




The Global Biomedical Industry: Preserving U.S. Leadership

Ross C. DeVol, Armen Bedroussian, and Benjamin Yeo



September 2011



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The background of the entire page is a repeating pattern of various chemical structures, including benzene rings, alkenes, and branched hydrocarbons, rendered in a light gray color.

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Ross C. DeVol, Armen Bedroussian, and Benjamin Yeo
with Kevin Klowden

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Executive Summary

Biomedical innovation is an intricate process that begins in the lab and spans years of effort to transform scientific discoveries into vaccines, diagnostics, devices, and therapies that improve patients' lives. Over the past few decades, the United States has created and refined a remarkably productive framework for developing new biomedical innovations and bringing them to the marketplace—in fact, it's one of the most dramatic success stories written by any American industry in the past century. Whether measured by international or domestic market share, revenue, jobs, number of regulatory approvals, patents, R&D expenditures, or publications in the biomedical field, the U.S. holds a commanding position.

Biomedical innovation is one of the most dramatic success stories written by any American industry in the past century.

Prior to 1980, European firms defined the industry, both in terms of market presence and in their ability to create and produce innovative new products. Historical advantages and an enviable concentration of resources fueled the success of firms in Germany, France, the U.K., and Switzerland. Japan had a presence in the industry as well.

But beginning in the 1980s, the United States surged to the forefront of biomedical innovation. This sudden and remarkable shift was no accident: It was the result of strong policy positions taken by the federal government. The absence of price controls, the clarity of regulatory approvals, a thoughtful intellectual property system, and the ability to attract foreign scientific talent to outstanding research universities put the U.S. on top.

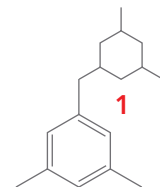
The resulting ecosystem—defined by university-business collaborations, industry clusters, private equity finance, and entrepreneurship—far surpassed the prevailing model in Europe. The innovative leaps made in biopharmaceutical research, medical devices, and diagnostics gave the U.S. a major advantage that it continues to hold today.

Based on the most recent data from the Bureau of Labor Statistics, private-sector employment in the U.S. biomedical industry in 2009 was 1,219,200. Breaking this total down into its three major components, there were 283,700 jobs in the biopharmaceutical industry; 409,200 in medical devices (including diagnostics); and 526,300 in related R&D, testing, and labs. Wages and output stemming directly from the industry comprised \$96 billion and \$213.2 billion, respectively. The average job in the U.S. biomedical industry paid \$78,600, more than 70 percent higher than the nation's average job. Once all the ripple effects of the biomedical supply chain are taken into consideration, the industry accounts for 5.3 million jobs, or 4 percent of non-farm jobs in the United States. Every job in the biomedical sector supports another 3.3 jobs elsewhere.

Table 1: Size of biomedical industry, 2009

Industry	Employment	Wages, US\$B	Outputs, US\$B
Biopharmaceuticals	283,700	\$29.0	\$82.4
Medical devices and equipment	409,200	\$26.5	\$66.2
Research, testing and medical labs	526,300	\$40.3	\$64.5
Total biomedical	1,219,200	\$95.9	\$213.2

Sources: Bureau of Labor Statistics, Moody's Analytics, Milken Institute.



But U.S. industry leadership, so carefully cultivated over the past 30 years, is eroding. Europe and Japan are working to close the gap, while China, India, and Singapore have made impressive strides. In addition to improving the quantity and quality of their scientific research, competing nations are developing mechanisms to support entrepreneurs and strengthen commercialization. They are also instituting regulatory reforms and a range of public policies to improve incentives for innovation. These efforts are part of larger economic development plans that increasingly focus on cultivating biomedical innovation for its economic contributions and high-wage jobs.

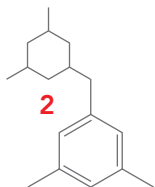
Multiple factors leave the U.S. vulnerable to falling behind: increasing complexity, rigidity, and uncertainties in the Food and Drug Administration's regulatory approval process; funding cuts at the National Institutes of Health and at the state level; a corporate tax rate and R&D tax credit that are not globally competitive; unfavorable coverage and payment policies that limit access to new medical advances; and public policies that hamper the nation's ability to develop and retain human capital.

The dominance enjoyed by the U.S. biomedical industry does not come with a long-term guarantee. The U.S. assumed the mantle of leadership by being the first to commercialize recombinant DNA research—and that achievement was made possible only because it had built an environment and infrastructure that allowed innovation to flourish. But if another nation duplicates or improves upon this formula by building a similar ecosystem and subsequently makes a pivotal scientific breakthrough in nanotechnology, personalized medicine, embryonic stem cell research, or some other cutting-edge field, it could tip the scales in the other direction. That scenario is a real possibility: While the U.S. led with 29.7 percent of nanotech-related patents granted between 1996 and 2008 (as measured by resident country of first-name inventor), China was a close second, with 24.3 percent of these patents.

Many countries are actively building the infrastructure for biomedical research and courting the private-sector operations associated with it in an effort to create high-wage, high-value-added jobs. They also realize that biomedical advances enable their citizens to live longer and more productive lives.

The U.S. could retain and bolster its leadership in biomedical innovation by taking the following actions to respond to a new era of heightened global competition:

- Increase R&D tax incentives and make them permanent
- Cut corporate tax rates to match the OECD average
- Extend support for emerging biomedical research fields
- Provide adequate resources for the FDA and the NIH to expedite regulatory reviews and clinical trials
- Leverage existing strengths in medical devices
- Build human capital for biomedical innovation
- Promote and expand the role of universities by adopting best practices in technology transfer and commercialization



Research Findings

The U.S. Ascent to Dominance

Pharmaceuticals and medical devices have a long history of innovation that can be traced back to 19th-century European apothecaries and the continent's early chemical industry. Merck, for example, began as a humble apothecary shop in Germany in 1668 and began producing wholesale drugs in the 1840s. German and Swiss firms were the world's first pharmaceutical manufacturers.

Europe established and refined the tradition of a research-based industry. Thanks to this strong foundation, its pharmaceutical and device companies were able to recover after World War II and continue to lead the industry for a number of years. European firms introduced innovative drugs and discoveries created through well-established research and distribution pipelines. But the lack of a unified European market, groundbreaking discoveries that fell outside the traditional reach of European firms, and significant changes to the U.S. regulatory system and its patent laws paved the way for a change in leadership.

The molecular biology revolution that began in the 1970s altered the landscape of drug discovery and development. Recombinant DNA technology allowed an upstart American company to pioneer the birth of a new industry. In 1976, Genentech, headquartered in San Francisco, was founded to take advantage of advances in large molecule drug development. Europe had actually been ahead of the U.S. in scientific advancements in this promising research area—but given the significant regulatory differences between the U.S. and Europe, the size of the U.S. market, and Europe's difficulties in commercializing research by smaller firms and universities, the United States positioned itself to seize momentum.

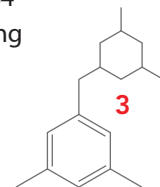
U.S. Public Policies and Regulatory Framework

The Bayh-Dole Act of 1980, subsequently amended in 1986, allowed universities and businesses operating under federal research contracts to have exclusive rights to the intellectual property they produced for further development and commercialization. Industry was now willing to collaborate more closely with universities since the results were easier to patent and bring to the market in a profitable manner. The biotech revolution was greatly aided by the Bayh-Dole Act, and clusters of small firms soon sprung up around universities in Boston, Greater San Francisco, San Diego, Raleigh-Durham, Greater Washington, D.C., Seattle, and elsewhere.

The biotech revolution was greatly aided by Bayh-Dole. Clusters of small firms soon sprung up around universities in Boston, Greater San Francisco, San Diego, Raleigh-Durham, Greater Washington, D.C., Seattle, and elsewhere.

The Bayh-Dole Act proved to be one of the most important pieces of legislation to come out of Congress since World War II. It made possible the birth of an industry that the United States subsequently came to dominate. It allowed universities with outstanding biomedical science capabilities to partner with entrepreneurs and large firms, and to gain access to venture capital.

Another landmark piece of legislation was the Drug Price Competition and Patent Term Restoration Act of 1984 (referred to as the Hatch-Waxman Act), which amended U.S. patent protection laws pertaining to drugs, extending coverage of intellectual property. Because drug discovery is a long, arduous, and costly process (now running in



excess of \$1 billion to bring a new therapeutic to the market), the financial risks are immense. A run of losing bets can even bring a large multinational firm to the brink of insolvency. Hatch-Waxman protects drug patents for either 17 years from the patent's issue date or 20 years from the date of the patent's first filing, thus giving firms more time to recoup their investment and restoring their incentive for innovation. While Hatch-Waxman was intended to balance the desire for increased competition from generic drugs with the need to maintain incentives for biopharmaceutical innovation, that balance no longer holds, with more than 70 percent of prescriptions being filled with generics and an effective patent life of less than 12 years for innovative medicines.

The passage of the Prescription Drug User Fee Act (PDUFA) was another critical regulatory policy change. Implemented in 1992, the act allowed the FDA to collect fees from the industry to provide resources for expediting the drug review process. Before this legislation passed, the number and complexity of new medication submissions had been escalating due to advances in scientific discovery, and the FDA found itself ill-equipped to handle their review in a timely manner, undermining firms' ability to bring treatments and cures to the marketplace. PDUFA cut the average review time for new innovative drugs from 30.2 months in 1991 to 16.9 months in 2003.

These legislative and regulatory changes provided a competitive advantage for U.S. firms—and an incentive for more European-headquartered firms to perform drug discovery in the United States. For example, Switzerland-based Novartis AG established its main research hub in Cambridge, Mass., in the early 2000s; another Swiss firm, Roche, acquired a majority stake in Genentech in 1990 and bought out full ownership in 2009. Sanofi, which is headquartered in France, announced a deal in February 2011 to acquire Cambridge-based biotechnology firm Genzyme. These moves are a positive reflection on the strengths of U.S. assets.

Another significant development in the rise of the U.S. biomedical industry occurred in the field of medical devices. In 1976, the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act became law. These amendments allowed the FDA to establish procedures and safeguards governing the introduction and usage of a broad class of products called medical devices. (Before the law, some diagnostic technologies made use of antibiotic drugs and were considered drugs for regulatory purposes, and the overall scope of the industry was limited.)

In the 1980s, the medical device industry saw rapid growth as a number of innovative U.S.-derived products were introduced into the health-care field, led by high-resolution imaging (notably radiographic and fluoroscopic units). By 2008, 12 out of the top 20 medical device companies by sales revenue were headquartered in the U.S.

The FDA's seal of approval has long been considered the world's gold standard for determining the safety and efficacy of new drugs and devices—a factor that has given the United States a major market advantage. Having a relatively streamlined, consistent, and well-defined approval process provides companies with a clear road map for commercializing their discoveries. Given the importance of this framework, recent increases in review times and a lack of transparency at the FDA raise concerns about our future competitiveness.

Innovation Measures: R&D, New Chemical Entities, and Drug Approvals

Examining the number of new chemical entities (NCEs) being produced is a good gauge of the innovative capacity of various countries. The accompanying table illustrates the dramatic changes from European to U.S. dominance over the past four decades. During the 1970s, the four largest European countries were responsible for 55 percent of NCEs produced by major nations, while the U.S. held a 31 percent share. But over the decade from 2001 to 2010, the U.S. share jumped to 57 percent, while France, Germany, Switzerland, and the U.K. saw their share of NCEs plummet to 33 percent in a complete reversal of fortunes.

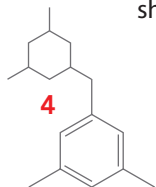


Table 2: New chemical entities
By headquarter country of inventing firm

	1971-1980		1981-1990		1991-2000		2001-2010	
Country	NCEs	% total	NCEs	% total	NCEs	% total	NCEs	% total
U.S.	157	31	145	32	75	42	111	57
France	98	19	37	8	10	6	11	6
Germany	96	20	67	15	24	13	12	6
Japan	75	15	130	29	16	9	18	9
Switzerland	53	10	48	11	26	14	26	13
U.K.	29	6	29	6	29	16	16	8
Total NCEs	508		456		180		194	

Sources: Arthur Daemrich, "Where Is the Pharmacy to the World? International Variation and Pharmaceutical Industry Location," Harvard Business School Working Paper, 2009; Milken Institute.

Because of the legal and regulatory framework discussed above and the subsequent formation of a superior ecosystem of biomedical innovation, U.S. firms were able to reinvest more of their profits back into R&D—and their European counterparts began to shift more of their R&D operations to the U.S. The research productivity of the United States tops all other nations as measured by the ratio of world-first patents filed for marketed new molecular entities relative to R&D spending by biopharmaceutical firms. Additionally, the U.S. captured 68.3 percent of total venture capital investment in the life sciences among OECD nations in 2007.

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The ability of a nation to maintain high levels of R&D expenditures is another reliable measure of its innovation capacity. In 1990, as the graph below illustrates, the United States accounted for 38 percent of the total biopharmaceutical R&D spending of leading nations. However, by 2004, the U.S. share was 55 percent of biopharmaceutical R&D spending. Somewhat troubling is the decline experienced since then, as the U.S. slipped to 51 percent in 2008. Nevertheless, even in the aftermath of the Great Recession, U.S. biopharmaceutical companies invested a record \$67 billion in 2010 to develop new life-changing and life-saving treatments—an increase of more than \$1.5 billion from 2009.

In the field of biotechnology, patenting activity provides a measure of innovation performance. The 2008 OECD Compendium of Patent Statistics shows that the U.S. accounted for 40.6 percent of world patents, while the European Union and Japan, at 25.1 and 17 percent, respectively, were second and third.

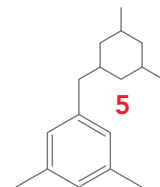
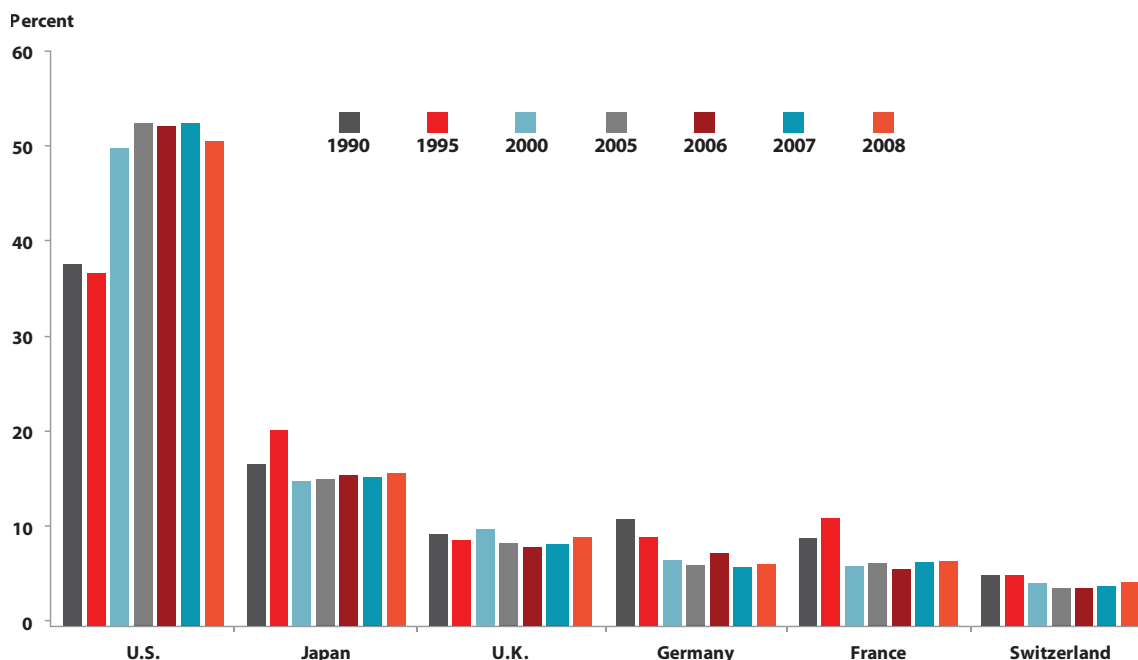


Figure 1: Share of total pharmaceutical R&D spending of key countries, 1990-2008



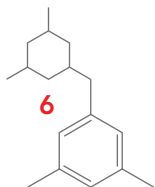
Sources: National trade associations; U.K. Ministerial Industry Strategy Group/Association of the British Pharmaceutical Industry report (2009).

The U.S. is also a leader in R&D investment in medical devices. R&D spending among medical technology firms in the U.S. was twice the average of all industries. U.S. R&D expenditures equaled nearly 13 percent of medical device sales, compared to the EU and Japan, where they were approximately 8 percent. As a measure of their commercial success, U.S. firms receive nearly half of their revenue from abroad.

The sheer size of its consumer market is another advantage for the U.S., but its well-established infrastructure for clinical trials is even more critical to U.S. biomedical prowess. Clinical trials are not only an important step toward commercialization, but also indicative of a region's depth of biomedical R&D and innovation. As of May 2011, the U.S. was far and away the leader in hosting clinical trials, with 54,063 under way. Europe had 27,240 active trials, while Japan had 1,840. Even after normalizing for population, the U.S. held a clear advantage with 174 clinical trials per million residents (Europe had 37 and Japan 15 per million people). In fact, 50.9 percent of all clinical trials in the world as of this date were being held in the U.S. Furthermore, the U.S. accounted for almost 54 percent of the 75 leading global medicines (new active substances as measured by worldwide sales).

By virtually any credible measure of biomedical innovation outcomes, only one conclusion can be reached: The U.S. not only leads but dominates this sector. But history shows that hegemony is not the divine right of any continent or nation. When competitive advantages are taken for granted, they can be lost.

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The Changing Landscape

Other nations are actively working to close the gap with the U.S. They are focusing on increasing scientific capacity and infrastructure at their academic and research institutes as well as developing entrepreneurial support mechanisms to improve commercialization (including access to early-stage financing). They are also implementing regulatory reforms and public policies to improve incentives for innovation. The mix of strategies being deployed varies depending on whether the nation in question has a long legacy of excellence in biomedical research or whether it is a relative newcomer to the industry with rapidly improving capabilities.

Increased Research and Entrepreneurial Support Around the World

Europe

Across Europe, governments are injecting financial support in a concerted effort to regain leadership in biomedical research and development, recognizing that it produces high-paying jobs, positive economic impact, and the potential for advances in treatments for disease. The European Union introduced the Innovative Medicines Initiative (IMI), a public-private partnership founded to boost the continent's competitiveness in biopharmaceutical research. IMI, with a budget of US\$2.66 billion, seeks to address bottlenecks in the drug development process and will focus on university and private institute startups.

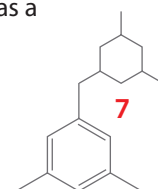
Universities in the U.K. are among the world's elite in biomedical research. The 2010 QS World University Rankings place the University of Cambridge and the University of Oxford second and third in the life sciences, respectively, and three other U.K. institutions are in the top 20. Building on this strength, the British government has invested in Engineering and Physical Sciences Research Councils at three university research centers to mobilize a collaborative effort between researchers and industry to commercialize academic R&D, mostly in regenerative medicine and medical devices. Further, the U.K. launched the Innovation Investment Fund in 2009 to support promising technology-based businesses, especially in the life sciences and clean tech. The government hopes to attract capital from the private sector and eventually create the largest technology fund in Europe, which could be worth up to £1 billion over its 12- to 15-year life.

Germany, a pioneer in pharmaceuticals, medical devices, and biological products, has taken steps to regain its former prominence. These efforts began with implementation of the 1993 Genetic Engineering Act, which reduced some regulatory hurdles, and continued with the launch of the BioRegion competition in 1995 and finally passage of Germany's version of the Bayh-Dole Act in 1999. These moves have promoted commercialization of university biotech research and the formation of several clusters. Looking forward, Germany's High-Tech Strategy 2020 seeks to facilitate closer ties between academia and industry, thereby enhancing the biopharmaceutical sector's competitiveness.

France initiated its Fonds Stratégique d'Investissements in 2008 in an effort to support the industry as part of the government's fiscal stimulus package. The fund has allocated US\$8.7 billion to invest in high-growth firms, and much of that capital will find its way into the biomedical area, potentially addressing long-standing complaints from French university startups and spinoff firms that it is difficult to secure financing. Switzerland, Italy, and other European countries have similar initiatives under way.

Asia

Multiple Asian countries are making aggressive moves to bolster biomedical research and commercialization as a means of advancing their knowledge-based economic development strategies.



Japan, for example, is building on the excellence of its universities to achieve these ends. The University of Tokyo and Kyoto University rank among the world's premier biomedical research institutions, in addition to several that are in the next tier down. Until recently, very few drugs or devices had been commercialized out of Japanese universities due to a lack of clear regulations on the ownership of intellectual property. But Japan instituted a Technology Organization Law and its own version of Bayh-Dole, and in 1998, technology licensing offices were first established. Japan has been funneling more funding into biotechnology and the life sciences in recent years, primarily at its universities and research institutes. Between 2003 and 2006, the number of biomedical startups rose by over 50 percent. Japan now has an extensive network of small- and medium-sized firms that are attractive for larger firms seeking to invest in niche areas. While there are still challenges to obtaining regulatory approval, reimbursement, and intellectual property protection, positive steps have been made to reduce barriers to biomedical innovation.

China is focusing its knowledge-based economic development efforts in the biomedical area. Chinese universities have long been highly centralized, but the government is attempting to break down bureaucratic barriers and provide greater incentives to support R&D and biotechnology commercialization. China's National Development and Reform Commission initiated 20 venture capital funds in 2009, involving seven provincial governments. Biomedical innovation is a key target for these funds.

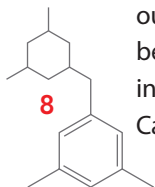
Another Chinese strategy involves encouraging the reverse migration of human capital from the United States. Beginning in the 1970s, thousands of native Chinese sought graduate degrees in the biomedical sciences in the U.S. In 2008, there were approximately 2,500 native Chinese life sciences faculty at U.S. universities, and 10 to 20 percent of scientists at U.S. drug and biotech companies were native Chinese. China is targeting this diaspora of biomedical talent and providing opportunities that will encourage these workers to bring their skills and training home. Some have dubbed returning Chinese scientists "sea turtles."

China is addressing the diaspora of its biomedical talent and providing opportunities that will encourage these workers to bring their skills and training home. Some have dubbed returning Chinese scientists "sea turtles."

Singapore, in addition to developing indigenous biomedical talent through excellent science education, has pursued a strategy of attracting top international biomedical researchers with experience in commercialization—including U.S. talent. It has developed the physical infrastructure to house and centralize these resources at an ambitious, modern facility called the Biopolis. Additionally, Singapore is seeking to create a more business-friendly environment by fostering public-private collaborations, enhancing its R&D infrastructure, and improving IP rights.

India has been encouraging Western multinational biomedical firms to make investments by demonstrating its commitment to funding and developing 20 biopharmaceutical research parks throughout the country. IKP Knowledge Park in Hyderabad, recognized as a world-class applied research center, includes a life science incubator. Several incentives for biotech R&D have been implemented, including a fully refunded rebate on private investment, fast-track clearance for foreign direct investment, and a 25 percent rebate for privately funded research in a publicly funded institution.

The rising research productivity of China and India can be seen in the growing numbers of inventions coming out of these two nations. Pharmaceutical patents that credit at least one inventor in China or India rose four-fold between 1996 and 2006—China held 8.4 percent and India 5.5 percent of worldwide patents. Other countries in Asia and around the world are also making advances, among them Taiwan, South Korea, Malaysia, Australia, Canada, Brazil, and Chile.



Public Policy and Regulatory Reforms

In several public policy areas, such as funding for the National Institutes of Health (NIH), the U.S. has been holding steady, while other countries have been improving. In regulatory areas, such as the predictability and efficiency of FDA drug and device approvals, the complexity of pre- and post-approval requirements, and clinical trial costs, the U.S. has seen declines in performance while other countries race ahead.

The NIH

The NIH (comprised of 27 separate institutes and centers) funds much of the basic biomedical science in the U.S., and in recent years, substantially more translational research. Under both Democratic and Republican administrations, Congress doubled the NIH budget between 1998 and 2003. However, since 2004, NIH funding has declined in real terms (excluding the \$10 billion appropriated to NIH in 2009 for short-term stimulus under the American Recovery and Reinvestment Act); it stood at \$31.2 billion in nominal terms in FY2010. In the recently approved FY2011 budget, NIH funding was cut by \$260 million. Other countries are increasing government support of biomedical research, while the U.S. is not.

Emerging Technologies

The U.S. continues to play a leading role in innovative fields such as advanced DNA sequencing, new imaging modalities, computational biology, and nanotechnology. Personalized medicine, using genetic and clinical information to develop customized solutions, provides an opportunity to revolutionize the way that drugs are discovered and prescribed. However, the current system of drug discovery and approval is not designed to support this type of innovation. Notably, although the U.S. produced 30 percent of the world's nanotech-related patent publications between 1996 and 2008, countries such as China and Japan are also performing well, with 24 and 15 percent, respectively.

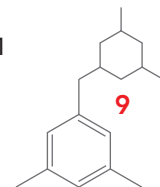
In stem cell science, other nations with sophisticated biomedical research infrastructure in place—including the U.K., Japan, France, Switzerland, and several others—have instituted more flexible government funding guidelines than the U.S. These nations have been attracting leading embryonic stem-cell researchers from countries with more restrictive policies. For example, American stem cell pioneer Roger Pedersen left U.C. San Francisco for Cambridge, England, in 2001, shortly after President Bush's executive order limited the scope of government funding. More recently, he has been active in stem cell efforts in Singapore.

President Obama lifted federal restrictions on developing new stem cell lines in March 2009 and instructed the NIH to review and update guidelines for funding “responsible, scientifically worthy” research. But as of this writing, legal challenges continue to cloud the issue. The U.S. is far behind where it might have been in developing stem-cell scientific and therapeutic breakthroughs, and substantially higher federal funding may be required to play catch-up.

Tax Environment

Research and development activities in the biomedical industry carry substantial risks. The sizable cost of undertaking these risks can be mitigated by effective R&D tax credits that encourage firms to invest in innovation. Many countries have introduced tax incentives to support sustained investments in R&D, and considerable evidence also shows a high association between R&D tax credits and R&D activities.

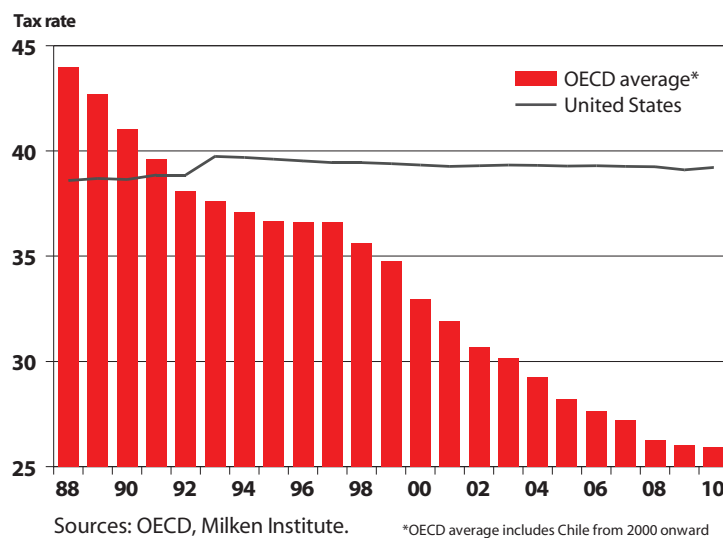
According to figures from the Organization for Economic Cooperation and Development (OECD), 12 member countries had these incentives in place in 1995, but that number was up to 20 by 2007. Although the U.S. pioneered this policy, it has not kept pace with other leading biomedical countries. It now ranks 17th out of 21 OECD members in the effective rate of the R&D tax credit. European countries have increased the size of their credits, while Asian competitors have initiated aggressive programs as well. Furthermore, while most other



countries focusing on the biomedical arena have made the R&D investment tax credit permanent, the U.S. has failed to do so, creating a climate of greater investor uncertainty. This is a particular issue for R&D-intensive industries; in the case of the biopharmaceutical industry, it takes 10 to 15 years to develop a new medicine.

Variations in tax policies, particularly corporate income tax rates, between countries can influence where firms choose to locate their R&D activities, production facilities, distribution networks, and even headquarters. As of 2011, the U.S. has the second-highest corporate tax rate (a 39.2 percent federal and state average) across OECD countries. Most disconcerting for the U.S. is that many European nations and other members of the OECD have been slashing rates over the past 20 years. The OECD average corporate tax rate fell from 47.5 percent in 1981 to 25.4 percent in 2011, undermining the competitiveness of U.S.-headquartered biomedical firms. Other European countries offer more attractive corporate tax rates than the U.S.: Switzerland (21.2 percent), the U.K. (26 percent), Germany (30.2 percent), and France (34.4 percent). Even China cut its corporate income tax rate to 25 percent in 2008. In addition, other countries are implementing a range of other R&D and tax incentives to attract foreign direct investments as a part of economic growth strategies.

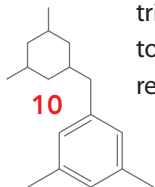
**Figure 2: Statutory corporate income tax rates
OECD average vs. United States**



FDA and Regulatory Approvals

In drug, device, and diagnostics approvals, the FDA has recently become more risk averse. Increasing complexity and rigidity has raised R&D costs and added a layer of uncertainty to the review and approval process. The FDA has been tightening safety requirements partly in response to legitimate public concerns over adverse drug reactions and their legal implications, along with pressure from Congress.

According to a study by the Tufts Center for the Study of Drug Development, unique procedures per protocol increased by 6.5 percent between 1999 and 2005. Clinical trials conducted between 2003 and 2006 were 69.6 percent longer than those held between 1999 and 2002. This translates to an extension of 460 to 780 days. As a result, the system has become less efficient and less effective. The median number of procedures per clinical trial increased by 49 percent between the periods 2000-2003 and 2004-2007, with a corresponding increase in total work burden per protocol of 54 percent. Volunteer enrollment and retention decreased by 21 and 30 percent, respectively, between the same periods.



The U.S. approval process tends to be rigid, with little transparency throughout the process. In the current system, clinical trials require the use of consistent methods, including statistical tests and sample sizes. Given the length of clinical trials, it is common for researchers to discover new developments that could alter the original methods and promote better and faster results, but they have not been allowed to change parameters midway through the process. Today there is a growing call for speedier expansion of a system of “adaptive trials” that can potentially increase efficiency and effectiveness by allowing for mid-course adjustments. Adopting more flexible practices would be beneficial when there is high uncertainty involved in the earlier stages, thereby increasing the success of Phase III trials. This may be especially applicable to novel therapeutics, diagnostics, and devices that have limited prior data and relevant literature for reference. While the FDA is beginning to accept a limited number of adaptive clinical trial designs, the current regulatory regime is not set up for implementation of adaptive trials on a broad basis, thus slowing innovation.

While the FDA has seen an increase in average review times, the European Medicines Agency (EMA) has been streamlining. After declining to 12.3 months in 2007, the average FDA review time for new drugs increased to 17.8 months in 2008. This number does fluctuate, and while it improved in 2009, anecdotal evidence suggests that the 2010 numbers will reflect a slowdown. Meanwhile, the EMA has reduced its drug approval time to 15.8 months. To maintain its position as the world’s leading regulator, the FDA will need additional resources to meet the twin goals of making reviews more efficient while maintaining the highest standards of patient safety.

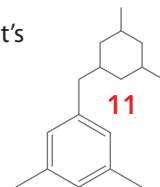
To maintain its position as the world’s leading regulator, the FDA will need additional resources to meet the twin goals of making reviews more efficient while maintaining the highest standards of patient safety.

Medical device approvals from the FDA have become even more problematic than drug approvals. In Europe, some devices are approved in half the time it takes for similar approvals by the FDA. The onerous pathway to FDA approval can inflict unnecessary regulatory burdens and discourage innovation in medical technologies. The opacity of the device approval process inhibits startup medical device firms from accessing private capital markets and adds to development costs, as companies must hire seasoned experts just to navigate the approval labyrinth.

Developing countries are not only modernizing their drug and device approval processes to meet international standards, but they’re also capitalizing on their ability to offer more cost-effective clinical trials than the U.S. Clinical trial costs in China and India are approximately one-half of those in the U.S. China is increasingly willing to streamline regulatory processes for clinical trial approvals. In addition, the government is enforcing stricter intellectual property protections, pledging to eliminate the copying and counterfeiting of drugs through reverse engineering—a practice that had made international firms leery of entering the Chinese market. Both China and India are coming into better alignment with international standards to bolster their ability to attract multinational firms.

Actions and Policy Recommendations to Retain U.S. Leadership

The U.S. remains the leading center of biomedical research and production. But innovation is not constrained by borders. It will follow future scientific breakthroughs wherever they occur, as long as the originating nation has the correct policies in place to support commercial application and production. Those include the right R&D infrastructure, economic and policy incentives, and an overall environment that encourages innovation. It’s entirely possible that biomedical innovation could quickly diminish in the U.S. and grow elsewhere.



But the U.S. can retain the retainable by making forward-thinking changes in policy, regulation, and government funding. These include:

► **Increase R&D Tax Incentives and Make Them Permanent**

Research and development activities in the biomedical industry carry substantial risks of product failure and investment losses. Tax incentives can mitigate these risks and encourage innovators and investors to commit time and resources to the cause. The United States should make its R&D investment tax credit permanent and increase it by 25 percent in addition to exploring other incentive proposals and approaches that promote greater domestic R&D investment.

► **Cut Corporate Tax Rates to Match the OECD Average**

All other things being equal, countries that impose higher corporate tax rates will lose investments to competitors with lower rates. A major revamp of the U.S. corporate tax structure would address this issue. We recommend cutting the federal corporate tax rate by 13 percentage points to 22 percent—essentially matching the OECD average.

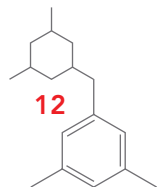
► **Extend Support for Emerging Biomedical Research Fields**

The U.S. can extend and enhance its global competitive position by supporting cutting-edge areas like nanotechnology, personalized medicine, and stem cell research, all of which hold immense potential. Additional laboratory and market creation initiatives are needed to spur discovery and commercialization.

Supporting R&D will give the U.S. the best chance of establishing a strong and sustainable foothold in the regenerative medicine arena. Adaptive trial design, the use of surrogate endpoints, and ensuring adequate scientific expertise at the FDA and NIH will also help ensure a platform for the applications of novel technologies. A viable and effective policy framework can facilitate the development of new frontiers that may provide the greatest financial and societal returns in the decades ahead.

► **Provide Adequate Resources for the FDA and the NIH to Expedite Regulatory Reviews and Clinical Trials**

The FDA needs additional resources to hire staff, better manage the review process, and improve the system of review. Congress should commit to robust funding for both the NIH and the FDA. Providing resources for the broader adoption of flexible approaches such as adaptive trials can address the rigidity of existing practices and create more efficient regulatory reviews, particularly for emerging fields with limited prior research. Beyond that, the NIH must be given additional resources to support clinical trials and translational research; increased funding for translational efforts at the NIH could improve research productivity throughout the scientific community. In addition, PDUFA should be reauthorized prior to its scheduled 2012 expiration.



► **Leverage Existing Strength in Medical Devices**

The FDA must again be given a firm mandate to create an efficient system for medical device approvals. This is necessary to ensure medical device companies are not deterred from seeking approvals in the U.S. Streamlining approvals for export licenses to developing countries such as China and India could improve U.S. export performance in medical devices even further.

► **Build Human Capital for Biomedical Innovation**

Building a 21st-century workforce requires a renewed commitment and funding to improve science, technology, engineering, and math (STEM) education in the United States, as well as providing skills enhancement and retraining in STEM fields for incumbent workers. Making STEM education a national priority will nurture homegrown talent, encouraging American students to become the scientists and innovators of tomorrow.

Additionally, the U.S. should provide an expedited pathway to permanent residence status and then a green card to foreign researchers in exchange for their participation in biomedical R&D over a stipulated period of time. Such changes could bring about international collaborations that leverage the foreign contacts of these global talents.

► **Promote and Expand the Role of Universities: Adopt Best Practices in Technology Transfer and Commercialization**

The U.S. has the most productive university technology transfer process in the world, but there is a high degree of variation in efficiency across universities. Convening university medical scientists and tech transfer officials together with industry experts and investors could focus U.S. efforts to adopt existing best practices more widely and enhance the interaction between universities and biomedical companies. Universities could play a more prominent role in early-stage biomedical discovery, helping the U.S. develop a new and sustainable model for R&D and enhance its competitive position.

However, there are increasing obstacles to collaborations between the private sector and academic research centers. Recognizing that such collaborations are foundational to the U.S. ecosystem of innovation, we need to explore ways to promote partnerships and remove the barriers preventing their success. This has to start with acknowledging the problem and recognizing the unintended chilling effects of conflict-of-interest and related policies.

To reiterate, the United States continues to dominate the global biomedical playing field. It still has the means to compete, but other countries are increasingly developing the kind of strength that could one day seize the lead. The seven recommendations detailed here are critical to the continued growth, sustainability, and preeminence of a vital U.S. industry.

Complete references are available in Parts 1, 2, and 3 of the report.

Part 1

The Global Biomedical Industry: Understanding the Factors That Led to U.S. Dominance

The United States has an undisputed reputation as a hotbed of innovation, due in large part to its track record of scientific achievement and commercial prowess in the biomedical field. This legacy represents one of the most dramatic success stories achieved by any American industry during the past century. But how exactly did the United States achieve this level of dominance? And how secure is its market share going forward?

This section will recount how the global biomedical industry evolved over time, first taking root in Europe before a burst of innovation shifted momentum to the United States. We will examine the various factors that made it possible for the U.S. to claim the mantle of global leadership.

But past and current success is no guarantee of future performance. Though the U.S. continues to hold a commanding advantage, serious global competition is on the rise—both from a resurgent Europe and from new contenders in Asia. Part 2 of this report will examine the changing competitive landscape, while Part 3 will outline policy recommendations that would position the U.S. to maintain its edge in the years to come.

Current Industry Parameters

According to the most recent data from the Bureau of Labor Statistics, private-sector employment in the biomedical industry in 2009 was approximately 1,219,200. Breaking this total down into its three major components, there were more than 283,700 jobs in the biopharmaceutical industry; 409,200 in medical devices (including diagnostics); and 526,300 in related R&D, testing, and labs.¹ Wages and output stemming directly from the industry comprised nearly \$96 billion and \$213.2 billion, respectively.² Thus, the average job in the U.S. biomedical industry paid \$78,600, more than 70 percent higher than the national average.

Table 3: Size of biomedical industry, 2009

Industry	Employment	Wages, US\$B	Outputs, US\$B
Biopharmaceuticals	283,700	\$29.0	\$82.4
Medical devices and equipment	409,200	\$26.5	\$66.2
Research, testing and medical labs	526,300	\$40.3	\$64.5
Total biomedical	1,219,200	\$95.9	\$213.2

Sources: Bureau of Labor Statistics, Moody's Analytics, Milken Institute.

When accounting for the multiplicative dynamics (that is, all other jobs impacted indirectly through the biomedical supply chain), the industry accounted for almost 5.3 million jobs, or 4 percent of U.S. non-farm employment in 2009.³ In other words, on top of its direct employment, the industry is responsible for generating an additional 4,042,600 jobs due to indirect and induced impacts. Furthermore, every job in the biomedical industry created another 3.3 jobs outside of the immediate sector. The following table summarizes the total impacts on employment, wages, and output.⁴

Table 4: Total economic impact of biomedical industry, 2009

Industry	Total impacts		
	Employment	Wages, US\$B	Output, US\$B
Biopharmaceuticals	2,127,983	\$110.3	\$206.1
Medical devices and equipment	1,554,952	\$98.1	\$152.3
Research, testing and medical labs	1,578,915	\$80.6	\$161.3
Total biomedical	5,261,850	\$289.1	\$519.7

Sources: Bureau of Labor Statistics, Moody's Analytics, Milken Institute.

The sheer size of the U.S. consumer market is a powerful lure for major firms. The North American market accounts for almost 40 percent of global sales, while the European market represents 31 percent.⁵ As of 2010, seven of the top 20 global pharmaceutical companies were located in the United States.⁶

U.S. dominance extends beyond pharmaceutical products and into the realm of medical device manufacturing. In 2008, sales of medical devices worldwide were estimated at about \$210 billion, with four-fifths of revenue originating from the U.S. and Europe. The U.S. accounts for 41 percent, followed by Japan (10 percent), Germany (8 percent), and France (4 percent).⁷ Since the U.S. market is so large, it is not surprising that U.S. firms dominate the list of the top medical device makers.

Innovation is the driver of ultimate market success, and the U.S. originated more than half of the leading 75 global medicines (new active substances as measured by worldwide sales) in 2009.⁸ Clinical trials are a critical step in the process of developing these treatments as well as a benchmark that reflects the degree of innovation taking place in a given location. As of early 2011, 50.9 percent of all clinical trials in the world were being held in the U.S.⁹ Despite this formidable share, the number of trials being conducted in emerging nations—especially China and India—has been growing by leaps and bounds in recent years. (See Part 2 for further discussion of this issue.)

As the birthplace of biotech, the U.S. remains on the cutting edge of new developments in this field. In 2007, the U.S. accounted for 33 percent of world's total biotech patents. This far eclipsed Germany (13 percent), Japan (11 percent), and Switzerland (2.8 percent).¹⁰ The Advanced Medical Technology Association (AdvaMed) reported an 80 percent increase in U.S. patents for breakthrough medical devices over the past decade.¹¹

But innovation has profound implications that extend beyond the marketplace; it also has a direct bearing on patient outcomes. Both medical device makers and pharmaceutical firms have recently increased their focus on cutting-edge diagnostics for early detection and evaluation of disease. The development of more sophisticated electromedical (imaging) and irradiation (X-rays) technology has contributed to life expectancy gains and lower disability rates. Death rates for the most common cancers have declined, and the length of cancer survival has also increased. Some 68.3 percent of cancer patients survived after being diagnosed in 2001 (the most recent year with five-year follow-up data available), compared to 60 percent only a decade prior.¹² Additional diagnostic advances include the first fully automated test for detecting congestive heart failure and monitoring treatment response, as well as the first oral specimen rapid HIV test.¹³

Both medical device makers and pharmaceutical firms have recently increased their focus on cutting-edge diagnostics for early detection and evaluation of disease.

The last decade alone has seen the first molecularly targeted cancer drug for leukemia, the first drug for severe Alzheimer's, a new monoclonal antibody treatment for colorectal cancer, a vaccine for the prevention of cervical cancer, and two new first-in-class HIV drugs.¹⁴ New devices introduced in recent years—including stents, heart valves, defibrillators, gastric bands, glucose monitors, and artificial joints—continue to expand the treatment options available to patients.¹⁵

Federal policies play an important role in influencing the U.S. biomedical industry's ability to innovate. The federal government's support encompasses everything from funding basic research to providing an efficient capital market environment. But perhaps the most crucial underpinning it provides is the U.S. regulatory infrastructure. The FDA's seal of approval has long been considered the world's gold standard for determining the safety and efficacy of new drugs and devices—a factor that has given the United States a major market advantage. Having a relatively streamlined, consistent, and well-defined review and approval process provides companies with a clear road map for commercializing their discoveries, thus giving them the potential to recoup their considerable R&D investments more efficiently.

The United States took a major step at streamlining the review and approval process in 1992 with the initial passage of the Prescription Drug User Fee Act (PDUFA), which was renewed in 1997, 2002, and 2007. The act allowed the FDA to collect fees from the industry to provide resources for expediting the drug review process. PDUFA cut the average review time from 30.2 months in 1991 to 16.9 months in 2003,¹⁶ apparently without a significant incremental impact on safety withdrawal rates.¹⁷

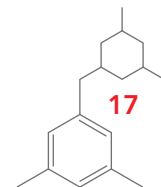
The FDA's strides in efficiency conferred major benefits on U.S. biomedical firms—and that fact was not lost on regulators in Europe. The U.S. enjoyed a strong advantage during the 1990s in terms of review times, but the European Medicines Agency (EMA) has set about closing the gap. According to one report that examined 99 drugs approved in 2000–2005, including 71 drugs approved by FDA, the average review time in the EU was 15.8 months compared to 15.7 months in the U.S. But 24 of the new drugs, or 33 percent, were approved faster in the EU.¹⁸

Average (mean) approval times can fluctuate quite a bit from year to year, but many U.S. industry executives report seeing a recent slowing trend. As it stands currently, the FDA still approves more drugs annually than the EMA, but the gap is narrowing.

Table 5: FDA mean approval times for new therapeutics and new biologics,¹⁹ 1999-2010

	New therapeutics		New biologics	
	Total number	Mean approval time (months)	Total number	Mean approval time (months)
1999	35	12.6	5	17.1
2000	27	17.6	6	25.8
2001	24	16.4	8	19.6
2002	17	17.8	9	30.1
2003	21	16.9	14	34.7
2004	36	18.1	2	19.8
2005	20	13.7	8	9.1
2006	22	14.9	7	16.2
2007	18	12.3	8	8.2
2008	24	17.8	7	15.2
2009	25	13.3	9	12.8
2010	21	14.3	5	11.1

Source: Pharmaceutical Research and Manufacturers of America (PhRMA), 2010 Annual Report and New Drug Approvals in 2010.



While the EMA has been expediting its approval process, the FDA seems to have become more cautious. Safety requirements have been tightened due to concerns of a public backlash and potential implications from adverse drug reactions. For example, the 1997 FDA Modernization Act allows for expedited approval of vital therapies such as cancer drugs. From 2001 to 2003, 78 percent of innovative cancer drugs were granted accelerated approval. But from 2004 onward, only 32 percent were granted that status. The FDA has even rejected or revoked approval of drugs already approved in Europe.²⁰

While patient safety is rightly considered the paramount goal, it is important to avoid creating a more drawn-out or inconsistent review process that can stifle innovation. Weighing the need for efficiency against safety concerns is a delicate balancing act, but it's worth remembering that in some cases, delays in bringing breakthroughs to the marketplace can cost lives, too. The approach taken by regulators has far-reaching consequences—not only for the vibrancy of the biomedical industry, but for the millions of patients who are waiting for cures.

The Evolution of the Biomedical Industry

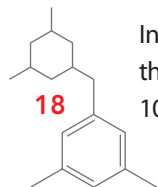
The modern pharmaceutical industry traces its lineage back to European apothecaries, which dispensed medical remedies and served as the forerunners of modern-day pharmacies. By the 19th century, many of these businesses had grown in scope and begun to focus on wholesale production of drugs. Merck, for example, which eventually migrated operations to the United States, actually began as a humble German apothecary shop in 1668 and later scaled up drug production in the 1840s. Other firms such as Germany's Schering and England's Burroughs Wellcome have similar roots.²¹ (Burroughs Wellcome claims to be the first drug company to employ research scientists to develop new therapies.²²) Other companies such as Bayer, Pfizer, and Hoechst germinated around this time, beginning as producers of organic chemicals and dyes.

As pharmaceutical chemistry and pharmacology became formal disciplines, these companies began working with academic research labs, and a new business model was born. Building on a scientific breakthrough made in the 1880s, Germany witnessed its first academic-to-industry technology transfer with the commercialization of a diphtheria serum.²³ In the late 19th and early 20th centuries, groundbreaking discoveries such as insulin and penicillin propelled the industry forward. A Bayer chemist synthesized aspirin, and the company soon commercialized the “wonder drug” beginning in 1899.²⁴ German and Swiss firms were the world's first major pharmaceutical manufacturers, and European countries refined the tradition of a research-based industry.

A similar story was unfolding in the United States. In 1860, John and Frank Wyeth opened a small research laboratory along with a retail drugstore, carving the initial footprint of what would become a pharmaceutical giant headquartered in Collegeville, Penn.²⁵ In 1903, DuPont's experimental station near Wilmington, Del., served as an important catalyst for scientific research, eventually leading to the establishment of one of the world's first industrial medicine facilities three decades later.²⁶ In addition to early pharmaceutical labs, the founding of several prestigious hospitals laid the cornerstone for what would eventually become a dominant health-care hub in the Greater Philadelphia region.

Even though the United States was developing its own sophisticated pharmaceutical industry in centers like Philadelphia and Boston, Europe maintained a strong legacy advantage that lasted well into the 1980s, leading in terms of the number and value of new drug molecules produced. In 1986, Europe invested US\$4.8 billion in R&D, while the U.S. invested \$3.9 billion, representing a gap of 24 percent.²⁷

In 1980, eight out of the top 10 drugs were discovered in Europe. But by 1989, after more R&D had begun to shift into the U.S., four U.S. firms (Merck, Bristol-Myers Squibb, American Home, and Johnson & Johnson) ranked among the top 10 pharmaceutical companies as measured by global sales, accounting for 44 percent of sales among the top 10.²⁸



Europe's heavy investment and extensive infrastructure, including well-established research and distribution pipelines, had kept its pharmaceutical and device companies on top for decades. But now the ground was shifting, due to the lack of a unified European market, groundbreaking scientific discoveries that fell outside the traditional reach of European firms, and significant changes in the U.S. regulatory system and patent laws.

The molecular biology revolution that began in the 1970s fundamentally altered the landscape of drug discovery and development. Recombinant DNA technology allowed an upstart American company to pioneer the birth of a new industry. In 1976, Genentech, headquartered in San Francisco, was founded to take advantage of advances in large molecule drug development. Europe had actually been ahead of the U.S. in this promising research area. But significant regulatory differences between the U.S. and Europe, the size of the U.S. market, and Europe's difficulties in commercializing research by smaller firms and universities left the U.S. industry better positioned to capitalize on the opportunities created by biotech.

While the U.S. was taking a leap forward in terms of a robust R&D infrastructure and new breakthroughs, the output of European firms declined. Due to the rising cost of R&D to meet regulatory requirements, increased use of price controls, delays in reimbursement, limitations on access across Europe, and the rise of biotechnology, Europe watched its global leadership erode by the end of the 1980s.²⁹

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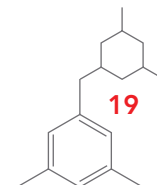
New Chemical Entities and Drug Approvals

By the 1990s, European firms typically held older product lines, while U.S. companies took the lead in producing wholly innovative "new chemical entities" (NCEs). Germany introduced an average of seven NCEs each year from 1985 to 1989, but that number had fallen to an average of only three per year by 1995-1999. The comparable U.S. averages for NCEs introduced in those two periods increased from 27 to 34. Germany's percentage of the global market dropped from 11.75 percent during 1985-1989 to 3.33 percent in 1995, while the U.S. increased its share of world sales from 42 percent to 59 percent over the same period.³⁰

Table 6: New chemical entities
By headquarter country of inventing firm

	1971-1980		1981-1990		1991-2000		2001-2010	
Country	NCEs	% total	NCEs	% total	NCEs	% total	NCEs	% total
U.S.	157	31	145	32	75	42	111	57
France	98	19	37	8	10	6	11	6
Germany	96	20	67	15	24	13	12	6
Japan	75	15	130	29	16	9	18	9
Switzerland	53	10	48	11	26	14	26	13
U.K.	29	6	29	6	29	16	16	8
Total NCEs	508		456		180		194	

Sources: Arthur Daemmrich, "Where Is the Pharmacy to the World? International Variation and Pharmaceutical Industry Location," Harvard Business School Working Paper, 2009; Milken Institute.



Europe lost ground as a research base as its firms transferred large portions of their R&D operations to the U.S., where they found a more favorable environment for pharmaceutical innovation. In 1990, the global research-based pharmaceutical industry invested 50 percent more in Europe than in the U.S. But by 2006, investment in the U.S. was 40 percent higher than in Europe.³¹

Table 7: New Drug approvals in the United States
By headquarters of sponsoring company

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
U.S.	52	38	34	31	30	26	24	21	22	21	21	24	24
U.K.	22	19	16	13	14	16	26	28	31	25	25	20	11
Germany	5	5	5	5	4	4	3	5	4	3	3	2	1
Switzerland	12	10	9	7	9	8	7	5	6	6	6	7	7
France	4	3	2	2	2	1	2	1	1	1	1	1	1
Japan	3	4	4	4	3	1	2	3	2	2	2	2	4

* 3-year moving average

Sources: Arthur Daemrlich, "Where Is the Pharmacy to the World? International Regulatory Variation and Pharmaceutical Industry Location," Harvard Business School Working Paper, 2009, p.7; Milken Institute.

Table 8: New Drug approvals in the European Union
By headquarters of sponsoring company

Country	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
U.S.	8	9	9	15	15	14	10	8	12	16	16	20	19
U.K.	4	3	6	6	6	4	4	3	5	10	10	12	11
Germany	3	3	3	2	3	3	3	3	3	4	4	5	6
Switzerland	3	3	4	4	4	3	4	3	4	4	4	5	10
France	3	4	3	4	3	3	3	3	5	5	5	5	5
Japan	0	0	1	1	2	1	1	0	1	2	2	2	3

* 3-year moving average

Sources: Arthur Daemrlich, "Where Is the Pharmacy to the World? International Regulatory Variation and Pharmaceutical Industry Location," Harvard Business School Working Paper, 2009, p.7; Milken Institute.

As a result of these shifting global tides—and in response to the vast potential sensed by the market in the new frontiers of biotech—the last few decades have seen a wave of mergers, acquisitions, and buyouts. Since small European biotech startups were struggling to successfully commercialize new discoveries, many larger firms on the continent decided to play catch-up in this field quickly. Instead of taking years to build their own capacity, they bought out innovative U.S. biotech firms with promising pipelines or embarked on joint ventures with them. Even Genentech, the biotech pioneer that started it all, was eventually acquired. (Roche Holdings, headquartered in Switzerland, acquired a majority stake in Genentech in 1990, and bought out full ownership in 2009).³² The major U.S. pharmaceutical firms, not to be left out of this trend, similarly snapped up promising biotech ventures. And the action was not limited to biotech: The entire biopharmaceutical industry began a move toward consolidation and mega-mergers. The resulting multinational giants hoped to benefit from economies of scale, more powerful research capabilities, and expanded drug portfolios.

But M&A was not the only strategy companies undertook to respond to capital and regulatory challenges. Firms also diversified their portfolios and expanded their focus on diagnostics, consumer health, and other capabilities. In addition, some large biopharmaceutical companies developed their own venture capital funding operations to support promising small biotechs.

As multinational conglomerates became the norm, European-headquartered firms increasingly shifted or expanded operations in the U.S., partly to gain access to a huge and lucrative market and partly to reap the benefits of product development under the FDA approval process. In the U.S., European and other companies could adapt their products and processes to meet consumer demand while taking advantage of production-related R&D, access to cutting-edge researchers, proximity to clusters of innovation, access to private/public funding, a favorable regulatory environment, and a free market.

While fundamental changes were sweeping through the pharmaceutical business, important developments were also under way in the field of medical devices and diagnostics. In 1976, the U.S. passed the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, allowing the FDA to establish procedures and safeguards governing the introduction and usage of a broad class of medical devices.

Beginning in the 1980s, the medical device industry experienced rapid growth due to the introduction of a number of innovations forged in the U.S., led by high-resolution imaging (notably radiographic and fluoroscopic units). Recognized as the largest consumer and producer of medical devices in the world, the U.S. receives up to half of its medical device revenues from abroad.³³ By 2008, 12 of the top 20 medical device companies by sales revenue were headquartered in the U.S.³⁴ Sales in the U.S. medical device industry were estimated at \$95 billion in 2010, accounting for half the world market,³⁵ while R&D spending among medical technology firms in the U.S. was twice the national average.³⁶ Higher rates of R&D investment such as this obviously create a more favorable environment for innovation to evolve at a more rapid pace.

The U.S. is home to many prominent medical device clusters, namely Minneapolis, Los Angeles, and Chicago, and Boston.³⁷ Attracting sizeable VC investment and offering solid concentrations of R&D infrastructure, these regions provide key competitive advantages for up-and-coming companies and entrepreneurs. Given the aging of the U.S. population, future opportunities are abundant—and more critical than ever.

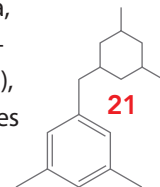
U.S. Competitive Advantages

A nation's biomedical industry cannot be viewed solely through the prism of the results achieved by individual firms. It is shaped in crucial ways by a broader set of institutions, market conditions, infrastructures, and government policies that influence those companies' strategies. The U.S. industry has been fostered by favorable intellectual property policies; government funding for basic research through the NIH, which has helped to build a strong STEM workforce; a competitive free market for innovative products; and the ability to access robust capital markets. Another major factor was the foresight of the federal government in adopting policies that support the connection between research and entrepreneurship, helping universities commercialize their discoveries in the marketplace. We will examine some of these advantages in the section that follows.

Size of the Consumer Market

The United States enjoys substantial benefits due to the sheer size of its consumer market. As of 2008, the U.S. biomedical product market was almost four times larger than Japan's, which ranked second in terms of total expenditures. Although the rise of the European Union allowed for greater economies of scale, the linguistic and cultural demands of its member nations keep the market more fractured than that in the U.S.³⁸

In 2008, Americans spent \$234 billion on pharmaceuticals and related products. This translates to \$769 per capita, the highest per-capita expenditure among the OECD countries and 25 percent higher than that of the second-highest-ranking country, Canada. On the other hand, Japan, Germany, and France spent \$60 billion (\$471 per capita), \$41 billion (\$501 per capita) and \$31 billion (\$488 per capita), respectively. The growth trend of these expenditures



has dramatically progressed since 1995.³⁹ Market sales of pharmaceuticals equaled 2.1 percent of U.S. GDP (France was second-highest in this measure at 1.54 percent).⁴⁰ In 2010, the U.S. medical device market was the world's largest at an estimated \$94.9 billion.⁴¹

Strength in Human Capital

Innovation is the key to the survival and continued growth of the biomedical industries—and well-educated and highly trained human capital is the driving force behind innovation. In 2006, the United States awarded the largest number of science and engineering doctoral degrees of any country, followed by China, Russia, Germany, and the United Kingdom.⁴²

Boston: A Hub of Biomedical Innovation

One of the world's most successful and renowned biomedical clusters, Greater Boston is home to some of the nation's leading hospitals and medical centers as well as multiple top-ranked universities. Capitalizing on the presence of Harvard and MIT, the region has been able to attract a large flow of life sciences R&D funding and a high concentration of workers with advanced degrees, ultimately creating a vibrant foundation for biomedical companies.

In 1978, Harvard and MIT research led to the founding of Biogen, one of the world's first biotech companies. Three years later, Genzyme grew out of research conducted at Tufts University.⁴³ In 2002, Novartis chose Cambridge as the headquarters of its global research operations (Novartis Institutes for BioMedical Research; NIBR), no doubt attracted by the wealth of talent concentrated here.⁴⁴

Helped along by investors and entrepreneurs, many other biotech companies have evolved out of this formidable research base. Venture capital investment in Boston's biopharmaceutical industry tripled between 1995 and 2000.⁴⁵ A 2010 MoneyTree Report from PricewaterhouseCoopers and the National Venture Capital Association showed New England attracting nearly one-fifth of total biotech VC funds.

Capitalizing on the presence of Harvard and MIT, the region has been able to attract a large flow of life sciences R&D funding and a high concentration of workers with advanced degrees, ultimately creating a vibrant foundation for biomedical companies.



The United States has built excellent biomedical science research competencies at its universities and research institutions, which are able to obtain funding from both federal and industry sources. When university R&D can be leveraged for commercialization in the private sector, the partnerships can be beneficial to both parties. Funding from commercialization enables an institution to further its research agenda and help recruit talent, while the biomedical industry can expand the scope and depth of its research with the help of outside experts, often at much lower cost.

The depth of a region's talent pool determines its ability to attract large corporations and small firms alike. Physical proximity to top universities and research institutions allows corporations to tap into the specialized human capital they need to build their workforces. Together they form an ecosystem that provides fertile ground for biomedical innovation.

According to the QS World University Rankings 2010, the United States has seven of the top 10 schools in the world for life science and biomedicine programs.⁴⁶ Harvard ranks No. 1, with MIT at No. 8; together these institutions form the cornerstone of a major life sciences cluster in the Boston metro area. Stanford and UC Berkeley rank 4th and 5th, respectively, fostering another cluster of innovation in the San Francisco Bay Area.

Table 9: QS World University Rankings 2010

Life sciences and medicine

Rank 2010	Rank 2009	School	Country	Score
1	1	Harvard University	U.S.	100
2	2	University of Cambridge	U.K.	92
3	3	University of Oxford	U.K.	82
4	4	Stanford University	U.S.	75
5	5	University of California, Berkeley	U.S.	70
6	7	University of Tokyo	Japan	66
7	6	Johns Hopkins University	U.S.	66
8	8	Massachusetts Institute of Technology	U.S.	64
9	9	Yale University	U.S.	63
10	18	University of California, Los Angeles	U.S.	60
11	17	Imperial College London	U.K.	58
12	12	University of California, San Diego	U.S.	57
13	20	National University of Singapore	Singapore	54
14	13 (tie)	University of Melbourne	Australia	53
15	22	University College London	U.K.	53
16	11	University of Toronto	Canada	52
17	34	University of Edinburgh	U.K.	50
18	13 (tie)	Kyoto University	Japan	50
19	15	University of Sydney	Australia	49
20	16	University of British Columbia	Canada	49

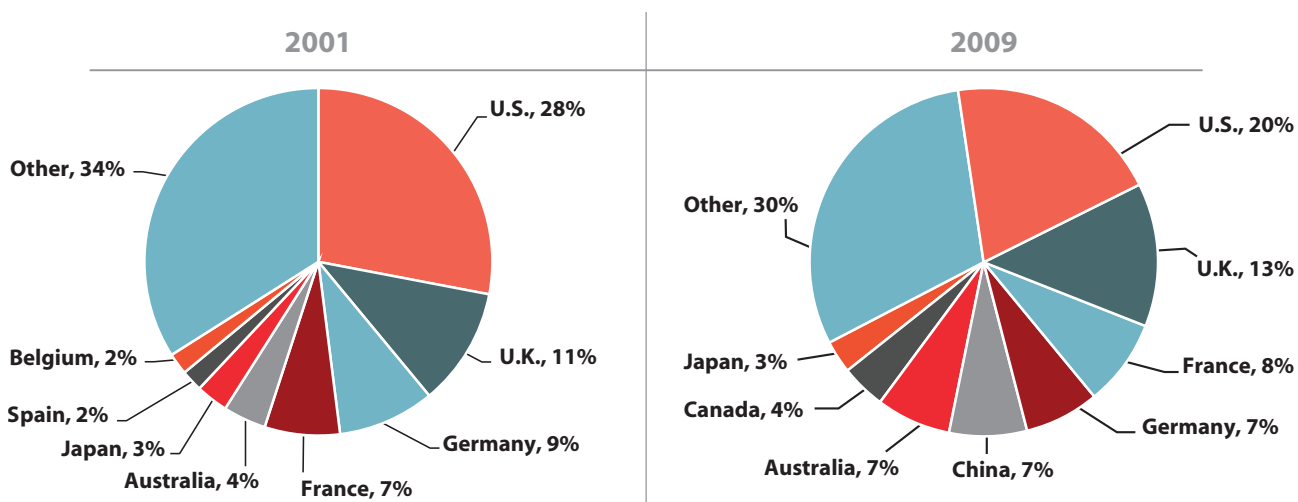
The clustering effect has taken hold in the U.K. as well. Oxford, Cambridge, and Imperial College of London, which are located in close proximity, have exceptional programs in the life sciences, as the rankings show. Public-private collaboration first initiated decades ago to build on this strength has borne remarkable fruit. In fact, London and Cambridge currently represent 60 percent of the U.K.'s life science industry, boosted by the presence of four of the nation's five Academic Health Science Centres.⁴⁷ With the University of Cambridge as its primary research anchor, the region is home to more than 30 research institutes and universities, 20 multinational biopharmaceutical firms, and four hospitals involved in biotech research.⁴⁸ Infrastructure is in place to assist startups, including the Babraham Institute's "Bioincubator" and UKBI.⁴⁹

In terms of converting research into viable economic output, however, the U.S. has held a significant competitive advantage over the last couple of decades. Comparing Boston to the London-Cambridge cluster reveals that despite similar amounts of research investment, Boston has created relatively higher economic value.⁵⁰ The lead, however, is beginning to narrow as other countries have learned valuable lessons from the U.S.

The excellence and prestige of U.S. universities is reflected in the large numbers of foreign students who flock to study here; they accounted for 30 percent of the graduate degree enrollment in 2008. Foreign students enrolled in U.S.-accredited institutions increased by 45 percent from 1999 to 2008, surpassing domestic enrollment growth of 23 percent during the same period. The trend toward enrollment in science and engineering fields has been increasing in general.⁵¹ More flexible labor laws in the U.S. have encouraged free flow of foreign students and talent in STEM fields.⁵² The resulting talent has created a rich ecosystem for entrepreneurial investment that has given rise to an array of startups focused on biotech and medical devices.

Although the pool of international students and highly skilled workers has greatly expanded over the past two decades, global demand for their talent is increasing exponentially. Universities and research institutions in various countries increasingly compete for the best foreign students. The general trend of migration flow has long been from Europe and Asia to the United States. Today, although the U.S. remains the destination of the largest number of foreign students worldwide (for both undergraduate and graduate), the trend has been slowing. Its share of foreign students worldwide decreased from 28 percent in 2001 to 20 percent in 2009.⁵³

Figure 3: Global destinations for international students at the post-secondary level, 2001 vs. 2009



Sources: OECD; Atlas of Student Mobility, Institute of International Education.

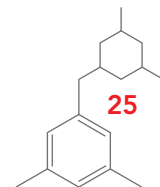
Outstanding U.S. research universities still attract the world's top talent, but that advantage is starting to erode. The direct benefits to the United States from the presence of foreign graduate students, particularly in the life sciences, are tied not only to their ability to acquire student visas and financial aid during their graduate work, but also to their ability to obtain work visas when they have completed their degrees. Many foreign-born scientists stay and work here after their training is complete. But in recent years, the difficulties of obtaining visas combined with increased opportunities at home (especially for Indian and Chinese scientists) have caused significant numbers of foreign skilled workers to return to their nations of origin rather than remaining in the U.S.⁵⁴ Meanwhile, countries such as the U.K., Canada, and Australia are specifically reshaping their immigration policies to attract and retain the best and brightest.⁵⁵ In fact, in Canada, 36 percent of immigrant visas were issued to those classified as "skilled workers," as compared to only 5.6 percent in the U.S.

Developing a strong workforce is not simply a matter of attracting foreign students. It's also imperative to shore up science education in K-12 systems and at the university level so the United States can develop and train homegrown talent. But public schools are increasingly falling short in this area, and budget cuts will only exacerbate the problem. In 2010, the OECD released international rankings based on testing 15-year-olds for educational attainment in math, science, and reading; the U.S. came in 25th in the math and 17th in science, while students in China's Shanghai district topped the rankings in all subjects.⁵⁶ While the absolute number of STEM degrees (over the last 40 years) has climbed in the U.S., it has actually declined as a share of all degrees.⁵⁷ Furthermore, the U.S. has one of the lowest ratios of STEM to non-STEM degree attainment in the world. According to the 2008 CRS Report for Congress, China's proportion of STEM degree production stood at 52.1 percent versus only 16.8 percent in the U.S.⁵⁸

Advantages in Research and Development

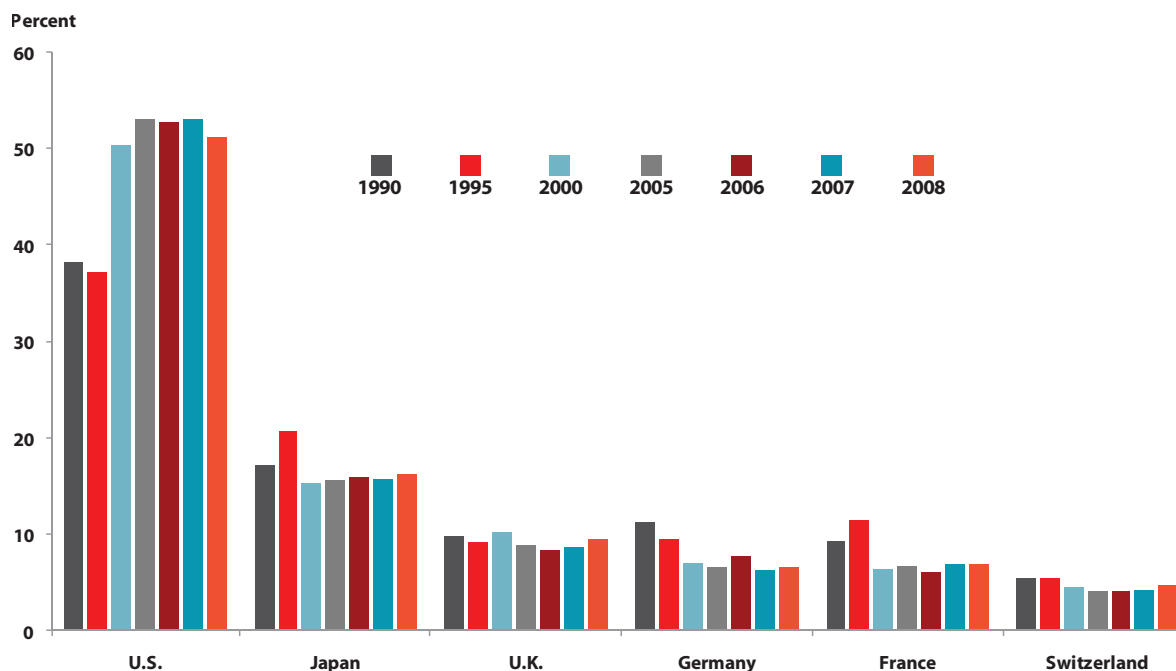
R&D for treatment and cures is the cornerstone of the biomedical field. The ability of a country to attract and maintain high levels of R&D expenditures is widely considered a reliable indicator of its innovation capacities. A nation with a better R&D infrastructure has the comparative advantage when it comes to attracting biomedical firms and a talented, educated workforce.

In some nations, research is largely driven by the public sector. But the U.S. has maintained tremendous levels of biomedical R&D investment from *both* the public and private sectors domestically, and has also managed to attract research assets and investment from foreign firms. U.S. R&D expenditures continue to outpace those of other leading nations, including Germany, France, Switzerland, and Japan. Even during 2010, hampered by the effects of a deep recession, U.S. pharmaceutical and biotech companies invested a record \$67.4 billion in R&D—an increase of more than \$1.5 billion from 2009.⁵⁹ The National Science Foundation found that the pharmaceuticals and medicines fields invested the greatest amount per R&D employee among all industries.⁶⁰



As the chart below indicates, the U.S. accounted for 50 percent of global pharmaceutical R&D over much of the past two decades.

Figure 4: Share of total pharma R&D spending of key countries, 1990-2008



Sources: National trade associations; U.K. Ministerial Industry Strategy Group/Association of the British Pharmaceutical Industry report (2009).

The U.S. also leads in R&D investment in the medical devices. In the 1990s, it directed an average of 8.3 percent of its share of sales into R&D.⁶¹ In the earlier part of the following decade, R&D expenditures comprised 10 to 13 percent of total sales, compared to about 8 percent in both the EU and Japan.⁶²

In addition to the private sector's own research efforts, academic research institutions play a major role in pushing forward biomedical R&D in the United States. U.S. universities attracted \$55 billion in R&D for science and engineering fields in 2009, recording an increase of 5.8 percent compared to 2008. The U.S. federal government continues to be the largest source of academic R&D funding. However, its share of universities' total R&D funding dropped by 6 percentage points, from 64 percent in 2005 to 58 percent in 2009, as the federal government struggled to restart the U.S. economy.

The NIH funds much of the basic biomedical science in the U.S., and in recent years, more translational research. Congress doubled the NIH budget between 1998 and 2003, but since 2004, NIH funding has declined in real terms (excluding the \$10 billion appropriated to NIH in 2009 for short-term stimulus under the American Recovery and Reinvestment Act); it stood at \$31.2 billion in nominal terms in 2010. Other countries have been increasing public-sector support of biomedical research, while U.S. public funding has remained flat or declined.⁶³

Among all science and engineering fields, the life sciences attract the lion's share of academic R&D funding in the U.S. (\$32.8 billion in 2009). The subfields of medical and biological sciences continue to account for over half of all R&D expenditures with \$18.2 billion and \$10.2 billion, respectively.⁶⁴ However, the share of university

R&D stemming from the private sector or industry has recently been on the rise. In fact, based on current data from the NSF, industry-funded academic R&D climbed 11.6 percent between 2008 and 2009.⁶⁵ While historically, nearly three-fourths of academic funding from all sources has gone to basic research, the proportion of applied research and development has recently been trending upward.⁶⁶

The share of total business R&D expenditures funneled into biotechnology R&D indicates the growing focus on this cutting-edge field. In the U.S., biotech R&D accounts for 10.4 percent of all business-sector R&D. The next-largest shares are posted by France (9.0 percent), Switzerland (8.6 percent), Sweden (5.4 percent), and Germany (5.4 percent).

The relative productivity of R&D activity, derived by comparing the share of patents to share of R&D expenditure, is a metric used to determine a country's competitiveness. By this measure, the U.S. has been the most productive nation in the world, as shown by the ratio of its proportion of world-first patents filed for marketed new molecular entities to its proportion of global R&D spending.⁶⁷

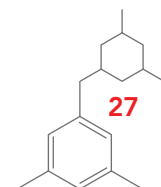
The U.S. has been the most productive nation in the world in terms of its ratio of world-first patents for marketed new molecular entities to its proportion of global R&D spending.

Taking a look specifically at biotechnology patents provides an indication of where biomedical innovation is taking place at a more accelerated pace. According to the most recent data compiled by the OECD, the U.S. accounted for 41.5 percent of all biotechnology⁶⁸ patent applications, followed by the European Union and Japan, at 27.4 and 11.9 percent, respectively. The U.S. lead was largely driven by innovations coming out of the San Francisco Bay Area, Boston, New York, Washington, D.C., and San Diego. Combined, these five regions comprised more than one-fifth of all international applications in biotechnology.⁶⁹

Table 10: Biotechnology patents
Top 10 regions, 2004-2006

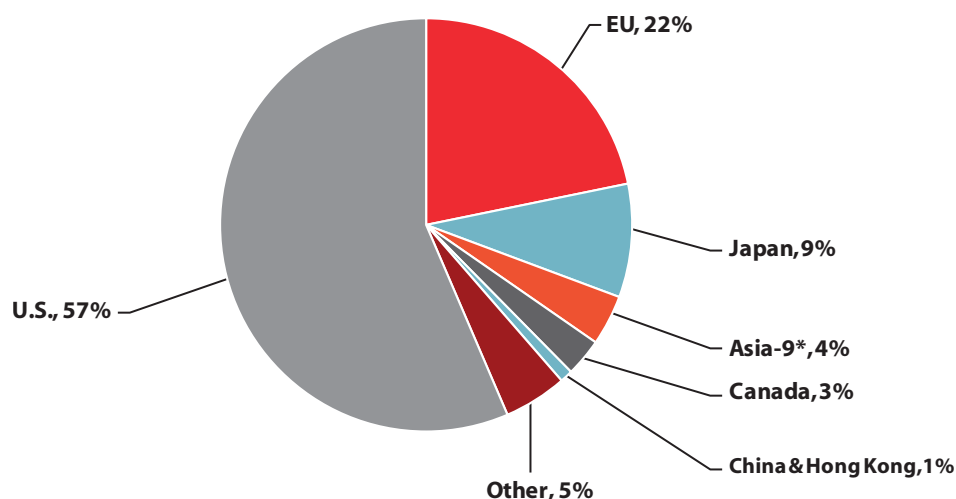
Region	Country	Biotechnology patents	Share (%) in total
San Jose-San Francisco-Oakland	U.S.	1,510	5.5
Boston-Worcester-Manchester	U.S.	1,422	5.2
New York-Newark-Bridgeport	U.S.	1,090	4.0
Washington-Baltimore-Northern Virginia	U.S.	811	3.0
Tokyo	Japan	729	2.9
San Diego-Carlsbad-San Marcos	U.S.	782	2.9
Los Angeles-Long Beach-Riverside	U.S.	613	2.2
Philadelphia-Camden-Vineland	U.S.	587	2.2
Nordrhein-Westfalen	Germany	506	1.9
Hovedstadsregionen	Denmark	454	1.7

Sources: OECD, Patent and REGPAT databases (2009); EPO Worldwide Statistical Patent Database (2008).



Denmark, Belgium, Canada, and Singapore have the highest concentrations of biotech patenting activity. In Denmark, 15.7 percent of all patents applications are in biotech, more than three times higher than the world share.⁷⁰ More recent patent data shows that as of 2008, the U.S. accounted for 57 percent of biopharmaceutical patents. Other countries, recognizing the relative importance of this field, are placing new emphasis on biomedical innovation. In China and the Asia-9 countries, the share of biopharmaceutical patents grew from 1 to 5 percent between 1998 and 2008.⁷¹

Figure 5: U.S. biopharmaceutical patents by location of inventor, 2008



Source: NSF, Science and Engineering Indicator (2010), Archstone Consulting.

* Asia-9 includes India, Indonesia, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam.

Collaboration Between Business and Universities

Bi-directional collaboration between academia and business sets the U.S. biomedical ecosystem apart from its international competitors. A balanced mix of excellence in basic research from universities combined with applied R&D expertise from biopharmaceutical firms provides a platform that accelerates drug discovery and development.

The U.S. government has played direct and indirect roles in creating this productive environment—most crucially by allowing universities and scientists to share the revenue generated by the products of their research. One of the most significant by-products of this collaboration has been the development of biotechnology clusters near top-ranked universities and research centers in the United States, as mentioned earlier in this section. Although a few examples of such geographical concentrations exist in Europe and Japan, these pockets of innovation are still largely an American phenomenon, facilitating the pooling of human capital, investment capital, and R&D assets.

Realizing the immense economic returns that can emanate from a regional cluster, individual U.S. states are aggressively implementing a range of policies to support innovation and R&D investment. Despite fiscal challenges, states are using various R&D tax credits to incentivize early-stage investment, often targeting angel investors and other individuals who invest in early-stage venture funds.⁷² In addition, 34 states exempt sales tax for biomanufacturing equipment used in R&D; others, including New Jersey, New Mexico, and Rhode Island, even provide exemptions targeted to specific bioscience firms.⁷³ With the intention of stimulating growth and enhancing their

R&D capacities, states are continually investing in life-science initiatives centered on their universities and key research institutions.⁷⁴

The highly successful relationship between academic and business research in the biosciences is a direct outgrowth of key policy decisions taken in the United States after World War II. The character of today's U.S. research university was influenced by the seminal 1945 report "Science: The Endless Frontier" by Vannevar Bush. Its central theme was that continual deployment of new scientific knowledge requires support from the federal government for basic scientific progress and the development of high-quality scientists and engineers. The report recommended forging a partnership among universities, industry, and the federal government rather than attempting to build separate research institutes or academies. This approach has proven to be remarkably fruitful.

Historically, it had been very difficult for universities to patent the results of federally funded projects. But in 1980, Congress passed two bills that opened up the transfer of publicly funded intellectual property to private firms: the Stevenson-Wydler Technology Innovation Act, which facilitated the transfer of technologies originating and owned by federal government to the private sector (later amended by the Federal Technology Transfer Act of 1986); and the Patent and Trademark Law Amendments Act, known as the Bayh-Dole Act, which permitted small businesses, universities, and nonprofit institutions to retain title to inventions resulting from federally funded grants and contracts. The Bayh-Dole Act allowed universities and businesses operating with federal contracts to have exclusive control over many government-funded inventions for further development and commercialization. Industry thus became more willing to fund university R&D projects since the results would now be easier to patent.

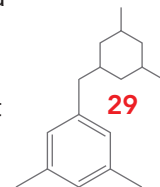
The Bayh-Dole Act of 1980 is often credited with facilitating the success of the U.S. university research model. It was enacted to strengthen U.S. competitiveness in global markets, which depended on more and better basic research and its commercial applications. Subsequently, U.S. universities were able to expand their patenting and licensing activities in the 1980s, contributing to the economic boom of the 1990s.⁷⁵

The U.S. General Accountability Office (GAO) found that by 1987, the Bayh-Dole Act had significantly stimulated business sponsorship of university research, which grew by 74 percent from FY1980 to FY1985.⁷⁶ According to the National Science Foundation, industry support for academic research grew faster than any other funding source until FY2002. It expanded from 3.9 percent of university R&D in 1980 to 7.2 percent in 2000 (though industry support dropped to 5.2 percent of academic R&D by FY 2008, due to the increasingly challenging economic environment).⁷⁷

Prior to 1981, U.S. universities filed fewer than 250 patents annually.⁷⁸ But by 1996, universities patented more than 1,200 patents yearly; by 2004, this number had soared beyond 2,300. Between 2001 and 2006, patent filings in biotechnology increased by 46 percent, while those related to pharmaceuticals and chemicals rose by roughly 42 percent.⁷⁹

The Bayh-Dole Act is considered one of the most inspired pieces of legislation to be enacted in America over the past half-century.⁸⁰ Along with the Stevenson-Wydler Technology Innovation Act, it revolutionized the management and utilization of intellectual property in universities and spurred technology transfer. University researchers were able to overcome previously daunting barriers to entry, license technology, and create spin-off and startup companies. The commercialization of university research breakthroughs by startup firms has become a key driver of operational change in the biomedical industry within the U.S. However, a recent U.S. Supreme Court decision in the case of *Stanford v. Roche* may have undermined the very premise of the Bayh-Dole Act (which granted exclusive ownership rights to universities for their inventions, allowing them to establish industry partnerships that

The Bayh-Dole Act is considered one of the most inspired pieces of legislation to be enacted in America over the past half-century.



would result in licensing revenues in the form of royalties). The case involved an HIV detection test, patented by Stanford researchers but developed by Roche Molecular Systems. The Supreme Court denied Stanford exclusive rights to the technology, essentially granting Roche co-ownership and freeing them of the need to pay royalties.

While some argue that Stanford's defeat in the case was the result of "imperfect language" used in the university's contract with Roche, the decision could have potential implications on universities' ability to further scientific research.⁸¹ Removing the assurances of incentives such as royalties creates more uncertainty in an already complex environment, and hence, could place a drag on university-driven innovation.

Increasing entrepreneurship and the commercialization of research created a new role for universities as engines of economic development. Universities around the world have expanded their mission beyond basic research and teaching to encompass patent development, public-private collaborations, and incubation for startups. Although public funding for high-level research continues to decline, research plays an increasingly important role in industrial processes. University research feeds industrial innovation, and in the United States, it is imperative that university-industry partnerships continue to multiply. While there is a desire for greater collaboration, the reality is that conflicts of interests and disclosures are creating more barriers between academic institutions and the private sector. Firms have found some university technology transfer offices (TTOs) increasingly difficult to deal with. TTOs, which are responsible for advancing commercialization, are often overburdened, and some observers have noted that they can create "bottlenecks" rather than streamlining the process of transferring ideas to the marketplace.⁸²

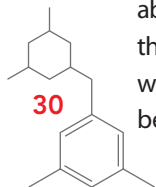
Impacts of Cluster Formation

A given region's success now depends on its ability to translate research into innovations, giving birth to new companies and fueling economic growth. Industry clusters⁸³ and their associated support infrastructure are a powerful force in driving this dynamic, both at the regional level and at the national macroeconomic level. Since knowledge is generated, transmitted, and shared more efficiently in close proximity, economic activity based on new ideas has a high propensity to cluster within a geographic area. Locations with top biomedical industry clusters will be less likely to see the economic benefits escape to other regions.⁸⁴ Furthermore, wealth creation generated through the network of interrelated industries is principally driven through the exports of goods and services beyond that region.⁸⁵

The biomedical clustering effect has distinguished the United States from all other nations, creating an unusually fertile environment for R&D. By effectively leveraging public funding to attract private funding, valuable partnerships and research collaborations have been formed. In dense regional biomedical clusters, strategic partnerships between public organizations (such as universities and institutes) and private firms have fostered cross-disciplinary research of the sort that lends itself to innovation.⁸⁶

As earlier studies conducted by the Milken Institute show, the leading U.S. regions in the life sciences are those where biomedical innovation has created the greatest economic impact. Our examination of outcome-based criteria, including size, performance, and diversity, suggests that the greater regions of Philadelphia, Boston, Raleigh-Durham, New York, and the San Francisco Bay Area are home to the most dominant clusters.⁸⁷

The top clusters provide a robust support network for entrepreneurs, including venture capitalists, high-tech absorptive capacity⁸⁸ and providers of professional services. Given the industry's growing importance, biomedical clusters have also become undisputed engines of economic growth, creating millions of jobs, many of which pay above-average salaries. Many states and localities have targeted the biomedical sector as an important component of their economic development strategies in an effort to add high-wage jobs and build their tax base. When combined with the intangible benefits of better-quality medical care, the benefits of building a strong biomedical industry have become clear to other nations, which are following the same formula and beginning to narrow the U.S. lead.



How California Became a Hotbed of Biotech

California is home to two of the nation's most innovative and productive biomedical clusters: one in San Diego and another in the San Francisco Bay Area. Their rise illustrates the productive interplay between industry and research institutions.

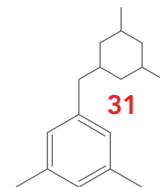
San Diego's first organized life sciences–related research started at the Scripps Institution of Oceanography (SIO); its role as a University of California research lab eventually led to the establishment of UC San Diego in 1961. Researchers here were able to benefit from an opportunity that arose in 1975, when the discovery of monoclonal antibodies by British scientists and subsequent government mismanagement of laboratory IP opened the door for commercial applications elsewhere. By 1978, a team of researchers at UC San Diego (Royston and Birndorf) capitalized on these advances by forming a new venture called Hybritech. The company attracted a robust network of VC investors, enabling them to recruit top talent from surrounding research institutions. Within five years of Hybritech's founding, a number spinoff companies were being formed.⁸⁹

Although the company was acquired by Eli Lilly in 1986, its lasting impact is apparent. More than 175 of San Diego's life science companies can trace their roots back to Hybritech employees.⁹⁰ The region's interlocked and multilayered cluster offers a uniquely entrepreneurial and creative dynamic. Its vast support infrastructure includes the Sanford-Burnham Medical Research Institute, UCSD, The Scripps Research Institute, the Salk Institute, and the Sidney Kimmel Cancer Center, among others.

Similar events in the early 1970s marked San Francisco's rise as the birthplace of biotech. The laboratories of Stanford and UC San Francisco made breakthroughs in recombinant DNA technology. These cornerstone developments in genetic engineering, pioneered by Stanley Cohen and UCSF's Herbert Boyer, created new approaches to diagnosing and treating disease. In 1976, with VC backing, Genentech was born to pursue product development based on these new developments; the firm eventually went public in 1980. Genentech's success led to a flood of interest in the biotech field from venture capitalists and other funding sources.⁹¹

Talent moves fluidly among the large and small firms in a given cluster, bringing with it know-how regarding tech transfer and commercialization. In the case of Genentech, 25 senior managers (accounting for 16 percent of all former senior managers) went on to found another 22 biotech startups. In San Diego, 83 percent of biotech scientists had previous industry experience, compared to only 22 percent in Germany.⁹²

The early 1970s marked San Francisco's rise as the birthplace of biotech. The laboratories of Stanford and UC San Francisco made breakthroughs in recombinant DNA technology.



The Historical U.S. Regulatory Advantage

Regulation and the regulatory process play a much larger role in the biomedical field than in almost any other industry. The biomedical industry value chain is highly structured, and the regulatory review and approval process largely sets the path through which biomedical drugs, devices, and diagnostics move from discovery through development to commercialization.

The efficiency of the process for approving clinical trials is a critical priority for successful drug development. A heavily regulated and bureaucratic approval process may strengthen safety by emphasizing control and standardization, but that approach increases the likelihood of delays in bringing new biomedical products to the market, leading to a major competitive disadvantage for a given country's industry and, in some cases, denying patients access to urgently needed treatments. The goal is to carefully balance the need for efficiency with appropriate concern for patient safety.

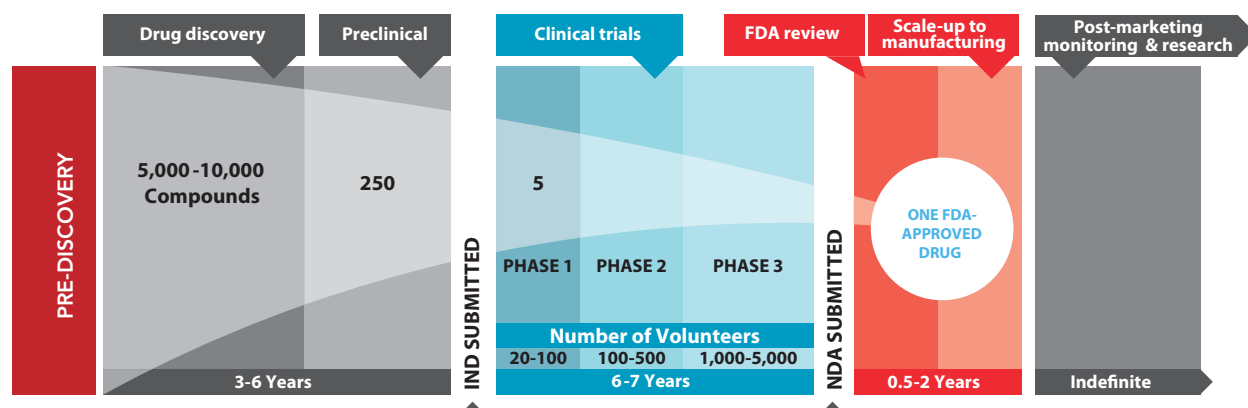
Differences in the European, Japanese, and U.S. regulatory systems shape individual firms' decisions about which market is the most attractive to pursue from a financial perspective—and thus determine where pharmaceutical companies will choose to base their R&D efforts in order to comply with regulatory requirements of that market.⁹³ It's no coincidence that the U.S. has attracted the largest share of biomedical R&D, with only Europe and Japan getting significant pieces of the pie, and the rest of the world receiving a far smaller share.⁹⁴ As we will examine in Part 2, this is starting to change, but for now, the U.S. retains the lion's share of biomedical R&D investment.

Several factors determine where a company chooses to pursue initial regulatory approval for a product: the predictability and efficiency of the approval process itself; the potential sales for the product once approval is granted; and patent protection, which allows the inventing company a sufficient amount of time to retain exclusive control over the product, thus recouping the costs of its research investment.

The regulatory framework in the United States gives the U.S. biomedical industry a strong advantage. Not only does the U.S. have a fairly efficient approval process as compared to other industrialized countries, but it also has a relatively mitigated regulatory regime that offers lower barriers to entry for international firms as compared to much of Europe. U.S. companies have benefited from streamlining the time required to go from discovery of a biotech compound to commercialization. They also benefit from the international perception that FDA approval is the gold standard—meaning that if a treatment clears the regulatory hurdles to be sold in the U.S., it will more easily win approval in international markets.

Figure 6: Pharmaceutical research and development process

Developing a new medicine takes an average of 10-15 years



Source: Pharmaceutical Research and Manufacturers of America (PhRMA).

The efficiency of the approval process rests with the FDA. Like any other regulatory body, it can experience periods of greater or lesser efficiency, activism, and industry feedback. Its approach may shift over time in response to a change in administration, new congressional mandates, or public opinion. Over the past century, the pendulum has swung both ways at various times, as Congress has alternated between expanding the FDA's legal authority in response to public concerns and then tightening its leash in response to pressure from industry. In 1962, for example, the Kefauver-Harris amendments gave the FDA more authority over the manufacturing, effectiveness, and promotion of prescription drugs. But this move resulted in delays in the launch of new drugs, a decline in the number of new drug introductions, and changes in industry structure in the 1960s and 1970s.⁹⁵

After a period of great efficiency in the 1990s, the FDA has steadily increased clinical trial requirements, adding to their costs and complexity. At the same time, the process has become less transparent, increasing uncertainty in the review and approval process. Medical device approvals from the FDA have become even more problematic than drug approvals. In Europe, many devices are approved in half the time it takes for similar approvals by the FDA.⁹⁶ The increasingly complex and unpredictable process of FDA approval discourages innovation in medical technologies. It inhibits startup medical device firms from accessing private capital markets and adds to development costs, as companies often resort to hiring seasoned experts just to navigate the FDA review and approval process. President Obama himself has recognized the extent of FDA red tape and, using medical devices as an example, penned an op-ed in the *Wall Street Journal* announcing plans to rationalize the process.⁹⁷

Table 11: Medical devices approval process

Device class	Application	Clinical requirements	Approval type	Mean time to approval
Class I (Low risk)	510(k)	Preclinical – Proof of good manufacturing standards, correct branding and labeling	Clearance	3-6 months
Class II (Medium risk)	510(k)	Preclinical – In addition to Class I requirements, mandatory performance standards, and post-market surveillance	Clearance	3-6 months
Class III (High risk)	PMA	Preclinical, Pilot trial, Pivotal trial – PMA submitted to CDRH for scientific and clinical review. CDRH determines endpoint of clinical testing and makes recommendation to FDA for final approval decision.	Approval	12-24 months

Sources: FDA Devices Program, Boston Consulting Group Analysis.

As described in the table above, medical devices are generally classified into three categories ranging from low to high risk. The average time for 510(k) products and (Pre Market Approval) PMAs has risen by 45 and 75 percent, respectively, since 2007.⁹⁸ In fact, even before applying for a PMA, an investigational device exemption must be granted by the FDA (since it involves human subjects); this prerequisite process can take a minimum of 14 months.⁹⁹

The FDA's counterpart in the European Union is the European Medicines Agency (EMA), which was established in 1995 as a centralized institution for drug approval of EU member states. Its formation has made the European industry more competitive, conferring some of the same consistency and predictability regarding the approval process that the U.S. enjoys under the FDA.

Pricing Policies

Regulation governs more than just the initial approval of new drugs and devices; it also governs how those products may be sold in the marketplace. In most countries, drug prices are regulated by federal authorities (directly or indirectly). But unlike the EU or Japan, the U.S. does not restrict prescription drug prices (though it does have indirect caps on drug prices through its Medicare/Medicaid reimbursement system). Price controls and other restrictions, such as the lack of an adequate reimbursement system for new drugs, diagnostics, and medical devices, have caused European-headquartered pharmaceutical firms to channel more R&D and investment to the U.S., which accounts for more than half of the world's drug sales and represents a much more profitable market. Traditionally, the U.S. has allowed the market, rather than a centralized government authority, to determine the value of a new technology. The free market has provided a financial incentive for biomedical companies to invest in the development of innovative products in the U.S. However, increasingly restrictive coverage and payment policies in the U.S. are challenging current business models and the ability of biopharmaceutical firms to earn a return on investment that is attractive to investors.

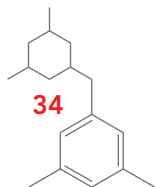
Intellectual Property Systems

Protection of intellectual property is crucial for the biomedical industry. It takes about 10 to 15 years to develop one new medicine, from initial drug discovery to approval. The average cost to research and develop each successful drug is estimated to average \$1.3 billion (Tufts). It is a high-risk business: For every 5,000 to 10,000 compounds entering the R&D pipeline, only one receives approval.¹⁰⁰ After investing in research, development, testing, and approval, companies can only recoup those huge costs and make up the costs of the many failures if they are afforded patents and data protection granting a set period of time in which others cannot use their data. This certainty ensures continued R&D investment as the effective patent life for new medicines averages 11 to 12 years.¹⁰¹

For every 5,000 to 10,000 compounds entering the R&D pipeline, only one receives approval.

Governments play a role in protecting this incentive through the manner in which they protect intellectual property rights. Determining the point at which exclusivity expires and generics can enter the market—along with how closely they can duplicate a given drug—is crucial to the profitability of biomedical firms.

The Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Act) was passed in 1984 to govern the introduction of generics into the marketplace. It was intended to balance the desire for the speedy introduction of lower-cost generic drugs with the need to maintain adequate incentives for biopharmaceutical R&D investment. The legislation helped restore some of the patent terms lost during the lengthy development, clinical testing, and approval process. However, over time, the balance sought by Hatch-Waxman has eroded, with generic drugs comprising 70 percent of prescriptions filled, effective patent life for innovative medicines averaging 11-12 years, and patent challenges occurring earlier and more frequently.

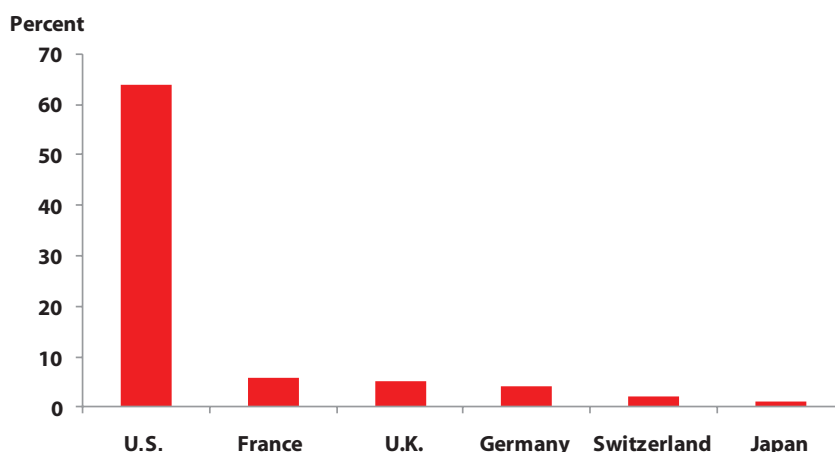


Risk Capital and Entrepreneurial Infrastructure

Venture capital is vital to young and fast-growing businesses, and the biomedical industry requires an unusually large amount of capital for research and development due to the length and intensive nature of the R&D process. The presence of an extensive VC network is an inherent strength of the U.S. biomedical industry.

There is a huge gap between the U.S. and its competitors when it comes to entrepreneurship and access to venture capital. In 2007, total venture capital investment in the life sciences for all 25 reporting OECD countries came to just over US\$8 billion. The United States captured 68.3 percent of the total. The EU members of the OECD accounted for 20.8 percent,¹⁰² followed by Canada and France at 5.7 percent and at 4.8 percent. According to OECD data, the United States had the largest number of active biotechnology firms (3,301 firms), followed by Japan (1,007 firms) and France (824 firms). The 15 reporting countries from the European Union have a total of 3,377 firms.¹⁰³

Figure 7: Share of total life science venture capital, 2007

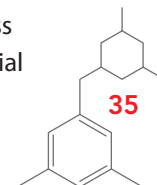


Source: OECD Biotechnology Statistics 2009.

Raising money has been more challenging for European biotech firms; many have struggled to attract VC investment or access the capital markets. Swiss and British biotech firms raised about \$380 million and \$250 million in VC financing in 2009, respectively.¹⁰⁴ That figure is substantially higher in U.S., despite the fact that venture capital placements in the U.S. biomedical industry declined by almost 43 percent from 2007 to 2009, falling to \$6.3 billion.¹⁰⁵

Venture capital was pioneered in the United States in the late 1950s and early 1960s, and it has always been a key ingredient for U.S. technology startups. The hotbed of this activity is Silicon Valley, though there are also concentrations in Boston and New York City. By the end of 2010, Silicon Valley and New England together captured approximately 45 percent of total biotech VC funds in the nation. Of VC dollars going exclusively to the medical devices industry in 2010, Silicon Valley accounted for the largest share at almost 30 percent.¹⁰⁶ San Diego is another prime example of a cluster where venture capital has nurtured numerous biotech startups. The presence of strong VC communities near biomedical clusters is no coincidence. Two of the most successful U.S. biotech firms, Amgen and Genentech, were first funded by venture capitalists.

The most successful venture capitalists investing in this field have become skilled in communicating with biomedical professionals. They work with the founding entrepreneurs to grow young companies. This business model, built on a quintessentially American openness to new ideas, has brought to life a host of entrepreneurial companies with new technologies.



U.S. venture capitalists, however, are inclined to invest at a more mature stage than their European counterparts. According to European Private Equity and Venture Capital Association (EVCA) and Dow Jones, while there was little difference between Europe and the U.S. in the number of lower-value venture capital deals signed annually between 2003 and 2010, the U.S. averaged more than 1,300 deals annually worth more than \$5 million—about six times more than Europe over the same period.¹⁰⁷

The United States has traditionally claimed the lion's share of VC financing, but as other countries develop their capacity, venture capital is more likely to flow to destinations like Singapore, which is aggressively recruiting entrepreneurs and scientific talent.¹⁰⁸ Two of the top five VC investors backing startups in Oxford's biomedical cluster were from the U.S.¹⁰⁹ Financing is one more area in which the U.S. needs to be aware of rising global competition. VC investment in medical technology rose 60 percent in Europe between 2000 and 2009, but declined by 40 percent in the U.S.¹¹⁰ State-level efforts to bolster such investment have fallen victim to the current tough fiscal environment, and regulatory uncertainty has also played a role. Furthermore, China and Brazil now represent the second- and third-largest sources of venture capital, respectively, after the U.S.¹¹¹

Venture Capital in Action

It takes a massive initial infusion of capital to develop new tools for fighting chronic disease. The VC community has invested nearly \$15 billion in cancer treatment and detection over the last two decades. Some key VC-backed innovations include the Doppler ultrasound, minimally invasive biopsies, the PSA test for prostate cancer, MRIs, Herceptin (a treatment for breast cancer), and Avastin (a drug that fights various types of cancer by blocking the growth of blood vessels that feed tumors). Similarly, R&D backed by venture capital has produced breakthroughs in the treatment of heart disease, including angioplasty, aortic aneurysm stent grafts, and atherectomy and minimally invasive bypass procedures. After investing over \$5 billion towards diabetes treatment over the last 20 years, the VC community also backed the One Touch self-monitoring glucose device.¹¹²

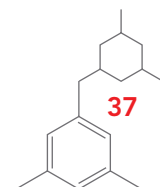
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Tax Policy: U.S. Advantage Lost

U.S. corporate tax rates are higher than those rates in Europe, leading U.S. firms to operate at a disadvantage. In 2011, the U.S. had the second-highest corporate tax rate (39.2 percent) of all OECD countries, trailing only Japan (39.5 percent). Many European nations and other OECD members have been slashing rates over the past 20 years. The OECD average corporate tax rate fell from 47.5 percent in 1981 to 25.4 percent in 2011, undermining the competitiveness of U.S.-headquartered biomedical firms.¹¹³ Other nations with lower corporate tax rates than the U.S. include Switzerland (21.2 percent), the U.K. (26 percent), Germany (30.2 percent), and France (34.4 percent).¹¹⁴ In addition, China cut its corporate income tax rate to 25 percent in 2008.¹¹⁵

Another area of tax policy that bears examination is the R&D tax credit. The U.S. pioneered the idea to spur innovation, and seeing its initial success, other nations have followed suit. Twelve competing OECD countries offered R&D tax credits in 1995, and by 2007, it was up to 20 countries. Although the U.S. initiated this policy, it has not kept pace with other nations. European countries have increased the size of their credits, while Asian competitors have initiated aggressive programs as well. Furthermore, the U.S. has failed to make the R&D investment tax credit permanent, while most other competitors have done so, creating a climate of greater investor certainty. (See Part 2 for a fuller discussion of this issue.)



Part 2

The Changing Global Landscape

Governments and businesses around the world increasingly understand that innovation is a key driver of economic growth, and accordingly, they are taking steps to gain an edge, especially in the life sciences. The U.S. is still the clear leader in terms of general scientific and technological advancements, but innovation is no longer constrained by borders.

The consumer market itself is becoming more global. In 2008, North America accounted for the majority (41 percent) of total pharmaceutical sales, while just 13 percent of the world's total sales were to emerging nations such as Russia, South Korea, India, Turkey, Mexico, Brazil, and China.¹¹⁶ But as these nations continue to create vast middle-class populations, they are opening up new markets with dramatic growth potential. China, for example, is poised to become the world's third-largest pharmaceutical market this year, and is projected to add an additional \$40 billion or more in annual sales by 2013.¹¹⁷

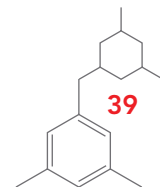
Along with these international market opportunities come new challenges for the U.S. biomedical industry: Emerging nations are not only generating heightened consumer demand—they are also developing their own scientific and technical capacity. The U.S. is already facing heightened global competition that will only stiffen in the years ahead. Not only is Europe reasserting its industry strength, but Asian nations, recognizing the economic benefits of a strong biomedical sector, are quickly building research and manufacturing infrastructure.

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China and India are fast becoming new centers of pharmaceutical R&D. In 2006, 5.5 percent of all global pharmaceutical patent applications credited at least one inventor working in India, while 8.4 percent named at least one inventor in China. These numbers were up fourfold from 1995.¹¹⁸ At present, local pharmaceutical companies in China and India have limited resources and regulatory expertise to develop products beyond phase II,¹¹⁹ but their increased collaborations with multinational firms are rapidly enhancing their abilities to innovate.

The wave of mergers, acquisitions, joint ventures, and research collaborations already discussed in Part 1 of this report has made the biomedical industry more global in nature. Multinational corporations can shift operations across borders or forge international collaborations to take advantage of new opportunities. In recent years, we have seen U.S. companies branching outward (as when Pennsylvania-based Cephalon acquired U.K.-based Zeneus Holdings in late 2005 in order to move into the European oncology market¹²⁰) as well as European companies making deals to expand their footprint in the United States (as with Roche's acquisition of Genentech or Sanofi's acquisition of Genzyme).

Joint ventures are stretching into Asia as well. Japan's Takeda Pharmaceuticals and U.S.-based Amylin Pharmaceuticals have a licensing deal worth \$1.1 billion.¹²¹ India's biggest drug maker, Ranbaxy Laboratories, was acquired by Japan's Daiichi Sankyo for \$4.6 billion in 2008, while another Indian firm, Shantha Biotechnics, was acquired by Sanofi for \$800 million.¹²²



Meantime, as drug development costs continue to mount at home, the major U.S. pharmaceutical firms have seen their business model come under increasing pressure. The average price-to-earnings ratio of six leading U.S. pharmaceutical companies (Abbott Labs, Bristol-Myers Squibb, Johnson & Johnson, Eli Lilly, Merck, and Pfizer) has fallen sharply over the past decade, from approximately 30 in 2001 to 10 in 2011.¹²³ U.S. firms must not only prepare to respond to new competitors, but they must do so when the U.S. environment for innovation is becoming more challenging and other countries are seeking to become more attractive to R&D investment.

Governments around the world are seizing the initiative to grow their respective biomedical industries, and we will detail some of these efforts in the pages that follow. Despite the intensifying global competition, the United States can enhance and regain the advantages that made it the leading country for biomedical innovation if it is willing to put the right strategies in place.

Global Approaches to Building the Foundation of Innovation

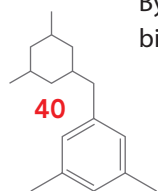
As discussed in Part 1, universities are key incubators of innovation, and in this area, the United States continues to hold a tremendous advantage. In addition to its top-flight research universities, the U.S. benefits from a legal framework that allows innovation to flourish. The Bayh–Dole University and Small Business Patent Procedures Act, as well as the Federal Technology Transfer Act of 1986, support technology transfers from the public to the private sector, facilitating the use of federally funded research for commercial inventions.¹²⁴ Further, the National Cooperative Research Act reduced antitrust restrictions and increased intellectual property (IP) enforcement capabilities.¹²⁵ In the U.S., university research complements robust private-sector R&D operations. Biopharmaceutical firms not only conduct R&D of their own, but support academic research and invest in outside industry R&D activities through licensing and partnerships with other companies. Together, these elements create a fertile ecosystem that developing markets seek to emulate.

China, for example, adopted its first patent and copyright laws in 1984 and 1990, respectively. The country's attempt to join the World Trade Organization spurred the further strengthening of its patent law in 1992 and 2001. China initiated the Act for Promotion of Technology Transfer in 1996, and it was subsequently reinforced in a similar vein to the Bayh-Dole Act to promote technology transfer from universities. In Russia, the state held ownership of all technological innovations until 1991, when the U.S.S.R. Law on Inventions granted exclusive ownership to inventors. Several changes were made subsequently to match its intellectual property rights protection with the WTO TRIP standard (trade-related aspects of intellectual property rights).¹²⁶

The U.S. has a decentralized system that supports increased competitiveness and independent research. Scientists can move fluidly between establishments, transcending academic and private-sector barriers. As a result, the U.S. enjoys a high rate of technological commercialization.¹²⁷

European universities, by contrast, have centralized financing systems that lead to greater hierarchical control. The relative lack of flexibility that results from that structure inhibits the life sciences innovation system.¹²⁸ Similarly, many countries in Asia have developed a more rigid approach to innovation. Although China has boosted scientific innovation through market incentives and decentralization of authority, its universities are still highly structured, with cumbersome bureaucracies and few incentives to support R&D and biotech commercialization.¹²⁹ Limitations on access to capital and intellectual property rights also hinder innovation in China.

By way of comparison, it is useful to look at the model that evolved in Germany, which was slow to make biomedical commercialization a priority, but is increasingly channeling efforts in this area. Though it had



Is the United States Experiencing “Reverse Brain Drain”?

The excellent scientific training available at U.S. universities continues to attract the best and brightest students from around the world. But after their education is complete, the U.S. only benefits if they stay to work here. This talent pool is immensely valuable: More than half of the engineering and technology companies started in Silicon Valley and a quarter of those started nationwide from 1995 to 2006 had immigrant founders. But in recent years, even highly specialized scientists have found it difficult to obtain work visas in the United States, while the opportunities in their home countries are growing more tempting.¹³⁰

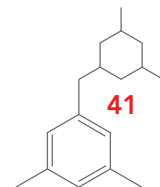
According to the Bureau of Labor Statistics, there were 205,000 biomedical scientists at work in the U.S. in 2008 (not including technicians). Approximately 2,500 faculty members at U.S. research universities were native Chinese, as were approximately 10 to 20 percent of scientists working in U.S. pharmaceutical and biotech firms. But that doesn't mean that the United States can bank on retaining their skills over the long term: Many of these scientists trained in the U.S. but are now leveraging their experience to establish startups and research laboratories in mainland China, drawing on their knowledge of the U.S. industry model.¹³¹

Observers are beginning to notice a trend of “reverse brain drain”: U.S. businesses are no longer the overwhelming long-term destination of choice for the global talent pool. In many cases, workers with valuable skills get their initial training with U.S. universities and companies, then take that experience back to their home countries to bolster U.S. competitors. The United States will need to address its immigration rules for highly skilled workers in order to stem these losses.

In fact, it's not even a given that the best foreign students will always continue to come to the United States for academic training. Several of the world's top universities in the life sciences are establishing campuses in Asia, especially in Singapore.¹³² India, too, is debating whether to ease the process of establishing foreign university campuses.¹³³ One day soon, the foreign students who have traditionally flocked to U.S. universities may be able to obtain a comparable education in their home countries.

But changes in immigration policy alone will not fully address the issue of human capital development in the U.S. There also needs to be a renewed commitment to developing homegrown talent by making STEM education a major priority, from K-12 through post-graduate study. A 2010 collaborative study by the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine showed that U.S. undergraduate students in natural sciences and engineering constituted 16 percent of their respective institutions' enrollment. This stands in sharp contrast with China (47 percent), South Korea (38 percent), and France (27 percent).¹³⁴ The U.S. needs bolder steps to encourage students to embrace these fields and excel.

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top-notch research institutions and long-established pharmaceutical and chemical industries, German R&D had historically been concentrated in manufacturing industries such as automobiles, electronic equipment, and industrial chemicals. While the German Research Center for Biotechnology was created in the 1970s, it wasn't until the 1993 Genetic Engineering Act that regulatory hurdles were reduced.¹³⁵ The launch of the BioRegion competition in 1995 and Germany's version of the Bayh-Dole Act in 1999 promoted commercialization of university research, and helped foster biomedical concentrations around Munich, the Rhein/Neckar Triangle and Rheinland.¹³⁶ By 2004, Garching Innovation GmbH (the technology transfer company of the Max Planck Society) ranked third in the world in research expenditures.¹³⁷ Looking forward, Germany's High-Tech Strategy 2020 seeks to facilitate closer ties between academia and industry, thereby enhancing the biopharmaceutical sector's competitiveness, though negative reimbursement policies could hinder the growth potential.

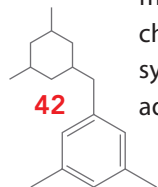
Compared to the long-established mechanisms in the U.S., Japan was relatively late to the game in facilitating university technology transfer. Japan's Law for Promoting University-Industry Technology Transfer was passed in 1998, enabling the establishment of Technology Licensing Offices (TLOs).¹³⁸ The University of Tokyo, Nihon University, Kansai OTT (jointly constituted by Kyoto and Ritsumeikan Universities, among others), and Tohoku Technoarch Co. (constituting Tohoku University and other universities in the Tohoku region) received approvals for the first four offices of technology transfer.¹³⁹ However, the Japan Patent Office is one of the three patent offices in the world¹⁴⁰ forming the Trilateral Patent Offices that support global innovation. Japan now has an extensive network of small- and medium-sized firms that are attractive for larger firms seeking to invest in niche areas.

A Changing Landscape for Approvals and Clinical Trials

The U.S. approval process for drugs and devices (which is governed by the FDA and described more fully in Part 1) has long been considered the world's gold standard. In the 1990s and beyond, the FDA successfully reduced the time needed for testing and approving new therapies. The total average clinical time dropped 10 percent from 1992 through 2007, even as trials became more complex, while average approval time declined almost 60 percent.¹⁴¹ This had a positive effect on innovation: Between 1997 and 2007, U.S. firms nearly accounted for 40 percent of all FDA approvals and slightly over 35 percent of all drugs approved by the EMA.¹⁴² The clarity and efficiency of the process encouraged firms to develop new products here.

But the FDA has recently become more risk averse, and increasing levels of complexity and rigidity have been introduced into the system. According to a study by the Tufts Center for the Study of Drug Development, unique procedures per protocol increased by 6.5 percent between 1999 and 2005. Clinical trials conducted 2003 and 2006 were 69.6 percent longer than those held between 1999 and 2002. This translates to an extension of 460 to 780 days. As a result, the system has become less efficient and less effective.¹⁴³ A more recent report by the same Tufts center found that the median number of procedures per clinical trial increased by 49 percent between the periods 2000–2003 and 2004–2007, with a corresponding increase in total work burden per protocol by 54 percent. Volunteer enrollment and retention decreased by 21 and 30 percent respectively between the same periods.¹⁴⁴

The U.S. approval process tends to be rigid. In the current system, clinical trials require the use of consistent methods, including statistical tests and sample sizes, and preliminary information is kept “blinded” until testing is complete. Given the length of clinical trials, it is common for researchers to discover new developments that could alter the original methods and promote better and faster results. (For example, researchers might discover midway through testing that a different dosage would be more effective.)¹⁴⁵ But they have been hampered from changing parameters midway through the process. Today there is a growing call for speedier expansion of a system of “adaptive trials” that can potentially increase efficiency and effectiveness by allowing for mid-course adjustments. This approach may be especially beneficial when there is high uncertainty involved in the earlier



stages, thereby increasing the success of Phase III trials.¹⁴⁶ This may be applicable to novel therapeutics, diagnostics and devices that have limited prior data and relevant literature for reference. While the FDA is beginning to accept a limited number of adaptive clinical trial designs, the current regulatory regime is not set up for implementation of adaptive trials on a broad basis, thus slowing innovation.

Today there is a growing call for expanded use of “adaptive trials” that can potentially increase efficiency and effectiveness by allowing for mid-course adjustments.

In particular, the advent of personalized medicine cannot be fully realized until the FDA becomes better prepared to deal with the unique challenges of evaluating these treatments and establishes a more tailored approval process. The rigid system currently in place is particularly ill-suited to efficiently evaluate personalized treatments, and may slow innovation in this field.

Illustrating its recent culture of regulatory caution, the U.S. has missed an opportunity (allowed under the FDA Modernization Act of 1997) to speed up approvals for drugs that treat severe illnesses, insisting instead on larger, longer trials. The FDA has also rejected some drugs that have won approval in Europe.¹⁴⁷

Eighty-two innovative drugs, including treatments for ovarian and bone cancer, were submitted for approval in both the U.S. and Europe between 2006 and 2009, but 11 were approved only in Europe. This reflects the greater willingness of other countries to undertake risks in view of the potential benefits. Pirfenidone, for example, is a drug that targets idiopathic pulmonary fibrosis. While the drug was rejected by the FDA, it was available in Japan in 2008 and Europe recently approved it as well.¹⁴⁸ If the FDA becomes notably more stringent than its international counterparts, it may open the door for foreign markets to capture greater investment.

Looking at the geographic concentration of clinical trials provides a general snapshot of the innovative activity taking place in a given region. As of May 2011, the U.S. was far and away the leader in hosting clinical trials, with 54,063 under way. Europe had 27,240, while Japan had 1,840.¹⁴⁹ Normalizing these numbers by population, the U.S. has approximately 174 clinical trials per million people. Europe has 37 and Japan has 15 per million people.¹⁵⁰

Innovation is the driver of ultimate market success, and the U.S. originated more than half of the leading 75 global medicines (or new active substances as measured by worldwide sales) in 2009.¹⁵¹ Clinical trials are a critical step in that process as well as a benchmark that reflects the degree of innovation taking place in a given location. As of early 2011, 50.9 percent of all clinical trials in the world were being held in the U.S.¹⁵² Despite the size of its clinical capacity, the average relative annual growth in the U.S. declined by 6.5 percent between 2002 and 2006. Meanwhile, trial growth, particularly among emerging nations, outpaced the U.S. during that time. In countries like China and India, average relative annual growth increased by 47 percent and nearly 20 percent, respectively.¹⁵³

However, the balance is changing. Other nations, particularly in Asia, are developing the expertise to conduct efficient and cost-effective clinical trials—a trend that is increasingly catching the attention of firms and investors. China and India, for instance, increased their global share of clinical trials three-fold between 2000 and 2006. In 2010, China had 298 drugs in development while India had 219.¹⁵⁴

Clinical trials are a lengthy and expensive step in the U.S., but other countries are finding ways to make trials faster and more cost-effective.¹⁵⁵ As shown below, emerging markets such as China and India can conduct clinical trials for about half the cost of those in the U.S. Russia is even more cost-effective and offers experienced researchers trained in “Good Clinical Practice” standards set by the International Conference on Harmonization. In Russia, 8,000 (or 1 in 86) physicians are involved in clinical trials.¹⁵⁶

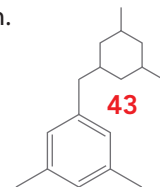
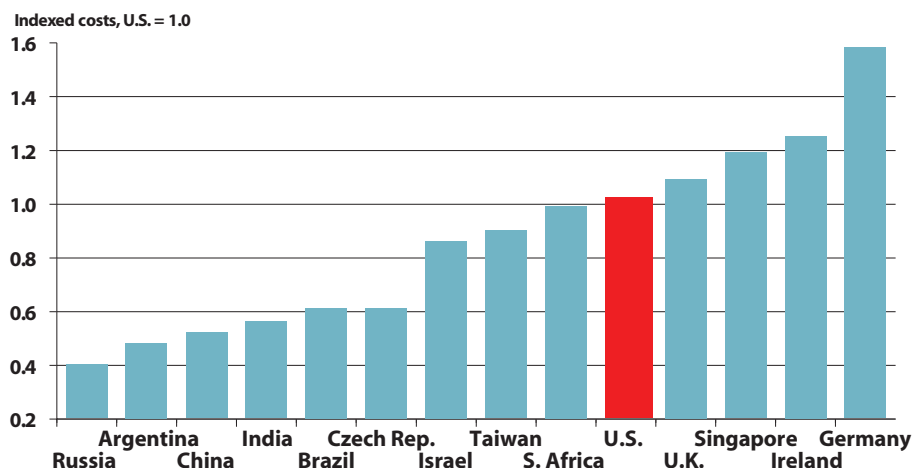


Figure 8: Clinical trial costs



Sources: Salary Expert.com; WDI Database; Economist Intelligence Unit; CBRE Global Markets Rent 2005; A.T. Kearney; Clinical Trial Offshoring.

In addition to cost advantages, these emerging nations also have vast populations that make it faster and easier to enroll the required number of patients in a trial. According to the Association of Clinical Research Organizations, completely enrolling patients in a phase III clinical trial for a cancer treatment would take almost six years in the U.S. However, if companies have access to a global pool of patients, the process could be cut to less than two years.¹⁵⁷

These new international options for clinical trials pose clear benefits to U.S. firms: They can conduct some portions of their testing overseas, reducing their time and costs while gaining valuable knowledge about how to adjust their compounds as they move through the U.S. approval process. An estimated 40 to 65 percent of clinical trials that investigate FDA-regulated products are conducted outside the U.S.,¹⁵⁸ although many of these trials are for comparative purposes.

But taking a longer view, this trend raises a cautionary flag for U.S. competitiveness. Clinical trials require scientific staff, and as other nations develop this specialty, they are amassing high-value experts, infrastructure, and technical capacity. U.S. firms will increasingly have to fight for their share of a finite pool of global talent and investment dollars, and the U.S. economy may lose high-wage jobs. In 1997, according to the Tufts Center for the Study of Drug Development, about 86 percent of FDA-registered principal investigators were based in the United States, but by 2007, that was down to only about 54 percent.¹⁵⁹

While the U.S. and Europe went unchallenged for many years as the sought-after locations for clinical trials, China is increasingly positioning itself as a viable competitor.¹⁶⁰ China has focused on speed and efficiency in clinical trials in an effort to attract collaborations with multinational firms. (However, foreign firms typically need to team up with local partners that have extensive operational knowledge and good working relationships with regulators in order to be successful.) Such collaborations speed outside firms' access to the China market and are quickly strengthening China's own scientific and technical capacity.

To become a full-fledged player in the global market, China is imposing new industry standards. China's State Food and Drug Administration (SFDA) had previously developed its own guidelines, but recently it has been bringing its regulatory process into better alignment with FDA procedures, which are considered the international standard. In 2007, the SFDA amended the Administration of Drug Registration to facilitate

collective decision-making on clinical trial approvals, thereby enhancing the rigor of clinical trials. In addition, this change empowers the SFDA to inspect facilities conducting clinical trials and drug manufacturing. These inspections seek to ensure the authenticity, accuracy and completeness of the process, thereby promising better quality drugs that conform to international standards.¹⁶¹

Shifting our focus to the other large rising Asian economy, India was long considered too burdened with cumbersome regulation to be a viable setting for clinical trials. But in 2005, the Indian government brought its regulatory framework into better alignment with FDA and International Conference on Harmonization standards.¹⁶²

Given its cost structure, its ability to facilitate timely patient recruitment, and its skilled English-speaking workforce, India is becoming an attractive destination for clinical trials.¹⁶³ A McKinsey study projects that by 2013, almost 3,000 clinical trials that conform to “Good Clinical Practices” will be conducted in India annually. Accordingly, substantially more investigators and professionals will gravitate there to support the R&D process.¹⁶⁴ Some of the world’s largest multinational biopharma companies are establishing clinical research capabilities in India.

In 2007, India eliminated its 12 percent service tax on R&D functions involving the development of new chemical entities. It also did away with import duties on investigational drugs. In addition, India has streamlined the import and export licensing process for study drugs and biological study materials as well as the clinical trials application and approval process, trimming months from the regulatory timeline.¹⁶⁵ Regulatory changes now allow for multicenter and multicountry trials if parallel trials are conducted in the U.S., the U.K., Switzerland, Australia, Canada, Germany, South Africa, or Japan.¹⁶⁶

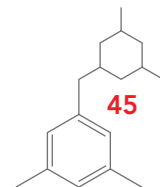
Despite the benefits offered by both China and India as a site for trials, testing and marketing products there also poses some hurdles for multinationals, including various regulatory barriers, the uncertainty of intellectual property protection, and negative pricing and reimbursement policies. All in all, European multinationals are still relocating or establishing R&D operation and sales centers in the United States, which has more robust biomedical clusters, the most lucrative drug market, and a fair IP system.

But the rise of China and India is a story that’s still being written, and the U.S. industry and policymakers will have to adjust accordingly to retain significant global market share in biomedical R&D moving forward. The innovation capacities of these two giants—as well as other emerging nations—continue to gain in sophistication and maturity.

China’s Changing Stance on IP Protection

For many years, multinational firms have been vexed by intellectual property infringement in China. Patent laws were nonexistent until recently, with multiple cases of reverse engineering, copying, and counterfeiting drugs. But coming into line with international standards will enhance China’s global business, and there are signs that the government is ready to ready to enforce stricter protections, particularly with regard to drug manufacturing.¹⁶⁷ In 2006, a Chinese court ruling upheld Pfizer’s patent of Viagra in a lawsuit against Chinese manufacturers of generics, sending a reassuring signal to foreign companies.¹⁶⁸ And at the end of 2010, Chinese officials in trade talks with the United States pledged greater vigilance in cracking down on violations of IP rights.¹⁶⁹ If the government successfully follows through in this area in the years to come, it should set the stage for more international firms to enter the Chinese market.

Chinese officials in trade talks with the United States pledged greater vigilance in cracking down on violations of IP rights.



Global R&D Expenditures

Around the world, governments recognize the economic value of the biomedical industry and have targeted significant spending in this area to boost innovation and nurture local firms.

In Europe, the Innovative Medicines Initiative (IMI) was founded as a public-private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations, an industry group. With a budget of US\$2.7 billion, the IMI seeks to overcome bottlenecks in the drug development process, enhancing the continent's competitiveness in pharmaceutical research and building a more collaborative ecosystem. It focuses on building networks of industrial and academic experts in Europe and supporting joint research projects that improve safety and efficacy, knowledge management, and education and training.¹⁷⁰

Singapore: Innovation as a National Priority

It may be a tiny island nation with a population of only 5 million, but Singapore is staking a claim as a global incubator of innovation. In 2009, it was ranked No. 1 in the world for innovation leadership in an index compiled by the Boston Consulting Group (the United States, interestingly enough, came in 8th).¹⁷¹ More than half the first degrees (equivalent to bachelor's degrees) awarded in Singapore were in science and engineering.¹⁷²

Singapore has quickly raised its profile with business-friendly policies, a commitment to public-private collaborations, strong IP protections, and outstanding science education. The development of its research infrastructure has attracted top pharmaceutical companies from across the globe. The heart of the action is the "Biopolis," an impressive and sprawling high-tech R&D facility that houses both corporate labs and public research institutes in one location to encourage collaboration.

In terms of R&D capacity, Singapore has built seven research institutes and five research consortia in key fields that include genomics, bioengineering, bioimaging, and immunology. It has created Investigational Medicine Units for early-phase trials in public hospitals and the Singapore Clinical Research Institute, which supports later-stage trials. It has also emerged as a major hub for manufacturing: International pharmaceutical and biotechnology companies have invested in dozens of commercial-scale manufacturing facilities that have been vetted by U.S. and European regulatory authorities.

This increased scientific and technical capacity has not gone unnoticed. More than 30 leading biomedical sciences companies have established regional headquarters in Singapore (including Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Genzyme, GlaxoSmithKline, Roche, and Sanofi-Aventis), while more than 50 companies are carrying out biomedical R&D.¹⁷³

Singapore is staking a claim as a global incubator of innovation.



The U.K. launched the Innovation Investment Fund in 2009. Its mission is to support promising technology-based businesses, especially in this life sciences and clean tech. The government has put up US\$231.8 million and is seeking additional capital from the private sector. It hopes to create the largest technology fund in Europe, which could be worth up to US\$1.5 billion over its 12- to 15-year life.¹⁷⁴

In 2010-2011, the British government will invest some US\$2.63 billion in health and biomedical research, primarily through the Medical Research Council and the National Institute for Health Research. The government is supporting various stakeholders to build a US\$927 million U.K. Centre for Medical Research and Innovation.¹⁷⁵

The British government also announced an investment of US\$108 million in Engineering and Physical Sciences Research Council (EPSRC) centers at Southampton, Loughborough, and Brunel universities, bringing researchers and industry together to commercialize academic R&D on innovative technologies. The centers are geared toward attracting investment and growing the medical devices industry, among other high-tech areas, with specific focus on photonics, regenerative medicine, and liquid metals.¹⁷⁶

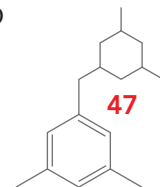
The biotech industry was a specific beneficiary of the French government's fiscal stimulus package. France initiated its Strategic Investment Fund in 2008 in an effort to support the industry as part of the government's fiscal stimulus package. The fund's mission is to invest in high-growth firms, and much of the capital will find its way into the biomedical area, potentially addressing long-standing complaints from French university startups and spinoff firms that it is difficult to secure financing.¹⁷⁷ In Italy, the Italian Institute of Technology (IIT) was established in Genoa in 2003. It focuses on multidisciplinary research emphasizing bio-nanotechnology, neuroscience, automation, and robotics. The Italian government allocated US\$40 million to the IIT in 2004, with an additional US\$80 million each year from 2005 to 2014.¹⁷⁸

Germany's High-Tech Strategy 2020 aims to facilitate closer ties between academia and industry to enhance its pharmaceutical sector's competitiveness.¹⁷⁹ Although no monetary figure has been given, the German pharmaceutical industry association VFA noted that the research strategy will focus on individualized medicine, including new drugs for Alzheimer's disease, diabetes, circulatory and cardiovascular diseases, cancer and age-related chronic pain. The government will also support R&D in genome research and biology to create new therapies and diagnostics.¹⁸⁰

In Scandinavia, there is Innovation Norway, a state-owned development agency that administers grants, soft money, and loans, while Russia has initiated a 10-year national plan to develop special economic zones for innovative biotechnology and several bioparks for biotech development.¹⁸¹ In 2008, Luxembourg initiated a strategic partnership with three renowned U.S. research institutions: the Translational Genomics Research Institute (TGen), the Institute for Systems Biology (ISB), and the Partnership for Personalized Medicine (PPM) to create a hub for molecular medicine.¹⁸²

China is investing aggressively to propel its biomedical industry forward. Opened in 1996, the Beijing Pharma and Biotech Center was launched to promote collaborations between Chinese and foreign companies. Today, in the coastal city of Taizhou, construction continues apace on the new China Medical City, which already houses China's regulatory agency and hundreds of biomedical firms. When completed, it will represent an entirely new city built specifically to cater to the pharmaceutical and biotech industries.¹⁸³

In 2008, the Chinese government approved US\$1.36 billion to support biopharmaceutical R&D in the "Mega New Drug Development Program."¹⁸⁴ China's National Development and Reform Commission initiated 20 venture capital funds in 2009, involving seven provincial governments, with biomedical innovation as a key focus.¹⁸⁵ China's R&D



expenditure was 1.2 percent of its GDP in 2009, with an annual growth of 26.5 percent between 2000 and 2007.¹⁸⁶ In 2009, the Chinese government committed another US\$9.2 billion to stimulate economic growth through new technologies, including biotech.¹⁸⁷

Australia, too, has established multiple programs, including an Innovation Investment Fund, tax incentives, government-sponsored Cooperative Research Centres, and the Global Opportunities Program, which helps Australian biotech companies form global partnerships.¹⁸⁸ On a regional level, the government of Queensland has unveiled programs to support biotech spin-outs, facilitating access to early- and later-stage financing and raising investor education and readiness.¹⁸⁹ In 2009, the Israeli government announced a new public-private life sciences fund to accelerate the growth of the Israeli biotech sector.¹⁹⁰ Since 2005, Malaysia has provided US\$1.4 billion in funding for biotech companies and projects; the government also established the Malaysian Biotechnology Corporation to support R&D and the sector's ongoing development.¹⁹¹

These initiatives represent only a sampling of international efforts to claim a larger piece of the future global biotech industry. But they are instructive to consider as the United States weighs the investments that will shore up its research base and continue its tradition of innovation well into the future. (See Part 1 for a fuller discussion of U.S. research funding models.)

Research and Development Incentives

In addition to public investments in research, a country's broader R&D incentive scheme can facilitate or inhibit innovation and private-sector investment. This set of factors includes both regulatory structures and reward systems.¹⁹² The substantial costs of conducting R&D can be reduced by effective tax credits that encourage firms to undertake the risks involved. Tax policies can stimulate innovation: R&D credit programs have been successful in encouraging industry investment.¹⁹³

In the late 1980s, the U.S. provided the highest R&D tax incentives comparatively on a global scale. But by 1996, Spain, Australia, Canada, Denmark, the Netherlands, and France were offering more generous credits than the U.S. The U.S. further fell to the 16th position in 2004. In 2005, 70 percent of 27 OECD countries offered R&D tax incentives, representing a substantial increase from 50 percent in 1996.¹⁹⁴

By 2008, the U.S. ranked 17th among OECD nations for the generosity of its credit. Japan's R&D tax incentive, for example, once lagged behind the U.S., but now its credit is roughly one-third more generous. The competition is not limited to developed nations. Emerging markets, too, are emulating this policy—and taking it even further. China, India, Brazil, and Singapore now also have programs that go beyond what is offered in the U.S. Every country that has an R&D tax incentive has expanded it during the last decade.¹⁹⁵

In the U.S., the alternative simplified credit (ASC) is a program that was introduced to increase the number of companies qualifying for R&D incentives, thus making the U.S. more attractive to R&D activities. In 2009, the ASC was increased to 14 percent¹⁹⁶ (a 2 percent increase), as a part of H.R. 1424, the Emergency Economic Stabilization Act of 2008.¹⁹⁷ By contrast, Ireland and Canada provide a 20 percent R&D tax credit to encourage innovation, while France has a special program that supports a 40 percent R&D credit on relevant expenditures exceeding the average R&D spending over the two preceding years.¹⁹⁸

In the meantime, the U.S. has kept its own R&D tax credit “temporary” for decades, creating an uncertain investment climate. As of this writing, calls to make the program permanent had not yet been successful, despite bipartisan support for the idea. While the incentive has been periodically renewed, companies must

contend with the possibility that it will someday be allowed to expire, which would upend their investment assumptions. Most other countries with top-tier biomedical industries have made it permanent, which reassures investors.

The U.S. has kept its own R&D tax credit “temporary” for decades, creating an uncertain investment climate.

On the bright side, however, a Therapeutic Discovery Tax Credit was included in the 2010 U.S. health-care reform law. It will bring new therapies to market faster, eventually presenting significant financial opportunities for small biotechnology companies.

As discussed at the end of Part 1, comparatively high corporate tax rates also place the U.S. at a disadvantage. Many competing nations have lower tax rates that make them more attractive to investments. For example, the U.K. announced a reduction of its corporate tax from 28 percent to 26 percent in April. Over the next three years, there are plans to further reduce the rate to 23 percent, making it 16 percentage points lower than the U.S.¹⁹⁹ The growing disparity between the U.S. and other countries makes the U.S. less competitive and thus less attractive to investments in general, including those from the biopharmaceutical industry.

Various other tax structures can also encourage innovation, as can the legal framework of invention ownership. In the U.S., small businesses, universities, and nonprofit institutions can retain their ownership of inventions stemming from federally funded studies.²⁰⁰ The legal framework encourages technology licensing, spin-offs, and startup companies.²⁰¹

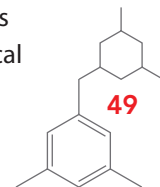
In European Patent Office regulations, inventors get a maximum of 25 percent worth of royalties from the gross sales by companies.²⁰² But other nations have very different ecosystems. By way of comparison, discoveries stemming from joint public-private company research in Japan are likely to be controlled by the firms involved.²⁰³

The Indian government has several incentives supporting biotechnology R&D investments, including fast-track clearance for foreign direct investment, a 100 percent rebate on privately funded R&D expenditures, and a 25 percent rebate if research is contracted in publicly funded R&D institutions.²⁰⁴ Although technologies may be transferred to a third party for commercialization, the third party, exclusively licensed to market the innovation in India, must manufacture the product in India.²⁰⁵ India revised its Schedule Y regulations in 2005, empowering local pharmaceutical companies to conduct first-in-man studies in India, on the condition that the molecule was discovered and developed in India (but, notably, this does not apply to drugs discovered outside India).²⁰⁶ Increasingly, other countries are exploring policies to promote the growth of their domestic industries and to attract foreign R&D investment.

Emerging Fields

The biopharmaceutical field is highly dynamic and rapidly changing. Advances in DNA sequencing are raising hopes that breakthroughs may be on the horizon, especially in cancer treatment. The U.S. has taken initiatives to advance research on the molecular basis of cancer through DNA sequencing, gene expression profiling, and epigenetic technologies in a project called The Cancer Genome Atlas (TCGA), led jointly by the National Cancer Institute and the National Human Genome Research Institute. Recent results on a deadly brain cancer, ovarian cancer, and adult leukemia from TCGA's studies can serve as a basis for effective and personalized treatments.²⁰⁷

There is widespread excitement that innovations in genomics mean that a new era of personalized medicine is at hand. But for this prospect to become a reality, the biomedical industry will have to overcome some logistical



barriers that may impede innovation in this area, not least of which is devising a business model for R&D funding that will work for smaller patient populations. It is also crucial to craft an FDA approval process that can accommodate the complexities of these treatments in a practical and timely fashion; given its nature, personalized medicine requires expedited clearance to be effective.²⁰⁸ Another challenge will be coverage and payment systems for these more tailored treatments.²⁰⁹

Nanotechnology is another frontier with enormous applications. Between 1977 and 2009, 60 percent of U.S. nanotech-related patents were awarded to U.S. inventors or owners. The bulk of the rest were held by innovators from Japan, Germany, and South Korea. Although the U.S. produced the most nanotech-related patent publications in the world (29.7 percent) as measured by residence country of first-named inventor between 1996 and 2008, China came close at 24.3 percent. Japan claimed 14.5 percent.²¹⁰

Human embryonic stem cell technology is another major breakthrough area that promises tremendous hope for curing multiple diseases. However, countries have adopted varying stances on allowing stem cell research. Several countries, including the U.S., Russia, China, India, and nations in Latin America, have restrictive or no policies in place for stem cell R&D. Others, such as Canada, Spain, France, England, Japan, Australia, and New Zealand, have flexible policies.²¹¹ The latter group has had the opportunity to seize the lead in what could be a game-changing field. Some competing countries have attracted U.S. stem cell researchers and investment from U.S. firms. Singapore, for example, has given scientists free rein. In 2006, it announced a \$45 million consortium to be led by American stem cell pioneer Roger Pedersen, formerly a researcher at UC San Francisco.²¹²

For years, the politics swirling around this issue in the U.S. hindered researchers. But their restrictions were somewhat mitigated in 2009 when President Obama signed an executive order lifting the ban on federal funding for human embryonic stem cell research. He also issued a memorandum to “restore scientific integrity in government decision making” and ordered the head of the NIH to review and update guidelines for funding “responsible, scientifically worthy” human embryonic stem cell research. But as of this writing, legal challenges continue to hamper this field in the U.S.²¹³

The EU committed US\$67.8 billion (€54 billion) to stem cell research from 2007 to 2013, but some member nations remain hesitant. Belgium, Spain, Sweden, and the U.K., however, have embraced this new field.²¹⁴ The U.K. prides itself on strong legislative support for the life sciences, including stem cell research. (Embryonic stem cell research and therapeutic cloning are permitted, but reproductive cloning is banned.)²¹⁵ The UK Stem Cell Initiative (UKSCI), a 10-year program comprising policy and funding support, was launched in 2005.²¹⁶ Finland is also in the forefront of stem cell research with its Regea Institute for Regenerative Medicine.

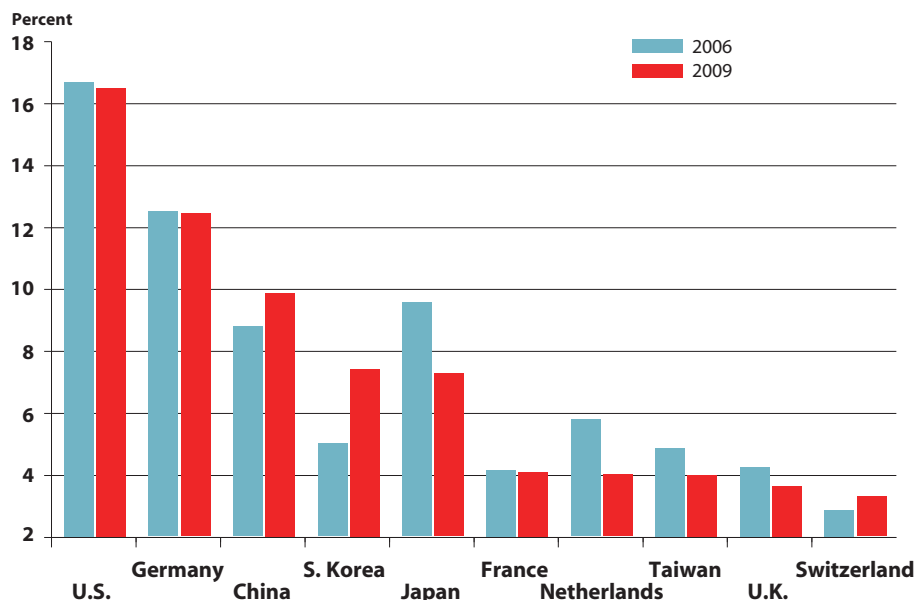
Medical Devices in the Mix

The United States accounted for more than 16 percent of the world’s medical devices exports in 2006 and 2009, with Germany following closely at more than 12 percent in both years. However, countries such as China and Korea are catching up, with increases in their respective shares over this period.²¹⁷

The countries shown in figure 9 have well-established medical devices companies, including Siemens and Braun from Germany, Hitachi Medical Corporation and Toshiba from Japan, and Philips Electronics from the Netherlands. But many of these firms have manufacturing activities in the U.S. In fact, Philips actually produces more medical devices in the U.S. than in Europe. China, Brazil, Korea, Taiwan, and India, with their lower costs of production, are emerging as competitors,²¹⁸ but the U.S. retains a strong legacy advantage.

Figure 9: Share of world medical device exports

Top countries, 2006 and 2009



Source: ITC.

In 2007, the global medical devices market was valued at \$210 billion. The three top markets were the U.S. (43 percent), Europe (30 percent), and Japan (11 percent). Demand is rapidly growing in Asia and Brazil.²¹⁹ The U.S. is home to several of the world's leading medical device companies. Notably, Johnson & Johnson and General Electric have attained estimated 2010 revenues of \$24.6 billion and \$16.9 billion, respectively, in this industry. Other U.S. companies like Medtronic and Baxter also performed very well in 2010, with revenues of \$15.8 and \$10.8 billion, respectively. However, the U.S. faces strong competition in the global market. Siemens (based in Germany), Covidien (Ireland), and Olympus (Japan), also posted impressive revenues of \$16.7 billion, \$9.5 billion, and \$7.8 billion, respectively.²²⁰

Emerging nations have begun to gain a foothold in this market. Malaysia, for example, supplies 80 percent of the world's catheters and 60 percent of its rubber gloves. It has the potential to position itself as a developer, manufacturer, and supplier of medical devices, becoming a hub for Asia.²²¹

China is implementing regulatory reform in order to enter this market. Its State Food and Drug Administration is actively improving medical device supervision and testing, and national testing centers now evaluate multiple devices to increase efficiency. More than 20 provincial-level medical device supervision and testing centers were also opened. Training has been implemented to standardize medical device evaluation.²²² Compliance with product regulations is a challenge in China. In response, the SFDA introduced the "Criterion for Medical Device Quality System Management," which requires medical device manufacturing plants to conduct periodic reviews and have clear quality-control objectives. Manufacturers must also document all design and development procedures for production. Also included is guidance to document design and procedures and to verify performance.²²³ The Chinese government appears to be taking a proactive approach to improve international perceptions of Chinese products.

Overall, the U.S. remains a powerhouse in medical device manufacturing. But other countries are increasingly gaining ground—while medical device approvals from the FDA have become even more problematic than drug approvals. Europe approves many devices in half the time it takes the FDA. The opacity of the FDA's device approval process inhibits startup medical device firms from accessing the capital markets and adds to development costs, as companies must hire seasoned experts just to navigate the approval labyrinth.

Minneapolis has built a cluster that is predominantly driven by its medical devices industry.



Minneapolis: A Cluster Built on Medical Devices

The founding of Rochester's Mayo Clinic in 1889 laid the foundation for future innovation in the medical field,²²⁴ and 3M, the region's venerable manufacturing giant, eventually diversified its product lines and became a major supplier of medical products.²²⁵ The region is also home to the largest medical devices company in the world, Medtronic, which was founded in 1949. In 1957, Medtronic was credited with developing the first wearable, external, battery-operated pacemaker at the request of University of Minnesota surgeon C. Walton Lillehei.²²⁶

Much like its coastal counterparts, the University of Minnesota provides crucial R&D-related infrastructure for the region. Not only did it develop the first bileaflet mechanical heart valve in 1972, but it was also the site of the first open-heart surgery using cross-circulation.²²⁷ Additionally, the combined presence of regulatory expertise and clinical infrastructure in the Twin Cities region provides startups and newcomers with the necessary resources to comply with FDA regulations governing medical devices.²²⁸

Part 3

Recommendations to Retain U.S. Leadership

The United States is still recognized the world over as the leading innovative and market force in the biomedical industry. But the U.S. will have to be nimble in its response to growing competition. The greatest impediment to U.S. biomedical innovation is in underestimating the risk of losing it. Protecting this legacy is not a task that can be left to the talented scientists and technicians working in the lab. Policymakers have an important role to play in creating the type of environment that allows innovation to flourish. Below we outline some concrete recommended steps that would shore up U.S. biomedical leadership.

► Increase R&D Tax Incentives and Make Them Permanent

It takes years of painstaking work and testing to transform a laboratory breakthrough into a new drug—and frequently the results don't pan out. In a business with such heavy R&D costs and such a high rate of product failure, investors risk incurring tremendous losses.²²⁹ Tax incentives, however, can mitigate these risks and possibly encourage investors to commit time and resources to the cause. Research shows that there is a positive relationship between R&D tax credits and R&D activities,²³⁰ as they stimulate growth in R&D expenditures.²³¹ Countries around the world have introduced tax incentives to support R&D investments.²³²

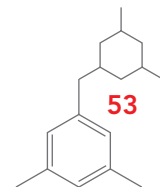
A 2010 Milken Institute study included a simulation analyzing the results if the U.S. were to increase its R&D tax credit by 25 percent and make it permanent. The outcome showed that while the reaction was not immediate, R&D spending grew substantially, indicating increased R&D activities.²³³ If this policy were applied to the biomedical industry, where R&D can represent 20 percent of sales, it would have an even larger proportional impact than in other sectors across the economy.

The U.S., which pioneered this policy, has now fallen behind most other developed nations in the generosity of its R&D tax credit—and its program has been “temporary” for decades, creating uncertainty for investors. Implementing a more globally competitive policy would be a positive step toward sustaining innovation. This requires an in-depth assessment of the adequacy of existing R&D incentives, especially those applicable to personalized medicine.

► Cut Corporate Tax Rates to Match the OECD Average

Innovation knows no borders: Talent and investment dollars are more mobile than ever before, and companies can choose among various international locations when deciding where to base a particular operation. Firms weigh a variety of factors when making that decision, including their potential tax burden—and its current corporate tax structure does not position the U.S. to be globally competitive.

Rates influence investors' decisions on where to place their investments: All other things being equal, countries that impose higher corporate tax rates will lose investments to those that have lower rates. The corporate tax rate in the U.S. is the second-highest among all OECD nations, a factor that can inhibit biomedical investment. We propose revamping the U.S. corporate tax structure to address the issue: Cutting the federal corporate tax rate by 13 percentage points, to 22 percent—essentially matching the OECD average—will increase domestic investment and enhance the accumulation of productive capital.



► **Extend Support for Emerging Biomedical Research Fields**

Technological advances have spurred the development of emerging biomedical fields that have tremendous implications for curing diseases. Extended support for R&D in cutting-edge areas such as nanotechnology and advanced DNA sequencing can strengthen U.S. innovation.

Given the immense potential of stem cells, the next blockbuster innovation may come from the field of regenerative medicine. Several countries in Europe and Asia have already seized the lead in embryonic stem cell R&D. The U.S. has not fully supported this type of research, while other nations have had a favorable regulatory framework in place for a decade. These countries are poised to create scientific and therapeutic breakthroughs from research in regenerative medicine, potentially leaving the U.S. behind.

In March 2009, President Obama relaxed restrictions on embryonic stem cell R&D. Although he released hundreds of millions of dollars to the cause, government-funded projects have yet to reach the clinical trial stage, as legal challenges slowed progress.²³⁴ The U.S. will need additional emphasis in this area to match the momentum established by other countries that have had supportive policies in place for years. Follow-up is needed to create more laboratories and market incentives to facilitate scientific discovery in regenerative medicine and the commercialization of subsequent therapeutic products.

The federal government can address challenges related to the speed at which biomedical innovation moves through the development and approval pipeline by investing in basic science and offering tax breaks to companies investing in translational research. The government can also provide a clear framework by signing international agreements, strengthening intellectual property protections in this field, and producing rigorous technical guidelines for the safety and efficacy of stem cell-based products.²³⁵

Supporting R&D will give the U.S. the best chance of establishing a strong and sustainable foothold in the regenerative medicine arena. Adaptive trial design, the use of surrogate endpoints²³⁶, and ensuring adequate scientific expertise at the FDA and NIH will also help ensure a platform for the applications of these novel technologies. A viable and effective policy framework can facilitate the development of cutting-edge fields that may provide the greatest financial and societal returns in the decades ahead.²³⁷

► **Provide Resources Needed by the FDA and the NIH to Ensure Efficient Regulatory Reviews and Clinical Trials**

The FDA review and approval process has been increasing in complexity and uncertainty, while the agency's international counterparts are improving the efficiency and transparency of their reviews. Emerging companies in the U.S. are especially burdened by complexities in the regulatory system.²³⁸ The broader adoption of flexible practices such as adaptive trials could address the rigidity of the existing process and potentially speed up regulatory reviews, particularly with trials related to emerging fields where there is limited prior research.

The FDA needs adequate resources to hire expert staff and better manage the review process (including the wider adoption of more flexible practices). Its mandate is to ensure the safety of human drugs and biological products—but it is also tasked with bringing high-efficacy drugs to the marketplace as quickly as possible. To ensure that the FDA is positioned to meet the needs of 21st-century science, Congress should support approval of a clean PDUFA reauthorization. The immediate challenge is for the FDA to improve the review and approval process without compromising quality and rigor—and policymakers must provide the agency with the tools it needs to get the job done.

The NIH also plays a pivotal role in the R&D ecosystem. In 2010, investments from the NIH led to an estimated \$68 billion in economic activity and supported 188,000 jobs in the U.S.²³⁹ Ensuring adequate funding for NIH is critical to sustaining basic research investment and developing the U.S. talent pool. Additional funding for translational efforts at the NIH could improve research productivity throughout the scientific community. Rather than waiting for biotech companies to take the lead, academic researchers can partner with NIH, along with the FDA, to speed up the regulatory process.²⁴⁰ To implement this new approach, the NIH must be given additional resources to support clinical trials. For example, the NIH's new Therapeutics for Rare and Neglected Diseases (TRND) program seeks to help innovative products with high potential make the leap from preclinical and clinical research.²⁴¹

Additional funding for such an NIH mandate, however, has not been made available to date. The 2011 federal budget cut NIH funding by \$260 million.²⁴² Fiscal discipline is necessary to confront the deficit, but we must carefully distinguish investments with positive rates of return, such as NIH funding, from expenses that should be trimmed. Providing adequate funding for the FDA will avoid bottlenecks in the approval process, making it more efficient without compromising scientific rigor. Furthermore, providing the NIH with the additional resources to support trials will encourage more collaboration and public-private sector partnerships.

► Leverage Existing Strength in Medical Devices

Medical devices represent a major strength for the U.S., but there is an opportunity to further enhance innovation in this area by streamlining regulatory reviews. Section 510(k) of the Medical Device Amendments allows companies to “build upon established clinical and scientific evidence of safety and effectiveness to more rapidly iterate and improve the innovations available to patients.” However, the FDA continues to demand large-scale data during the premarket period. Companies have lamented that the FDA has become less transparent and less efficient.²⁴³

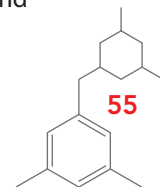
The FDA must be given a new mandate to create an efficient system for medical device approvals. The legal foundation is in place; all that remains is executing the Medical Device Amendments effectively. In 2009, the FDA announced it had commissioned the Institute of Medicine (IOM) to examine the premarket notification program, known as the 510(k) process, which is used to evaluate medical devices. During the course of the study, the FDA's Center for Devices and Radiological Health (CDRH) has focused on attempting to ensure consistency across FDA decisions in this process.²⁴⁴

The IOM report, released in July 2011, set off a storm of controversy with its recommendation to scrap the existing review process; many industry leaders and officials within the FDA itself took issue with the findings. Reform is clearly on the agenda, but as of this writing, the extent of the changes that will actually be made has yet to be determined.²⁴⁵

Beyond resolving regulatory uncertainties, streamlining approvals for export licenses to countries such as China and India also could improve U.S. export performance in medical devices even further.

► Build Human Capital for Biomedical Innovation

Top international talent flocks to U.S. research universities, and over the years, many outstanding innovators and entrepreneurs have stayed in the U.S., making crucial scientific and economic contributions. But today we are starting to see “reverse brain drain.” Retaining the best international human capital must be a priority.



The U.S. should provide an expedited pathway to permanent residence status and then a green card to foreign researchers in exchange for their participation in biomedical R&D over a stipulated period of time. This program can potentially bring about collaborations that leverage the foreign contacts of these sought-after scientists.

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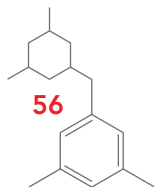
In addition, the United States needs a renewed emphasis on top-flight STEM education at all levels to develop homegrown talent, encouraging American students to become tomorrow's top scientists.

► **Promote and Expand the Role of Universities: Adopt Best Practices**

The most efficient way to enhance the U.S. competitive position is to build on existing strengths—and in the case of the biomedical industry, outstanding research universities are the prized asset. It is possible to adapt the existing configurations to build an even stronger collaborative structure.²⁴⁶

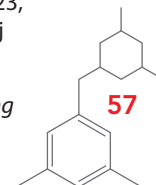
A 2011 study by the National Academy of Sciences recommended steps to improve universities' intellectual property management systems and create an even more efficient and effective technology transfer process. These proposals included increased transparency and committees to support technology transfers, and increased collaboration with larger institutions and private entities.²⁴⁷ In conjunction with our recommendation above to allocate additional resources to the NIH, it would also be advantageous to encourage universities to participate more fully in the drug discovery, development, and approval processes.

The U.S. has the most productive university biomedical technology transfer process in the world. But there is a high degree of variation in efficiency across universities. The U.S. can continue and step up efforts to bring together university medical scientists and tech transfer officials with investors and experts from biomedical firms to ensure that existing best practices are adopted more widely and enhance the interaction between universities and biomedical companies.



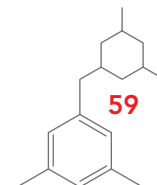
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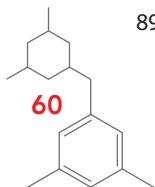


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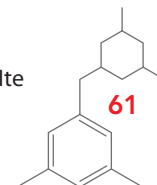
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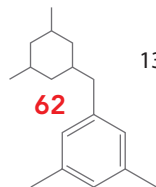
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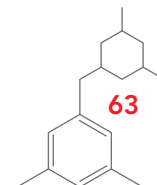
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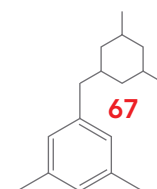


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