutionizing the standard of care, shifting diagnostics from the hospital setting to point-of-care analysis.

#### **NOBIOTECHNOLOGY APPLICATIONS**

The specific medical applications for nanotechnology include:

##### **Clinical Diagnostics / R&D**

- (a) *Rapid and inexpensive DNA characterization using nucleic acid arrays*
- (b) *Development of new imaging technologies for earlier detection of cancer and other diseases*

##### **Sensors**

*Sensor systems for the detection of pathogens (in vivo and ex vivo)*

##### **Medical devices**

*Effective and less expensive healthcare using remote and in vivo devices (e.g., monitoring of blood glucose levels and release of insulin correspondingly)*

##### **Drug delivery**

*New formulations and routes for drug (and gene) delivery*

##### **Gene therapy**

*Methods for correcting specific mutations in individual genomes using artificial proteins as “nanorobots”*

#### **Exhibit 28. Nanotechnology applications in healthcare**

Some companies working with nanotechnology:

- **NanoSystems** – drug delivery applications
- **Nanospectra Biosciences** – drug delivery applications
- **Carbon Nantechologies** – sells plain carbon nanotubes by the gram
- **Ambri Biosensor** – biosensors
- **Nanosphere** - diagnostics

#### **Imaging technologies . . .**

. . . are now recognized as standard care in medicine and are projected to continue growing in the coming years (Exhibit 29). A number of imaging technologies that are mainstays of medical diagnosis today include:

*Magnetic Resonance Imaging.* MRI is one of the most important diagnostic techniques used today and is expected to become even more commonly utilized in the future. Undoubtedly, the reason the MRI is so highly regarded is because it is non-invasive, low energy, three-dimensional, and temporal in nature. MRI imaging affords millimeter resolution throughout the body by relying on the inherent contrast of different bodily

tissues.<sup>33</sup> Physicians use this technique as a guide for interventional procedures, to image cancer, broken bones, torn ligaments, cardiovascular problems, and other conditions.

*Computed Tomography.* CT or CAT scanning is another indispensable medical diagnostic technique in which high-energy X-rays are used to image the body. Although this technique is much faster than MRI, it gives lower resolution for soft tissues and cannot be performed as often as MRI due to its use of radiation. Despite these drawbacks, CT is the gold standard for diagnosis of many diseases. It can be used to image coronary arteries, bones, intracranial pressure, abdominal disease, and as a guide for interventional procedures.

*Positron Emission Tomography.* PET is a technique used to image biological processes. This is accomplished by injecting a radioactive isotope into the body and imaging its decay. PET is invasive and yields a much lower resolution than MRI or CT. Yet the technique has proven very useful in clinical oncology, neurology and cardiology research.

Modality	% Annual Growth (2002)	% Annual Growth (2008)	Key Growth Areas
PET	79	25	Oncology applications
MRI	22	18	MR angiography, functional MRI, cardiac MRI
CT	16	18	Cardiac CT, CT angiography, virtual colonoscopy, lung CT
Interventional X-ray	12	12	Applications used during minimally invasive procedures
Ultrasound	11	8	Offered through private offices
Mammography	4	6	CAD enhanced mammography
X-ray	1	-3	Hospital DR/CR*; private office CR*

\*DR: Digital Radiography; CR: Computerized Radiography

**Exhibit 29. Projected growth of imaging techniques.**

Source: Sg2 consulting report “Imaging Services,” February 2004.

**Seeing is believing: bringing together devices, optics, and molecular genomics**

Technology breakthroughs are occurring at the interface of many disciplines, including that of drug and medical device development. The first product of this convergence was the drug eluting stent. While stents are certainly important in cardiovascular care and significant as the first drug/device, the interface between fields and industries is fertile ground for many other medical products and services. Other methods, such as transdermal drug delivery and products such as implantable drug delivery wafers, have benefits ranging from localized and more controlled release to greater convenience for

<sup>33</sup> New magnetic resonance contrast agents as biochemical reporters, *Current Opinion in Neurobiology*, 13, 2003, 597-602

both doctors and patients. Perhaps the most promising convergence of all, however, is at the nexus of imaging and molecular biology.<sup>34</sup>

### **Molecular Imaging**

Perhaps the most dramatic diagnostic advances to be made in the near future are in the field of molecular imaging. Molecular imaging differs considerably from anatomic imaging. It also goes beyond traditional functional imaging, which shows a general metabolic process. Molecular imaging involves targeting at a much finer level of resolution — at that of the cell or even individual molecule. It involves combining genetic information and new chemistries into new imaging probes that can be detected by sophisticated imaging technologies.<sup>i</sup>

Because pathologic conditions involve changes at the genetic and molecular levels within cells and because molecular imaging involves targeting specific molecules, the field has the ability to transform how biomedical research is done, change the drug development process, and ultimately help remake the clinical practice of medicine. Molecular imaging will utilize a wide variety of imaging modalities and has the potential to affect care in a variety of medical conditions, from cardiovascular and neurological diseases to cancer. Within oncology, it may permit earlier detection, improve therapy, and make possible real-time monitoring at an unprecedented level of detail.

### ***Therapeutic Modalities of the Future***

#### **Stem cell therapy**

Few areas in biomedical technology spark as much interest, hope, and controversy as stem cell research. And in spite of the controversy about its ethical status, few scientists dispute the astonishing potential of this research to transform the treatment of disease. Stem cells have the ability to continuously divide and differentiate into specific cells and tissue types. In 1998, Professor James Thomson, at the University of Wisconsin, isolated and grew stem cells from human embryos.<sup>35</sup> Shortly thereafter, researchers from Johns Hopkins University replicated the results with human germ cells or cells from the gonadal ridge of aborted fetuses.<sup>36</sup> These discoveries set in motion a wave of research around the globe focusing on three areas: developmental research, birth defects, and therapeutics.

There are essentially two kinds of stem cells: embryonic and adult. Embryonic stem cells are harvested in the blastocyst stage of a fertilized egg, and are described as *totipotent*, able to develop into all body cell types including the placental tissue. Adult stem cells are bone marrow cells or cells from early stages of tissue development. They can be *pluripotent*, able to give rise to any type of cell in the body except those needed to develop a fetus, or *multipotent*, able to give rise to a small number of specific cell

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<sup>34</sup> Chad D. Holland, "GE's Opportunities at the Interface: Biotech & Medical Devices Converge," Kellogg Center for Biotechnology, 2004

<sup>35</sup> Thomson, J.A., J. Itskovitz-Eldor, S.S. Shapiro, M.A. Waknitz, J.J. Swiergiel, V.S. Marshall and J.M. Jones. 1998. "Embryonic Stem Cell Lines Derived from Human Blastocysts." *Science* 282: 1145-1147.

<sup>36</sup> Gearhart, John. 1998. "Potential for Human Embryonic Stem Cells" *Science* 282: 1061-1062

types. An example of multipotent cells are haematopoietic cells—blood stem cells that can only develop into several types of blood cells.<sup>37</sup>

Stem cells offer great hope of finding a cure for heart disease. Congestive heart failure today afflicts 5 million people in the U.S. When heart muscle is damaged, functional tissue is replaced with scar tissue, which doesn't have the ability to contract. Geron Corporation has generated functioning human cardiomyocytes, or heart muscle cells, in culture from embryonic stem cells. These could potentially replace scar tissue. Similarly, Baxter healthcare is conducting clinical studies using adult CD34 stem cells to reverse the effects of heart disease. In preliminary studies, company researchers have found dramatic positive "hints" of efficacy.

#### Applications for stem cells

- Stem cells are being studied for vascular tissue engineering to help cure different cardiovascular diseases.<sup>1,2</sup> Better understanding of what happens to stem cells, their proliferation and differentiation, will increase the patency of tissue engineered grafts.<sup>2</sup>
- Natural cardiac repair *in vivo* is only possible through the introduction of new cardiomyocytes or by stimulating endogenous cells to divide.<sup>3</sup> Research continues with different injection methods and growth factors to stimulate endogenous cells or introduce stem cells to repair damaged cardiac muscle.
- Parkinson's disease (PD) is caused by the degeneration of nigrostriatal dopaminergic neurons<sup>4</sup>. There is currently no cure for this debilitating disease and stem cells show the greatest promise. Proof of principle studies using human fetal mesencephalic tissue to survive and reinnervate the striatum for as long as ten years.<sup>4</sup> This is the first step for more research and a possible cure for PD.<sup>5</sup>
- One potential solution for type 1 diabetes would be a mechanical device that can monitor and administer insulin within the body. Progress on this front is slow, but another potential cure involves using stem cells. The Edmonton protocol of islet cell transplants has provided a "cure" for diabetes, but there is a shortage of islet cells (either from cadavers or live donors). And its in dealing with this supply problem that stem cells might be able to help. Stem cells appear to be a logical choice to create more islet cells.<sup>6</sup> Research on this possibility is ongoing.

<sup>1</sup> Update on therapeutic neovascularization, *Cardiovascular Research*, 65, 2005, 639-648

<sup>2</sup> Advancing vascular tissue engineering: the role of stem cell technology, *Trends in Biotechnology*, 23, 2005, 461-467

<sup>3</sup> Cardiomyocyte differentiation from embryonic and adult stem cells, *Current Opinion in Biotechnology*, 16, 2005, 498-502

<sup>4</sup> Stem cell therapy for human neurodegenerative disorders-how to make it work, 2004, 42-50

<sup>5</sup> Regenerative medicine in Parkinson's disease: generation of mesencephalic dopaminergic cells from embryonic stem cells, *Current Opinion in Biotechnology*, 16, 2005, 487-492

<sup>6</sup> How to make pancreatic  $\beta$  cells – prospects for cell therapy in diabetes, *Current Opinion in Biotechnology*, 26, 2005, 524-529

Another potential therapeutic application for stem cells is the treatment of insulin-dependent diabetes mellitus, a disease affecting approximately 1.4 million Americans. Daily insulin injections have profound effects on a patient's quality of life and cannot reverse the disease. Embryonic stem cells have been induced *in vitro* to become insulin-secreting cells and transferred to diabetic animals, restoring the normal glucose balance within a week.

<sup>37</sup> Dr. Yu Oyama, presentation, Kellogg Biotech Bootcamp, 2005

Perhaps the most potentially miraculous opportunity that stem cells provide is in treating and curing neurological disorders. Researchers who recently transplanted embryonic stem cells into the brains of mice found that the cells differentiated into dopaminergic neurons, restoring partial function (80%) in the rat and mouse version of Parkinson's Disease. Similar, albeit preliminary, results have been observed in animal models of spinal cord injury<sup>38</sup>.

Two recent developments could radically alter research in the development of stem cell therapies. In a study on women's autopsies, the *Proceedings of the National Academy of Science* reported the presence of neuronal cells with the male Y chromosome in the brains of women who had bone marrow transplants from male donors. This suggests that stem cells migrate from bone to brain, implying that cell therapies do not need to be administered locally, and that cells can migrate to the "correct" target.

In a second recent study, Verfaillie *et al.* at the University of Minnesota found that adult stem cells from bone marrow were capable of differentiating into every type of human tissue, a finding with great potential significance for those seeking a way to avoid the phenomenon of immune rejection. The finding also implies an alternative to therapeutic cloning -- the cloning of human embryos to obtain cells that the body will accept.<sup>39</sup>

*Stem cell therapies in development:*

**Bioheart** — cardiology

**Osiris** — arthritis, cardiovascular, GVHD

**ViaCell** — cardiac, diabetes

**Geron Corp** — oncology

**Baxter** — cardiology

### **Gene therapy**

Gene therapy holds much promise, despite the bad press it has gotten in recent years. Researchers in the field suffered highly publicized disappointments in the 1990s. But in technological and scientific terms, the future of gene therapy has never been brighter than today. In contrast to early efforts in gene therapy to deliver a normal copy of a missing or defective gene, gene delivery is now being used to replace missing or defective genes; to deliver genes that catalyze the destruction of cancer cells or cause cancer cells to revert to normal tissue; to deliver viral or bacterial genes as a form of vaccination; and to deliver genes that promote the growth of new tissue or stimulate regeneration of damaged tissue. We believe that demonstrated results in these areas will tend over time to diminish public distrust and/or hostility to gene therapy, just as positive results overcame public opposition to recombinant DNA technologies at the dawn of the biotech age.

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<sup>38</sup> Ramón-Cueto A, Cordero MI, Santos-Benito FF, Avila J. 2000. "Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing cells." *Neuron* 25:425-435

<sup>39</sup> Westphal, S, 2002. "Ultimate Stem Cell Discovered", *NewScientist.com*, January <http://www.newscientist.com/news/print.jsp?id=ns99991826>

### Applications for gene therapy

- Cells that continuously replicate because of a genetic mutation in a cell and its progeny cause cancer. Malignant Glioma (MG), among other cancers, is currently being studied as a candidate for gene therapy.
- Prevention or regression of atherosclerosis (fatty deposits in the arteries) has been researched using gene-based therapeutics. In rabbits, this approach causes diminution of the atherosclerotic lesions. Problems still remain in human trials, but according to experts in the field, “the goal of effective treatments is obtainable.”<sup>2</sup>
- Patients with Type 1 diabetes also may stand to benefit from gene therapy. The insulin protein can be delivered to the liver in two ways: in a form susceptible to regulation by blood glucose; or an engineered form that is cleaved by proteases in the liver. Researchers found a slow response to changing glucose levels, but the results do show promise in the field.<sup>3</sup>

<sup>1</sup> Gene Therapy for malignant Glioma: *Current Clinical Status, Molecular Therapy*, 12, 2005, 585-598

<sup>2</sup> Potential of gene therapy for myocardial ischemia, *Current Opinion in Cardiology*, 19, 2004, 517-523

<sup>3</sup> Gene Therapy for Autoimmune diseases: Quo Vadis?, *Nature*, 4, 2004, 800-811

*Gene therapies in development:*

**Cell Genesys** - ALS

**Neurologix** - Parkinson's disease

**Genetix** - sickle cell anemia and B-thalassemia

**Transgene** - skin lymphomas<sup>40</sup>

**Targeted Genetics** - inflammatory arthritis (tgAAC94), AIDS Vaccine

### Pharmacogenomics and personalized medicine: toward tailored treatments

Pharmacogenomics is an umbrella term that refers to the use of genetics to optimize drug discovery and development. It also often refers to the concept of “tailor-made” drugs or personalized medicine -- developing the “right” drug for the “right” person.

*Personalized medicine is the marriage of genomics and molecular pharmacology.*

Pharmacogenomics seeks to find and characterize correlations between the patient's genotype (genetic profile) and his or her therapeutic responses, with the aim of developing drugs specific to each patient. For the last 5-7 years, genomic and proteomic tools have propelled the development of this field. But a new technology is emerging as an important addition to the personalized medicine toolkit — RNA interference (RNAi). RNAi is also a powerful weapon to cure and prevent diseases.

### RNAi

RNA interference, or RNAi, is a recently discovered functional tool of considerable promise. It is a powerful example of the value of basic research, being a technology accidentally discovered as a result of experiments performed by plant scientists in the U.S. and the Netherlands (Napoli et al., 1990) that sought to produce petunia plants with improved flower colors.

RNAi is a method of post-transcriptional gene silencing that has the potential to enable scientists to therapeutically regulate gene expression. RNAi can be visualized as a smart bullet that will travel around the body to switch off individual genes that cause

<sup>40</sup> Biotech 2004:Back on Track, Burrill & Company.

disease, with precision and specificity.<sup>41</sup> This technology uses a special kind of RNA called double-stranded RNA to activate a protein that will either bind to or cut messenger RNA, the template for protein expression. The aim is to selectively stop gene expression, in effect by targeting its corresponding protein.<sup>42</sup> According to Dr. Nagesh Mahanthappa of Alnylam Pharmaceuticals, RNAi is a fundamentally new way of treating disease that uses a natural mechanism to silence the genes. He believes that RNAi therapies will eventually complement current methods of treating diseases (i.e., small molecule drugs, protein drugs, and antibodies); specifically, RNAi may be used to tackle diseases that conventional therapies are unable to address effectively.<sup>43</sup>

The main hurdle to delivery of RNAi therapies is that RNA molecules tend to degrade quickly in the bloodstream. Researchers have been able to chemically modify RNA molecules, however, so that they remain potent after being injected into the blood. This is a critical advance and an encouraging sign that should allow for growth in the field..

*RNAi therapies in development:*

- **CytRx** — obesity, diabetes and cancer.
- **Sirna Therapeutics** — hepatitis C virus and macular degeneration,
- **OSI Pharmaceuticals** — cancer drug discovery programs.
- **Benitec** — AIDS
- **Intradigm** — cancer
- **Alnylam Pharmaceuticals** — Respiratory Syncytial Virus (RSV), Spinal Cord Injury (SCI), Parkinson's Disease (PD), Cystic Fibrosis (CF) (collaboration with Medtronic)

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<sup>41</sup> "Silence of the transcripts: RNA interference in medicine," *J. Molecular Medicine*, 83, 2005, 764-773

<sup>42</sup> "The Silent Revolution: RNA Interference as Basic Biology, Research Tool, and Therapeutic," *Annual Review of Medicine*, 56, 2005, 401-423

<sup>43</sup> Nagesh Mahanthappa PhD, presentation, Kellogg Biotech Bootcamp, 2005

## **PART III**

### **Business Models for Future Profits**

There are many opportunities for developing biotechnology companies, but only one way of creating a successful business -- the old fashioned way: by creating unique value that can be captured as profits. The challenge of the biomedical industry is to find the balance between value creation and value capture; that is, weighing the business risks and high cost of innovation against the necessary infrastructure investments required to capture value in a highly complex technical, financial, social and political environment.

The biomedical industry, and particularly the biotech sector, has so far operated in a highly entrepreneurial mode, and will continue to do so for the next decade, provided the stream of innovation continues to flow. As science and technology have advanced, companies have been constantly adapting their business models in search of the perfect balance between value creation and value capture.

The most common business models used in the industry today will once again morph in the next decade to respond to the imminent global social and scientific transformations noted in section 2 of the Executive Summary. These macro transformations include:

- *The globalization of technical innovation*
  - More diverse sources of technical innovation will emerge around the globe
  - Technologies that drive pharmaceutical, biotech, diagnostic, and medical device businesses will continue to converge
  - Rapid technological change in the physical sciences will make possible more precise ways to determine and monitor disease predisposition, more precise ways to treat and deliver treatments, and better ways to prevent disease
  - IP and patents will come under increasing pressure in a globalized marketplace
  - Competitive edge in the biomedical industry will tend to shift from technical innovation to supply-chain innovation
  
- *Global redistribution of wealth, characterized by pockets of affluence surrounded by areas of intense poverty*
  - New diseases will emerge, prompting large pharmaceutical companies to find ways of coping with “accordion-type” markets that materialize in response to epidemics and rapidly contract when they wane
  - Product markets will become more fully globalized
  - There will be explosive growth in international alliances
  - Pricing will exert profound pressures on biomedical firms and healthcare providers
  - Outcome-based medicine will predominate, increasingly requiring product innovators to demonstrate clear pharmacoeconomic benefits
  
- *Global population growth, population aging*
  - The global market for chronic treatments will expand significantly

- In highly developed and major emerging nations like India and China, patients will become more knowledgeable and empowered
- In these nations, consumers will demand preventive, predictive, and cosmetic medicine

Other conditions affecting future business models in the biomedical industry include:

- *A favorable, but tenuous, policy environment*
  - In the U.S., the Bayh-Dole Act will continue to spur technology transfer and encourage the continuous development of innovative start-ups
  - Biologics, or protein-based biotech drugs, will continue to be protected from generic pressures
  - In the U.S., the Orphan Drug Act will incentivize the market for personalized medicine
  - The 2006 Medicare Modernization Act will incentivize companies seeking to address the expanding aging market
  
- *A favorable funding environment, marked by a diversity of public and private funding sources [Exhibits 14, 17]*
  - With minor market calibrations, federal and private funding sources will continue to nurture the biotech industry, the incubator of innovation for personalized medicine. Consistently rising industry R&D expenses historically have fueled an even higher rate of growth in aggregate industry revenues [Exhibit 7].
  - New private sources will emerge as pharma, biotech, and medical device companies begin to form more creative alliances with health delivery and employer organizations
  - New funding sources will emerge globally as the industry creates alliances with non-traditional global organizations, particularly in China and India.

Given this constellation of transformative forces and conditions, biomedical firms will be seeking to tap new opportunities presented by globalizing markets. Successful pharma companies will be those that forcefully compete on the global stage through robust infrastructure and supply-chain innovation. Successful biotech companies will be those that innovate in the predictive, preventive and personalized medicine areas, and develop highly specialized and efficient infrastructure to market their products. The parameters of future success for various segments of the biomedical industry are fleshed out below.

## **Business Models for the Global Market: The Challenge for Big Pharma and Medical Device Makers**

Changing demographics, patterns of disease and wealth suggest an explosive growth in global health markets, particularly in the aging and anti-infectives markets. This presents a great opportunity for big pharma. On a global playing field, these companies will have to reckon with increasing infrastructure costs and pricing pressures. Successful players will be those that focus on building robust core competencies and take measures to introduce supply-chain innovations.

**Successful global players (Pharma and Medical Device companies) will . . .**

**. . . build core competencies that include:**

- **Robust infrastructure** capable of forging global, yet specialized, channels of distribution
- Knowledge of **global regulatory** agencies and laws
- Secure **global intellectual property** rights

**. . . focus on supply-chain innovation characterized by:**

- Increased **efficiencies** and **reduced development costs**. This will most likely be accomplished by creating global development and outsourcing networks and alliances.
- Streamlined **supply chains** that reduce costs
- Increased **supply-chain flexibility**, able to respond to “accordion-type” markets, notably the global market for anti-infectives. This will most likely be accomplished by creating robust global development and outsourcing networks and alliances.

**. . . occupy markets that demand:**

- Increased focus on results, demonstrated in **outcome-based health economics data**
- Treatments that address **aging, chronic diseases, and anti-infectives**

**. . . address the problem of sustainability by:**

- Maintaining a **full and deep pipeline** of products, in part by forging multiple alliances allowing the firm to “mix-and- match” multiple technologies
- Employing **supply-chain innovation to maintain global competitiveness**
- **Forging global alliances** to assure supply-chain flexibility

The winners in this market will be global pharmaceutical and medical device companies that focus on supply-chain innovation and costs efficiencies. *Growth through alliances, rather than acquisitions*, will be the modus operandi for the next few years as firms will need to increase their flexibility both at the technical and supply-chain level. This has an important implication for biotech firms: in the coming years it will be harder for smaller biotechnology companies to provide exits for their early investors by being acquired. With this “exit” effectively closed, *we forecast an increasing number of biotech IPOs in the years ahead.*

## **Business Models for Personalized Medicine: The Challenge for Biotech and Diagnostics**

We predict that small and mid-sized biotech companies will be the primary source of scientific and technical innovation that enables the coming revolution in personalized medicine. The future market for personalized medicine will not be as broad as that for traditional pharmaceutical products. The prime early opportunity exists in the most advanced economies, such as the U.S. and Europe, although with the passage of time, markets for personalized medicine will surely arise in economies just now “breaking out,” most notably those of China and India, but also select economies in Asia, along the Pacific Rim.

Successful companies in the personalized medicine field (primarily biotech) will . . .

*. . . build innovative core competencies that include:*

- Integrated and **deep knowledge in specific disease groups**
- A base of highly specialized, innovative and efficient **clinical knowledge**
- A focus on the 3 P’s: **Predictive, Preventive, Personalized medicine**

*. . . reinvent the supply chain by:*

- Associating closely with **disease advocacy groups**
- Developing innovative **clinical delivery services**
- Integrating with **health care delivery systems and payers**
- Developing a network that will offer **complete health solutions** to the patient

*. . . occupy markets that demand*

- **preventive and cell therapies**

*. . . and develop products*

- tailored to specific **niche markets**.

*. . . address the problem of sustainability by:*

- Maintaining a full and deep pipeline through **internal research capabilities**
- **Licensing** cutting-edge tools to maintain an innovative research platform
- Competing through **product innovation** and **highly specialized channels**
- Developing **non-traditional alliances** with health providers, government, and employers’ organizations

The winners in the personalized medicine market will be highly profitable, highly specialized small and medium-size companies, mainly in the biotech sector, focusing on research and health delivery innovation. Delivery of their products will require sophisticated training of providers, and the creation of strong relationships with provider groups. We will see an increase in the number of companies forging alliances with non-traditional groups, away from pharmaceutical companies. *These companies will not look for acquisition as an exit strategy but rather will remain private or will move to the IPO market.*

## **PART IV**

### **Personalized Medicine and the Healthcare Delivery System: Mutual Impact, Threats and Opportunities**

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Personalized medicine offers great promise for human health – earlier and more precise diagnoses, treatments tailored to the individual, reduction of side effects and adverse reactions to drugs, breakthroughs in treatment, and ultimately prevention, of major diseases such as cancer, diabetes and Alzheimer’s.

The key question is this: as scientific and technological breakthroughs in personalized medicine are achieved in the coming years, will the American healthcare system, now in a state of crisis, be able to deliver them to the population? How will the healthcare system need to change? What can participants in the healthcare and biomedical industries do *today* to accelerate the pace of personalized medicine discovery and adoption?

The following sections provide (i) a review of personalized medicine and its business ecosystem; (ii) an assessment of the potential impact of personalized medicine on the healthcare and biomedical industries; (iii) an analysis of opportunities for industry to develop new business models that will accelerate the rate of development and adoption of personalized medicine.

This chapter is a result of extensive literature research and interviews with more than twenty representatives of various healthcare areas, including: pharmaceuticals, health insurance, medical care providers and healthcare industry experts.<sup>44</sup>

#### **Understanding personalized medicine**

Personalized medicine translates scientific discoveries in molecular disciplines such as genomics, proteomics, metabolomics, and other innovative fields, into a set of medical methods and practices. It encompasses areas such as genetic testing, pharmacogenomics, genomic and proteomic profiling, gene therapy, synthetic protein therapy, personalized drug design, targeted molecular therapy and other methods.

The Human Genome Project, completed in April 2003, has dramatically fueled developments in personalized medicine and underlying molecular disciplines. But we are only at the beginning of a new era of medicine. The field is very complex even for medical doctors, as attested by many of them in our interviews. There is little common language that the entire industry – scientists, doctors, hospital executives, insurance strategists, underwriters, consumers and legislators -- can speak.

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<sup>44</sup> Although the interviewed individuals may not necessarily agree with our analysis, we are grateful to them for their insights.

The framework in Exhibit 30 indicates the potential utility of personalized medicine in healthcare.

Diagnostics	Treatment	Prediction	Prevention
<ul style="list-style-type: none"> <li>• Earlier and more precise diagnosis</li> <li>• Prediction of the course of the disease</li> <li>• Prediction of the reaction to drugs and treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Treatment of the cause rather than the consequence of disease</li> <li>• More targeted, proactive and effective treatments</li> <li>• Prevention of symptoms and severe onsets</li> </ul>	<ul style="list-style-type: none"> <li>• Ability to assess the probability of future disease in individuals</li> </ul>	<ul style="list-style-type: none"> <li>• Ability to prevent future disease in individuals</li> </ul>

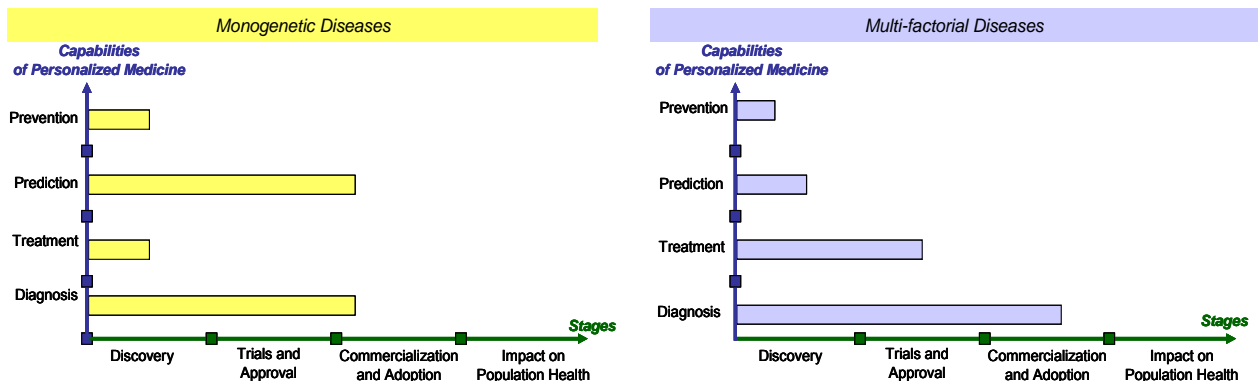
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**Exhibit 30. Capabilities promised by personalized medicine**

These potential capabilities represent not only great advances in medicine, but also great challenges to the business of healthcare – to medical provider models, insurance practices, and all other business aspects of healthcare. In fact, the business challenges posed by personalized medicine may present a greater challenge than attainment of the medical and scientific innovations necessary to make individualized treatment possible.

An individual’s genetic makeup will allow for a probabilistic assessment of predisposition to disease factors. Yet ethical, psychological, social, legal and constitutional concerns may complicate the business challenge of adopting such innovations; these concerns could jeopardize acceptance and commercialization of personalized medicine.

Although personalized medicine is in its infancy, many important achievements have been made. Exhibit 31 conceptually illustrates where personalized medicine is today on the progression from discovery of new methods, through trials and approval, to commercialization and conversion of methods into clinical capabilities, and finally to the impact of these capabilities on population health. As Exhibit 31 illustrates, capabilities for monogenetic diseases are today at a different stage than capabilities for multi-factorial diseases. Monogenetic diseases are caused by a variation of a single gene. Multi-factorial diseases are caused by a combination of gene mutations and environmental factors such as a person’s lifestyle, eating patterns, and exposure to various environmental factors.



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**Exhibit 31. Current capabilities of personalized medicine**

Genetic testing can today help to diagnose and predict many monogenetic diseases such as Huntington's, but there is no cure or prevention for such maladies, much less individualized or personalized treatment options.

The picture is different for multi-factorial diseases such as cancer, diabetes and hypertension: personalized medicine capabilities are more advanced for diagnosis, followed by treatment, with prediction and prevention remaining a great challenge.

**EXAMPLE: THE STATE OF CAPABILITIES RELATED TO CANCER AS A MULTI-FACTORIAL DISEASE<sup>45</sup>**

Diagnostics for different types of cancer are becoming much more precise based on genetic analysis of tumors. Pharmacogenomics also provides more effective treatment capabilities that predict the efficacy of treatment options such as chemotherapy based on genetic analysis. Six molecular-based treatments for cancer were approved in 2005, and many more are in development and trials. Some prediction capabilities exist (breast and ovarian gene testing) but they are only applicable to a small portion of a population. Only conventional and highly invasive preventive methods are available, such as prophylactic mastectomy.

The gap in capabilities between diagnostics and treatment, especially prediction and prevention capabilities for a given disease, presents not only medical but also business challenges to the healthcare delivery system. It is, too, a source of fears, ethical dilemmas, and discrimination concerns. It creates an atmosphere of public anxiety around the whole field of genomics and personalized medicine. Studies and empirical evidence suggest that patients will be reluctant to undergo predictive genetic testing, for instance, in the absence of effective and non-invasive prevention or treatment options.

*Narrowing the gap between predictive and preventive capabilities will do much to promote public acceptance of genomic-based methods of personalized medicine and will tend to foster a more productive public, political and legislative environment.*

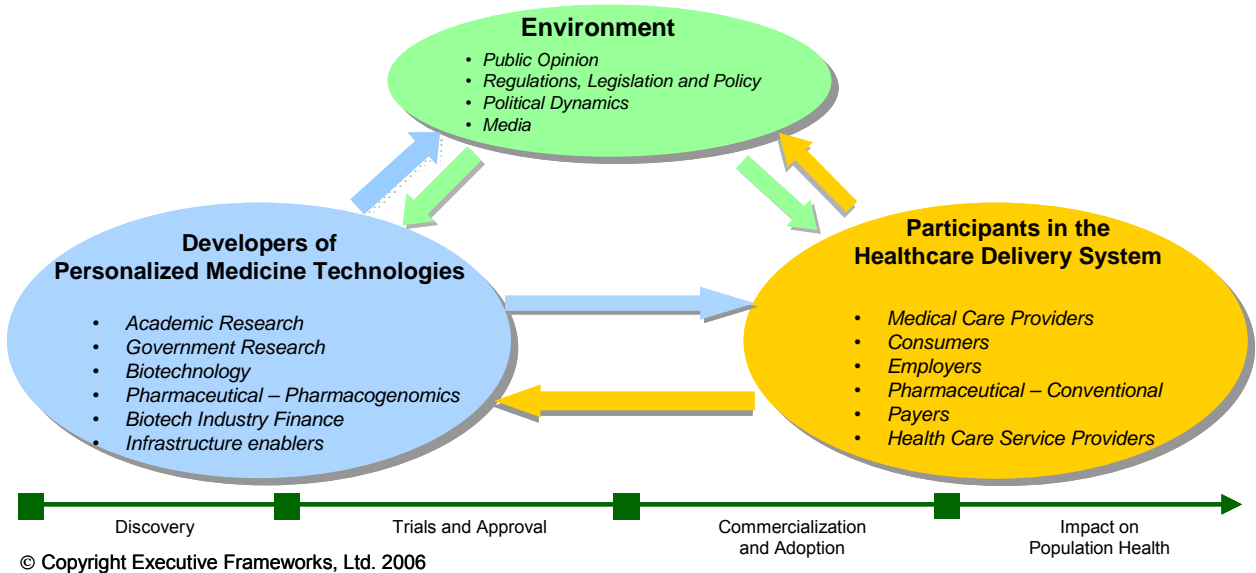
## **The Business Ecosystem of Personalized Medicine**

Exhibit 32 depicts the business ecosystem of personalized medicine. This ecosystem has three principal components:

- ***Developers of personalized medicine technologies.*** This component includes the biomedical industry, academia, and other players who conduct and directly enable scientific discovery in personalized medicine and underlying disciplines such as genomics and proteomics. The commercial players in this ecosystem segment take discoveries through the trial and regulatory approval processes, at the end of which successful products become ready for delivery to patients.
- ***Participants in the healthcare delivery system.*** This ecosystem segment includes the users of personalized medicine (consumers and medical providers) as well as payers and employers who provide health insurance benefits and determine what is reimbursed.

<sup>45</sup> [www.nih.gov](http://www.nih.gov) – National Institutes of Health website

- **Environment.** This segment encompasses all of the political, regulatory, social, and other external forces affecting how personalized medicine is developed and how it will be delivered to consumers.



**Exhibit 32. Personalized Medicine Business Ecosystem**

All three aspects of the business ecosystem are highly interdependent. The ultimate success of personalized medicine is contingent on their alignment and mutual support. *However, these three components are currently disconnected and misaligned*<sup>46</sup> (see Exhibit 33).

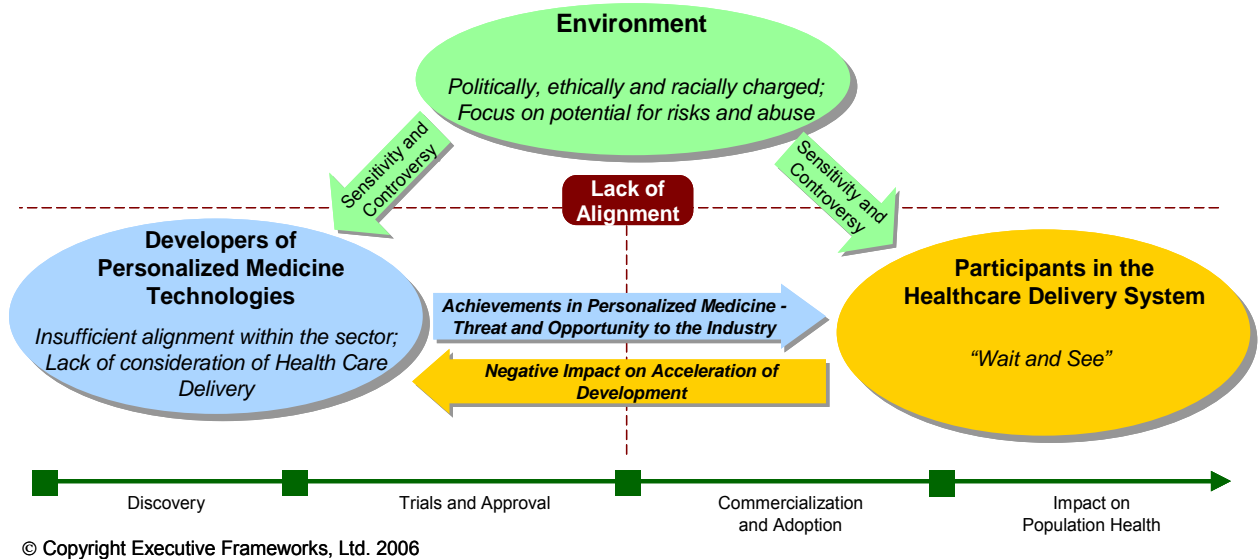
- **The healthcare delivery system is not yet prepared to adopt achievements in personalized medicine or to adapt in order to embrace them.** Many healthcare players are in the “wait and see” mode.<sup>47</sup>
- **Developers of requisite science and technology (the biomedical industry) are not aligned and tend not to consider, in macro terms, future healthcare delivery processes and channels.** The focus within the industry is typically on issues of reimbursement and distribution channels for specific products. Lacking broad perspective on future business models and industry infrastructures, players place at risk their own long-term success. The first companies that succeed in arriving at the “big picture” and adapting accordingly will have an opportunity to become leaders in personalized medicine in their respective markets.

<sup>46</sup> In this framework, the pharmaceutical industry performs two functions, taking part in the development of personalized medicine technologies (pharmacogenomics) and the delivery of personalized medicine products (conventional pharma). This reflects disconnects even within single companies, as reflected in the push to advance the state of the art scientifically and the pressure to market blockbuster drugs.

<sup>47</sup> Allison Bell. Insurers Shy Away From Human Genome. *National Underwriter*, Jul 10, 2000; 104, 28. Discovery p. 4

- **The macro environment is not conducive** to the development and adoption of personalized medicine. It is politically and emotionally charged, and tends only to fuel the public's existing discrimination and privacy concerns.<sup>48</sup>

The lack of alignment we are identifying has the effect of decelerating development and jeopardizing adoption and delivery personalized medicine solutions. Perhaps even more important, the present situation is one in which key participants in the healthcare delivery system perceive personalized medicine solutions not as an opportunity but a threat.



**Exhibit 33. Disconnects in the personalized medicine business ecosystem.**

## Impact of personalized medicine on the healthcare industry

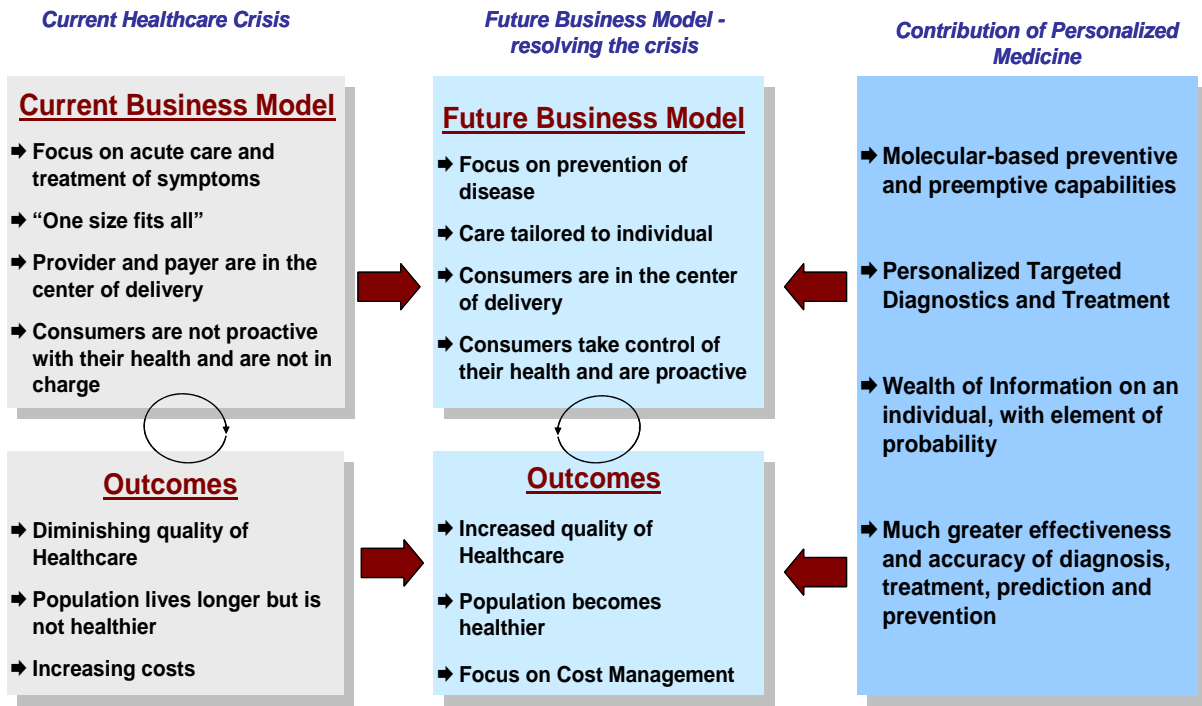
The current state of healthcare in the United States is full of challenges and is characterized by many experts as a crisis, marked by skyrocketing costs and diminishing quality of care. Personalized medicine has the potential to help bring healthcare out of the crisis (Exhibit 34).

*One of the central factors contributing to the healthcare crisis is the current industry business and revenue model, which is focused on acute care and the treatment of symptoms rather than on the prevention of disease. This model creates a downward-spiral effect: doctors, hospitals, insurance payers, and pharmaceutical companies are focused on “cookie-cutter” treatment of symptoms and known conditions. There is little incentive or encouragement for consumers to be proactive or to take charge of their own health. This yields a sicker population and diminished effectiveness of the care that is delivered, the focus being almost exclusively on acute care. The current strategy is to manage costs -- staying firmly within the acute-care rubric -- at the expense of proactive programs that would emphasize the maintenance of good health. Other issues tend to*

<sup>48</sup> Ellen Wright Clayton, M.D., J.D. Ethical, Legal, and Social Implications of Genomic Medicine. *New England Journal of Medicine*. 349 (562-569)

magnify this tendency, including the aging of the population, a high rate of medical malpractice litigation, and the healthcare system's general lack of transparency.

To resolve the current crisis, a counter-cycle needs to be created, with new business models focused on *prevention, proactive approaches to health, and an active role for consumers*. In the coming years, as scientific and technological achievements in personalized medicine reach the adoption stage, they may serve as a catalyst for creating this counter-cycle and enable a shift to the new model. The availability of preventive capabilities, coupled with public pressure for adoption, will help the biomedical and healthcare industries to *shift the focus to prevention*. Consumers will be empowered as never before with personalized health information, setting out a range of choices that will stimulate them to take charge of their health.



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**Exhibit 34. Personalized medicine points to a way out of the present crisis in healthcare delivery.**

Personalized medicine is by nature applicable to smaller populations than conventional methods. It will serve markets that are more fragmented,<sup>49</sup> making it more difficult to build economies of scale and achieve affordable pricing. However, as adoption gains momentum and new healthcare delivery and reimbursement models are introduced, the industry will be able to satisfy the pressure for affordability.<sup>50</sup>

As advancing science and technology make personalized medicine feasible in the coming years, new business models will emerge in the healthcare and biomedical

<sup>49</sup> Muin J. Khoury, Julian Little, Wylie Burke. *Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease*. Oxford University Press. 2003

<sup>50</sup> Stan Bernard. 5 Myths of Pharmacogenomics. *Pharmaceutical Executive* October 2003

industries, which, in turn, will threaten existing business models. Players failing to evolve and participate in the industry transformation will not succeed and ultimately will thwart patients seeking to reap the benefits of the new technologies.<sup>51</sup> See Exhibit 35.

Healthcare Delivery Player	Current obstacles to delivery of personalized medicine solutions	Potential Threats and Risks
Medical Care Providers	<ul style="list-style-type: none"> <li>Hospitals are not interested in adoption, as personalized medicine will result in more proactive care outside of hospitals</li> <li>Doctors are not educated or trained to employ genomic methods; they fear legal implications</li> <li>Medical culture is conservative and doesn't support change or innovation</li> </ul>	<ul style="list-style-type: none"> <li>Public pressure to use the new methods</li> <li>New legal risks if new methods are used or not used</li> <li>Financial risk caused by inadequate reimbursement models</li> </ul>
Payers and Healthcare Service Providers	<ul style="list-style-type: none"> <li>Current insurance policies, benefits and formularies don't address innovative methods</li> <li>The current insurance model can't sustain investment in proactive care due to member turnover and potential legal conflict related to genetic information</li> <li>The costs of new methods may be prohibitive for reimbursement</li> <li>Current insurance practices can't handle genetic-based probabilistic prediction</li> </ul>	<ul style="list-style-type: none"> <li>Public pressure for reimbursement; criticism for lack of access and creating "genetic underclass"; related legal risks</li> <li>Disease management models are in jeopardy</li> <li>Threat to the underwriting model<sup>52</sup> and the private insurance model<sup>53</sup></li> </ul>
Pharmaceutical companies	<ul style="list-style-type: none"> <li>The current blockbuster drug model doesn't support fragmented markets, different distribution channels or different development cycles.</li> </ul>	<ul style="list-style-type: none"> <li>Financial viability of the current blockbuster drug model is at risk</li> </ul>
Employers	<ul style="list-style-type: none"> <li>In the self-insurance model, insurance and employment issues may become intermingled</li> <li>The employer-sponsored insurance model doesn't support investments in preventive benefits due to employee turnover</li> </ul>	<ul style="list-style-type: none"> <li>The employer self-insurance model is at risk</li> <li>High costs of personalized medicine will "crash" corporations and make them less competitive in the global marketplace</li> </ul>
Consumers	<ul style="list-style-type: none"> <li>May demand access to personalized medicine solutions as they become available, before they become "standard of care," and will not be reimbursed</li> <li>Are not properly educated to make decisions in their best interest</li> </ul>	<ul style="list-style-type: none"> <li>Emergence of a "genetic underclass"</li> <li>Inability to handle the personal dilemmas posed by genetic information</li> </ul>
Overall Industry	<ul style="list-style-type: none"> <li>Absence of a logistical infrastructure to adopt genome-based methods</li> <li>The legal structure may not be ready to support the new methods</li> </ul>	<ul style="list-style-type: none"> <li>The healthcare industry crisis may intensify</li> </ul>

**Exhibit 35. Personalized medicine's potential threat to current healthcare delivery models**

<sup>51</sup> Chris Myers, Nicole Paulk, Christine Dudlak, and Maxwell J Mehlman. Genomics: Implications for health systems / The effects of genomics on health. *Frontiers of Health Services Management* Spring 2001: 3-44

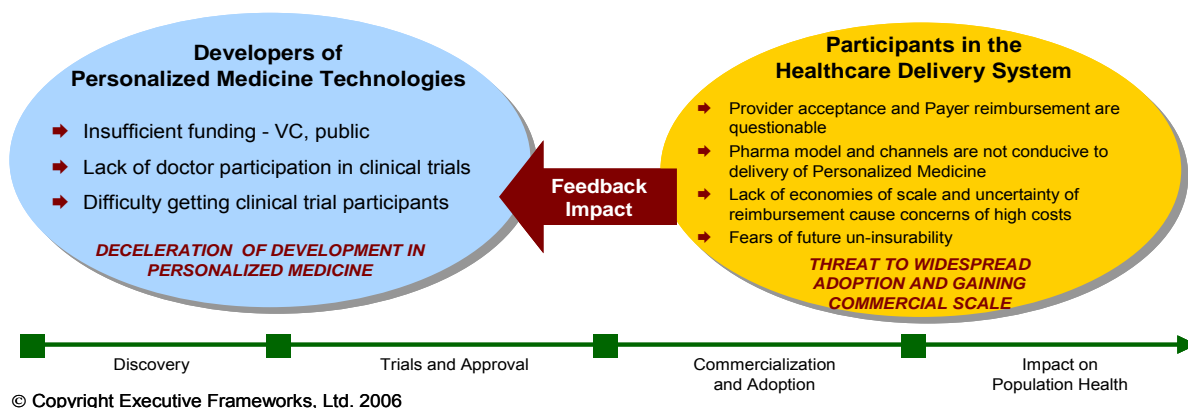
<sup>52</sup> Mark A. Rothstein (Editor). *Genetics and Life Insurance: Medical Underwriting and Social Policy*. Massachusetts Institute of Technology. 2004

<sup>53</sup> Jennifer S. Greeter. Coding for change: The Power of the Human Genome to Transform the American Health Insurance System. *American Journal of Law and Medicine*, 28 (2002): 1-76

*In summary:* if participants in the healthcare delivery system don't begin to "align" and prepare to support and effectively deliver the growing capabilities of personalized medicine to the public, the systemic crisis will only deepen, placing many participants at significantly increased business, legal, and financial risk.

## New Healthcare Delivery Models Are Key to Innovation and the Availability of Capital

The state of the healthcare delivery system presents not only challenges to the future adoption of personalized medicine, but barriers to its development today (Exhibit 36). Negative feedback tends to slow progress among the scientific and technological developers of personalized medicine solutions, both public and private.



**Exhibit 36. Present Obstacles to the Development of Personalized Medicine**

**a. Insufficient Funding.** Venture capital firms and stock market investors anticipate the challenges, knowing that "discovery" precedes adoption and that adoption is problematic. Venture capitalists don't see an easy and reasonable-term exit; the stock market is skeptical about the business and financial viability of biotech products given uncertainties of acceptance, reimbursement, and care-delivery models. As a result, venture capitalists are leery of financing ventures before Phase 3 of clinical trials. The rate of IPOs in the biotech industry in the past several years has not provided the influx of money that could fuel acceleration of development.

**b. Tepid doctor participation in trials.** Mainstream medical doctors are not trained to use genetic and genomic methods. Few medical schools in the country are able to provide a genetics curriculum of sufficient depth to bridge the gap in the near-term. The result is a shortage of clinical geneticists. Couple this with the traditional conservatism of the medical community and often insufficient funding for clinical trials, and the result is difficulty recruiting doctors to perform clinical trials and to participate in research in general. To illustrate the point, one of our interviewees said: "The situation will not get better until all current doctors retire."

**c. Difficulty getting clinical trial participants.** Current insurance practices, coupled with intimidating media commentaries on privacy and discrimination, give rise to a fear of genetic testing among patients. This leads to unwillingness to participate in trials that have anything to do with genetics. Many biomedical companies go abroad to recruit trial participants, often in less developed countries where insurance and employment concerns are not an impediment. However, populations in these countries may not be comparable in their genetic makeup to the U.S. population, nor comparable in terms of environmental factors such as climate and lifestyle.

The “feedback” impact of anticipated adoption challenges is not the only barrier to the development of personalized medicine. Other factors include lack of alignment among developers of the technology (government, biotech companies and academia) and intellectual property issues. Nor should we neglect the unpredictability of the scientific discovery process. Even infinite money and human resources may not be able to speed up solutions to nature’s puzzles. However, if the industry-related barriers are removed or mitigated, more time can be devoted to making scientific progress, which is obviously the bottom-line condition for future adoption of personalized medicine.

### **Impact of the Macro Environment on the Rate of Development and Adoption of Personalized Medicine**

The ethical, socioeconomic, and legal challenges of development in genomics and personalized medicine have received substantial literature coverage. Juan Enriquez and Ray A. Goldberg have pointed out that *“Escalating public opposition poses the greatest single threat to the successful growth of the life-science business. Left unchecked, it will force companies to spend ever greater amounts of time and money calming the public and clearing regulatory hurdles”*<sup>54</sup>.

We should note an important recent phenomenon related to the future adoption of personalized medicine. Beginning in the late 1990s, unchecked excitement about the Human Genome Project and associated developments in genomics fueled often exaggerated and oversimplified predictions in the media. The future of personalized medicine was put in peril by unsubstantiated warnings that before long, banks, employers, and government agencies would have access to information indicating when individuals would get sick, and would take action harmful to individuals accordingly. The resulting public fears and discrimination concerns have created a politically charged, reactive, and highly sensitive environment. This helps explain the “wait and see” attitude to personalized medicine taken by the healthcare delivery industry, in which genomics is considered a “hot potato.”

Public sensitivity feeds the conservatism of the medical community, and heightens the reluctance of insurers and pharmaceutical companies to change. There is a rational fear of legal ramifications. In short, the environment directly and indirectly influences factors contributing to a slow-down in the pace of development of personalized medicine, which is manifest in investor reluctance, tepid doctor participation in new approaches, and difficulty securing participants for clinical trials.

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<sup>54</sup> Juan Enriquez and Ray A. Goldberg. “Transforming Life, Transforming Business: The Life-Science Revolution.” *Harvard Business Review*, March/April 2000: 96-104

## Drivers of personalized medicine

Although there are many challenges, the prospect is not that ominous. We have identified a host of potential drivers that will have the effect of accelerating discovery and promoting adoption of personalized medicine. **There are three primary, or “macro” drivers:**

- The unrelenting force of **technological and scientific discovery and innovation, sourced in leading research universities and in emerging biotechnology companies**, which will make a personalized approach to medicine possible in the first place;
- **The aging of a growing and affluent population** in developed nations, which will increasingly demand personalized treatment;
- **Withering pricing pressures** in the increasingly globalized market for healthcare. Experienced as a “crisis” in the U.S., this pressure will force players in the biomedical industry to adapt their business models and adopt personalized medicine as a curative, in effect bypassing longstanding institutional obstacles and impediments.

*In the U.S., there are a number of other potential drivers:*

- **International competition**, especially from countries where concerns about discrimination, ethics and privacy are muted, would serve as a catalyst to development and force the U.S. to address challenges to its healthcare system sooner rather than later.
- Investments and support from **visionary corporations**, such as IBM, will help build the **technology and information infrastructure** necessary for research, development, and delivery of personalized medicine.
- **Government support**. Although the National Institutes of Health budget has not increased significantly in the last several years, U.S. government spending on health-related research is higher than that of any other country in the world. New government-funded genomics efforts, such as The Cancer Genome Atlas project, provide a significant boost to development. Government-sponsored efforts to fight bioterrorism also may provide additional funding and fuel further research.
- **Increased participation of players in the healthcare delivery system**. Some healthcare and insurance companies are already involved in creating adoption models for personalized medicine and educating the public and the industry (Aetna, Kaiser Permanente, and others). The pharmaceutical industry is demonstrating an increased interest in partnerships and mergers with biotechnology companies, a factor we deem favorable to progress in personalized medicine.
- **Positive changes in the FDA process**. Certain changes in FDA operating procedures and policies would promote the development of personalized medicine; these include: clarified genetic research rules,

rededication to Fast Track, and endorsement of pharmacogenomic methods for use in drug trials.

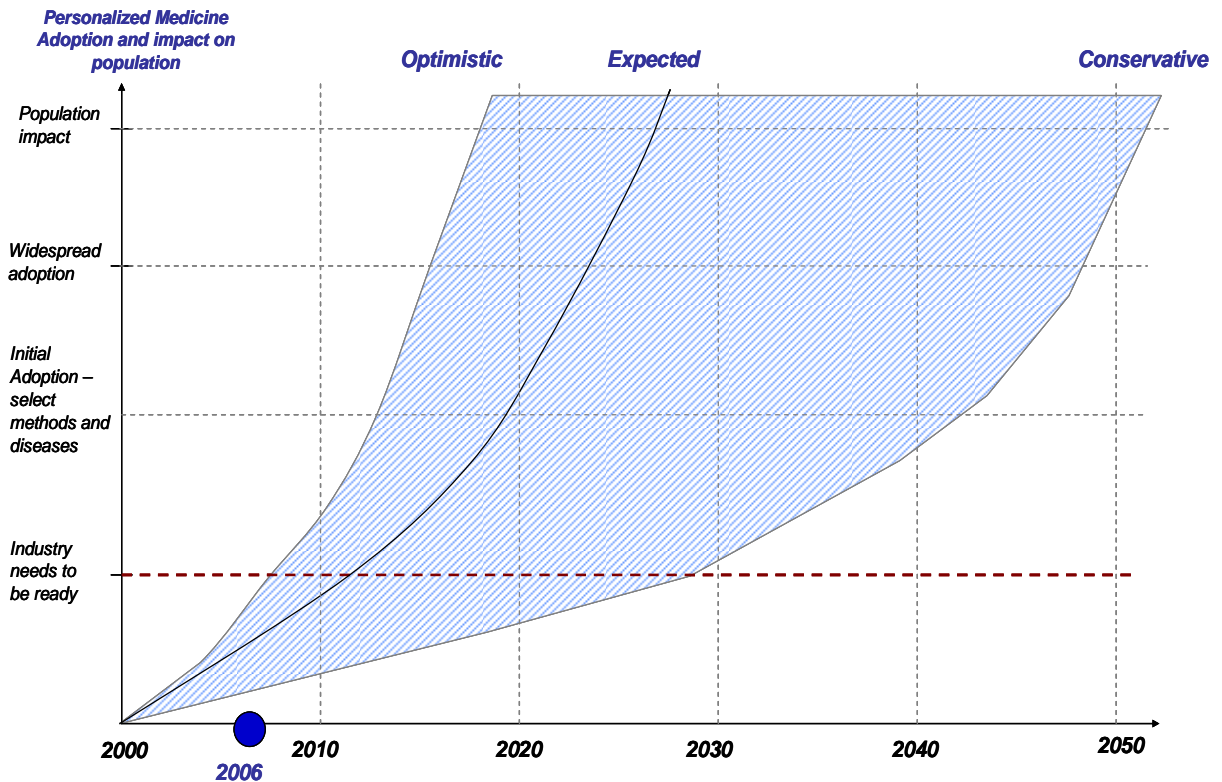
- ***Favorable biotechnology industry financing.*** Periods of increased interest from venture capital investors, perhaps spurred by the excitement over advances in personalized medicine science and technology, should give rise to an increasing number of biotech IPOs. We view this prospect as very favorable to further advances in personalized medicine.
- ***Rising demand of the baby-boom generation.*** Aging baby boomers are likely to demand effective tailor-made medicine that supports their affluent lifestyle. This “macro” driver is particularly important in the United States, where medical consumers are already more empowered than in any other nation.
- ***Growing impact of public advocacy “disease” groups.*** These bring attention to pressing health and medical issues -- for example, the Susan G. Komen Breast Cancer Foundation.

## **Prospect and Forecast for Personalized Medicine**

When will personalized medicine reach the boundaries of clinical practice and be ready for adoption? When should the healthcare and biomedical industries start seriously to consider, and prepare for, the delivery of personalized medicine solutions to consumers?

As noted in the previous section, the “ecosystem” of personalized medicine is highly complex. Many interrelated barriers and enablers will impact the rate and time horizon of discoveries. So too will the fact that some advances in the field are not foreseeable and are subject to random forces always part of scientific and technological discovery and development. We searched the literature and asked various professionals in biomedicine and healthcare delivery: “When will personalized medicine happen?” Opinions were given reluctantly and varied dramatically from, “We will not see any achievements in practice for 50 to 100 years,” to “Within 10 years we will see significant achievements.”

We have developed a conceptual model to assist in forecasting the future of personalized medicine (Exhibit 37). The model reflects the wide range of opinions to which we have referred. In statistical terms, the most likely scenario falls somewhere between the extremes, and is indicated by the curve labeled “Expected” in the accompanying exhibit. Our model suggests that institutional adoption of personalized medicine methods and solutions is most likely to begin around 2020 and that population benefits will be evident in the years immediately following 2025, roughly two decades from now.



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**Exhibit 37. Conceptual model for timing the arrival of personalized medicine**

This is a qualitative model which can serve as a basis for further quantification. The model illustrates several important points discussed earlier in this report:

- *The biomedical and healthcare delivery industries have to be ready not only when new personalized medicine technologies and capabilities become available, but well before. Creators of the technologies must have effective distribution channels in place; providers and payers must make necessary adjustments so that the new capabilities can be integrated into the healthcare delivery system.*
- *Assuming that the actual scenario will fall within the “optimistic” area of the model, the industry needs to be ready in the next decade and should start active alignment efforts now. Even pessimistic scenarios require the industry to be ready within the next 10-20 years, with discussions and initiatives beginning in the next few years.*
- *The healthcare and biomedical industries, if they act in a forward-looking manner, may well be able to shift the actual development curve to the left, compressing the time horizon of discovery, healthcare delivery, and realization of the benefits of personalized medicine.*

**Advances in science and technology, cost pressures, aging population, and globalization point to the advent of personalized medicine; How can biomedical and healthcare delivery companies capitalize on the opportunity?**

We have discussed a number of factors, mainly cultural and institutional, working against early maturation and market adoption of personalized medicine. We have also indicated some of the ways in which development and adoption may be accelerated. It is reasonable to ask: *What motive forces and factors will cause players in biomedicine and healthcare delivery to change their current outlook and business models?* The short answer is “opportunity.”

There is reason to believe that forward-looking firms, institutional players, and government officials will take actions tending to bring the time of personalized medicine closer. Some of the changed behavior we envision will be motivated by a sense of the greater public good; some of it will be driven by dynamics internal to the process of scientific discovery; other aspects will be driven by the profit motive and the corporate imperative to remain competitive. Importantly, however, we believe that two fundamental forces -- the unrelenting drive of scientific and technological innovation, and the increasing burden imposed upon society by rising healthcare costs in an era of increasing global competition -- will motivate players across the biomedical industry and within the healthcare delivery system to embrace and adopt personalized medicine.

It has been widely recognized that the development and adoption of personalized medicine will require unprecedented partnership and cooperation of governments, academic and research institutions and the private sector. Critical mass will also form around an array of smaller alliances and individual companies' efforts -- particularly those of niche biotechnology companies -- to expand their own business ecosystems and experiment with new business models.

There are many different ways for individual companies and organizations to take advantage of the opportunities that personalized medicine presents. We offer suggestions below as a provocation to companies and organizations in both the biomedical and healthcare delivery industries. Some biomedical and healthcare companies are already successfully applying these or similar actions to their products and markets (Exhibit 38).



### Opportunity 1

- Biotechnology companies: to an extent that will not jeopardize intellectual property protection, consider research and trial alliance models with academia, government research organizations, and other biotech companies to foster research collaboration and leverage each other's platforms.
- Academic research organizations: consider more effective alliance models with biomedical and pharmaceutical companies to expedite technology transfer.
- Investors and capital markets: create financial incentives for better research collaboration among biotechnology companies and academic and government research organizations
- Legislators: create more effective legal support for intellectual property rights protection to encourage research collaboration

***Benefits and time horizon:*** Alliances and collaborations will accelerate discovery, in part by making possible more, and more effective, clinical trials.



### Opportunity 2

- Biotechnology companies: continuously study and work to improve distribution models and channels.
  - Map the entire distribution process for products including all potential participants. Consider distribution and payment alternatives and options.
  - Understand the interests and business models of the target segments throughout the distribution process, identifying potential conflict with acceptance and adoption of your product. Make efforts to alleviate the conflict by altering the distribution model.
  - Seek partnerships to gain faster and broader access to distribution channels. Partnership examples include reimbursement arrangements with health insurance companies -- these may open access to the insurer's provider networks and their respective patient bases.
  - Identify knowledge gaps among distribution channel participants related to your product. Invest in addressing the knowledge, education and communication gap
- Healthcare delivery companies: identify personalized medicine innovations early in the pipeline and consider early adoption; collaborate with biomedical companies to effectively deliver innovations through the healthcare channel.
- Investors and capital markets: strengthen financial incentives and recognition of investment in distribution channel partnerships for both biomedical and healthcare delivery companies.

***Benefits and time horizon:*** Biomedical companies will benefit directly and early in the adoption process by expanding their target markets and gaining visibility to potential challenges in the distribution channel (which will provide opportunities to address them).

*By incrementally rebuilding their business models and channels around delivery of personalized medicine, healthcare delivery companies can strengthen their future positions.*



### Opportunity 3

- Healthcare delivery companies:
  - Investigate the impact of personalized medicine on your business model
  - Identify components of current business models that will not be sustainable in preventive healthcare and will be obstacles for personalized medicine adoption
  - Make proactive efforts to rebuild business models and channels in preparation for personalized medicine
  - Collaborate with channel partners up and down the stream to develop and pilot revenue and financing alternatives to insurance reimbursement. Examples include new revenue models for doctors, hospitals, disease management services and preventive care centers.
  - Facilitate broad educational efforts in your channels and markets related to personalized medicine
- Investors and capital markets: create financial incentives, recognizing investment in healthcare-model pilots and educational efforts by healthcare delivery companies

**Benefits and time horizon:** *Healthcare delivery companies will be seen as thought-leaders and innovators able to incrementally rebuild their business models and channels around delivery of personalized medicine solutions and thereby strengthen their positions in the future healthcare industry. As in the case of Opportunity 2 above, the direct financial returns of these efforts for healthcare delivery companies may be more remote.*



### Opportunity 4

All players: participate in collective and individual efforts to educate the public, government, and the media on the subject of personalized medicine. Continuous communication and collaboration with public advocacy groups is necessary to prevent misconceptions about personalized medicine's predictive aspects.

Ensuring reasonably objective media coverage will be an ongoing challenge and responsibility. As one of our interviewees pointed out, *"The hype exceeds the current reality about what [personalized medicine] can deliver today; this will lead to a backlash that will make it hard to generate trust when the science improves. This is a common problem with our 24/7 information glut and the need to jump on the latest finding or paper and push it beyond its limits. [Personalized medicine] needs to be nurtured and supported. We have to give it time, not hysteria."*

**Benefits and time horizon:** *These efforts will have both immediate and longer-term benefits for development, acceptance, and adoption of personalized medicine. In addition to benefiting the entire industry, they will tend to generate a positive "forward-looking" and "cutting-edge" image for pioneering companies.*

**Exhibit 38. Building alliances and successful distribution channels – the example of Genomic Health, Inc.**

*(Source: Genomic Health Quarterly reports<sup>55</sup>)*

Genomic Health develops and commercializes genomic-based diagnostic tests for cancer. As part of its commercial success, it builds alliances with other players in the biomedical sector and governmental groups. These initiatives include:

- Sponsorship of the Kaiser Permanente epidemiology control study of Oncotype DX, Genomic Health's diagnostic test for breast cancer patients.
- Collaboration with a National Cancer Institute-funded cooperative group, NSABP, for additional studies regarding applications of Oncotype DX
- Collaboration with Bristol-Myers Squibb and ImClone Systems to develop a genomic test to predict the likelihood of response to Erbitux in colorectal carcinoma.

The company also drives the adoption and commercialization of its product by improving and expanding its distribution channel:

- The Oncotype DX test is now reimbursed by a number of private insurance companies and government programs such as Medicare and Federal Employee Benefit Program. One of the first insurance companies to cover Oncotype DX was Kaiser Permanente – Genomic Health's research collaborator and proprietor of a vast hospital and provider network. This broadens the potential of exposure of Oncotype DX to the provider channel.
- Genomic Health also invests in educating physicians, laboratory personnel, and other healthcare professionals on their genomic technologies. In these efforts, the company explains how the Oncotype DX test was developed and validated and describes the value of the quantitative information that Oncotype DX provides. It also sponsors continuing medical education, participation in medical meetings, and dissemination of scientific and economic publications related to Oncotype DX

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<sup>55</sup> "Genomic Health Announces Fourth Quarter and Year-end 2005 Financial Results and Business Progress." Press Release, Feb 13, 2006. [www.genomichealth.com](http://www.genomichealth.com)