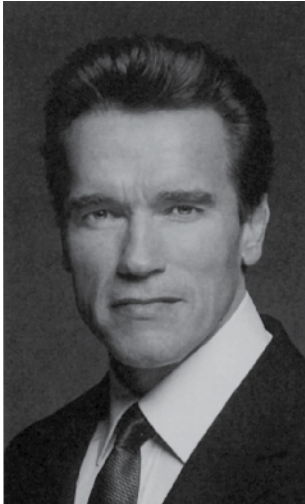




California's Biomedical Industry

Contents

01	Letter from the Governor
04	Letter to our stakeholders
06	Defining the biomedical industry
08	Employment
16	Investment
24	Product development
30	Biomedical manufacturing
36	Academic research
46	Methodology



October 2006

Dear Fellow Californians,

California's biomedical industry is a vital and growing component of our state's high-tech economy. Reflecting the California spirit, biotech and medical technology are rooted in innovation and ingenuity, and thrive through the commitment and hard work of scientists, entrepreneurs and academic leaders alike.

California is the birthplace of biotechnology and remains the global headquarters for advanced medical technology. Our life sciences businesses and academic institutions employ more than 250,000 Californians, many of them trained in our state's great universities. The rich intellectual and commercial infrastructure the industry has built over the past twenty years promises to foster medical progress for decades to come.

Opportunities to work at the cutting edge of science in fields like genomics and stem cell research draw the world's leading researchers to California. Once here, many of them expand their careers beyond basic science, founding companies that translate laboratory discoveries into practical treatments for patients. These breakthrough products benefit people around the world and deepen our medical understanding. At the same time, the revenue and jobs our companies and institutions generate enable us to provide vital services for people right here at home.

I have proposed a comprehensive plan that among many things, provides the best schools and universities to prepare our young people to compete in the new economy, and creates more jobs and opportunities for the people of our state. I have a vision to build a California for the future, one that serves the people and remains a great engine of progress. The biomedical industry exhibits this same commitment to progress, a fact reflected in this report.

I know that by working together, we will ensure that California's biomedical industry continues to be a powerful, job-creating force in our state – a force able to deliver on its promises for improving the lives of people everywhere.

Sincerely,

Arnold Schwarzenegger





Letter to our stakeholders



October 2006

The United States leads the world in life sciences: from basic research to biotechnology to innovative medical devices and diagnostics. And, as this report clearly shows, the U.S. is led by California. Today our state is home to a vast network of academic institutions and commercial businesses, investigating and investing in technologies for hundreds of diseases that will affect billions of people.

Growth in human life sciences creates two kinds of benefits. The first is economic. From an airplane window at 30,000 feet, an observer can see the new clusters of biomedical innovation – in San Diego, Orange County, Thousand Oaks, Silicon Valley, South San Francisco, Mission Bay – where research laboratories and manufacturing plants have mushroomed on a scale unimaginable 30 years ago, at the dawn of biotechnology. These facilities represent tens of billions in investment capital and, more important, sources of high-wage employment for some 260,000 Californians. If you could design an economy from scratch, these are the kinds of jobs you would create: high levels of education and specialized skills, export-oriented, environmentally clean, and devoted to making products that improve and save people's lives.

Saving and improving lives by inventing novel approaches to the prevention, treatment and cure of diseases is the ultimate goal of the life sciences industry, and its greatest benefit to humankind. Thanks to biomedical innovation, disorders that were previously untreatable can be managed and, in some cases, cured. Deaths from coronary artery disease have declined sharply with the introduction of pacemakers, stents, statins and clot-busting drugs. People infected with HIV can manage their illness with a single pill, taken daily, and live a normal lifespan. And many forms of cancer, once considered hopeless, are susceptible to monoclonal antibodies and other biotech drugs. With recent advances in decoding the human genome and understanding the potential of stem cells, the outlook for gaining control of dread diseases, from multiple sclerosis to Alzheimer's, has never been so bright.

Still, there are storm clouds in the California and national political environment that could dampen the industry's prospects. These include:

- **The Food and Drug Administration (FDA) and product safety** – After last year's experiences with COX-2 inhibitors, antidepressants, and a pacemaker-defibrillator recall, the FDA has in some areas raised the bar for product approval, requiring larger studies and more data to confirm that products are safe and effective. Since most drugs and devices carry some risk, it is critically important that FDA (and members of congress) strikes an appropriate balance between risks and benefits that encourages continued development of innovative products.

- **Government intervention in the drug and device marketplace** – Continuing increases in healthcare costs, soaring Medicare and Medicaid spending, and a steady rise in the numbers of uninsured Americans have pressured federal and state government to seek ways to restrain healthcare spending. The Centers for Medicare and Medicaid Services (CMS) has undertaken, and continues to explore, several initiatives, including evidence-based medicine and cost-benefit analysis, that could fundamentally reshape the market for drugs and devices. Meanwhile, in California, the governor and legislative leaders have introduced legislation to create a discount pharmaceutical program for low-income citizens, a program that would require manufacturers to meet state-dictated price controls or risk exclusion from its Medi-Cal program.
- **Risks to intellectual property** – Strong intellectual property protection, mainly patents, is the bedrock of California's life sciences industry. Congressional efforts to rewrite patent law, interest in enabling the FDA to expedite follow-on biologics (which some liken to generic versions of biotech products), and the desire of some state lawmakers and government agencies to create a stronger role for the state in regulating intellectual property developed with state funding – each of these has implications for investors and their willingness to fund inherently risky biomedical technology enterprises.

California's life sciences industry is coming of age. Employment, product pipelines and revenue growth are stronger than ever. Buoyed by \$3 billion from Proposition 71, academic institutions are planning major initiatives in embryonic stem cell research. Companies have discovered fresh sources of capital; mergers, acquisitions and technology licensing are more robust than ever. Daunting as its challenges are, the industry has never been better positioned to meet them, and to strengthen California's position as the global headquarters for life sciences R&D.



David L. Gollaher, Ph.D.
President and Chief Executive Officer
California Healthcare Institute

Industry sectors

This report encompasses several sectors which combine to make up the California biomedical industry:

Academic research // Scientific exploration in California's universities and public and private research centers leads to discoveries that frequently enter the commercial biomedical industry through technology transfer. Such transactions can include contract research, licensing agreements and spin-off companies.

Biopharmaceuticals // These are companies whose biologics or bio-engineered products are produced by altering or replicating proteins (including antibodies) or nucleic acids (DNA, RNA or antisense oligonucleotides) for therapeutic or diagnostic purposes. Pharmaceuticals, in contrast, are drugs manufactured from chemical compounds

Diagnostics // This category encompasses technologies that analyze biologic samples for medical purposes. Examples include magnetic resonance imaging scanners in hospitals, tests used to keep the blood supply safe and such over-the-counter products as home pregnancy tests. Diagnostics are also a key component in biomedical research and include reagents, cell analysis instruments, high-throughput screening devices and every imaginable instrument vital to science.

Laboratory services // Laboratories that test patient or research samples use highly technical, precisely calibrated and strictly regulated equipment and procedures to ensure accurate results.

Medical devices // Encompassing all mechanical means for improving or diagnosing human health and mobility, medical devices can be further sorted into two general categories. Instruments include tools used by medical professionals in their work. Examples include scalpels, lasers and heart monitors. Implants are medical devices, such as artificial hips or heart valves, that are surgically placed to perform a function that the body cannot provide or adequately perform for itself.

Wholesale trade // Managing the import, export and exchange of pharmaceuticals, medical devices, diagnostics and research reagents and other supplies, wholesale trade companies are an important segment of California's biomedical industry.

Defining the California biomedical industry

California's biomedical industry is its own unique ecosystem. Anchored by more than 2,700 biomedical companies and 100 public and private research institutions, the industry has spawned a network of highly specialized suppliers and service providers. And it has commercialized countless products that contribute to the health and well-being of people around the world.

It is little wonder that California, which values creativity, innovation and entrepreneurship, is global headquarters for advanced biomedical technology. San Francisco-based Genentech was the world's first biotechnology company, quickly joined by Chiron and Amgen. Using the new technology of genetic engineering, these companies set out to manufacture human proteins, which could be used to cure certain diseases. A generation later, the emerging genomics and proteomics fields also are being led by California companies. These firms are identifying genetic mutations and the underlying cause of life-threatening diseases. Biopharmaceutical companies that specialize in small-molecule products are discovering precise targets for potential medications, and the industry's diagnostics and device sectors are developing the tests and delivery mechanisms to accurately identify and treat patients with life-threatening conditions.

The scientific research behind biomedical breakthroughs comes both from California's academic research institutions and from company laboratories. Genentech's first biotech product – recombinant human insulin – was based on discoveries at UCSF. Of the respondents to the CHI/PwC survey, 24% credited a California academic research institution with the idea central to the creation or growth of their company. Breakthrough discoveries also are being made in company labs, where, on average, 42% of revenues are churned back into R&D. In 2005, companies invested \$26 billion into developing new drugs, devices and diagnostics to meet an increasing worldwide demand for innovative medical products.

In the industry's early years, seed funding came mainly from venture capital investments. Private investment continues to be a significant source of revenue, and California life sciences companies attracted \$2.9 billion in venture capital investment in 2005. Companies also have turned to the equity markets for funds. Currently California biomedical companies account for 68.5% of the market capital of all of the NASDAQ-listed life sciences sector.

As the industry has expanded, so have the funding opportunities. Genentech, Amgen, Gilead Sciences and others have grown exponentially since the 1980s and have the resources to sponsor research agreements, in-license new compounds and acquire other companies. For early-phase companies, promising compounds or research services can command high prices today as fierce competition and close investor scrutiny has placed product development pipelines under greater pressure.

Another significant source of research funding is product sales. Combined, California life sciences companies generated \$62 billion in revenues in 2005.

Highlights

Total biomedical companies	2,700
Total estimated revenues	\$62 billion
Total estimated employment	258,600
Total estimated wages and salaries paid	\$18.2 billion
Total NIH grants awarded	\$3.6 billion
Total estimated venture capital investment in California biomedical companies	\$2.9 billion
Total reported private investment in research and development	\$26 billion

Among the respondents to the CHI/PwC survey, 62% had products on the market, and 36% reported that all of their revenues came from product sales.

Industry maturation has also given newer companies an advantage that the pioneers did not have. Amgen, Genentech and others founded in the early '80s had to build capabilities for each stage of product development as they went. Today, specialized functions can be outsourced to proven vendors, accelerating development while reducing capital risks. With a predictable demand for their products and services, suppliers' prices have come down and quality and reliability have increased. Companies can more readily find "research-ready" space and equipment at a discount than they could have 10 or 20 years ago. And local community colleges as well as universities offer training programs to prepare individuals for careers in life sciences companies – careers that were still being created in the '80s and '90s.

The biomedical industry is maturing yet it is still quite young. Approximately 86% of California's life sciences companies were founded between 1980 and 2003. And among the respondents to the CHI/PwC survey, most (57%) are small businesses – 46% employ fewer than 50 people; 11% have between 50 and 100 employees.

The biomedical industry is a solid, significant and growing component of California's economy. This report discusses key facets of the biomedical industry in more detail. It also explores what the future may hold for the biomedical industry in the Golden State.

Employment

Nearly 260,000 Californians work in the biomedical industry, which in 2005 paid more than \$18 billion in wages and salaries.

California's biomedical industry is one of the state's leading high-tech employers. Approximately 260,000 Californians work in the biomedical industry, and their specialized jobs span a wide spectrum. There are molecular biologists and chemists; lab technicians; engineers designing the next generation of pacemakers; specialists hand-stitching artificial heart valves; biostatisticians monitoring clinical trials; assembly-line supervisors; experts in regulatory affairs ensuring that products meet FDA requirements; sales and marketing professionals; warehouse staff; accountants; human resources directors; database managers – all these jobs and dozens more make up the industry's rich and diverse employment base.

The industry employs people with high school diplomas and multiple doctorate degrees. Further, many are expanding their educations through their employment positions. Examples include pursuing a higher degree or certificate program with company-sponsored education benefits or serving in a post-doctoral research position in a university or company lab. The biomedical workforce encompasses dozens of ethnic groups and frequently includes specialists from other countries. Perhaps more than in any other field, biomedical employees' job satisfaction derives from knowing that their work expands scientific knowledge, advances medical progress and improves the lives of patients around the world.

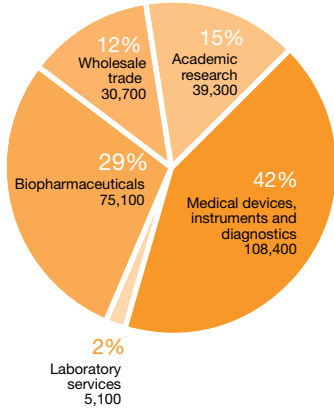
California's biomedical industry remains dynamic and growing

Increasingly, skills acquired in one sector of the biomedical industry are transferable – and in demand – in another. While this has long been true for general and administrative functions, barriers are diminishing among the scientific and engineering disciplines as well. Diagnostics companies are reaching out to geneticists in biotechnology and research organizations. Medical device companies seek specialists in regulatory affairs and quality assurance – experts who may have begun their careers in engineering.

As companies advance through product life-cycles, their personnel needs change. Environmental factors such as NIH funding for academic researchers, changes in tax incentives for manufacturers and increased competition within certain markets can have an impact on the kinds of skills and experience employers demand. Adapting to such changes, California's biomedical companies and educational institutions are providing programs to help workers transfer into the functions where they are needed most (see page 12).

Currently, employment in the industry may be grouped into a handful of basic sectors: 42% of employees work in businesses making medical devices, instruments and diagnostic tools; 29% in biopharmaceutical companies; 16% in academic research; 12% in wholesale trade; and 2% in laboratory services.

Distribution of employment in biomedical industry 2005



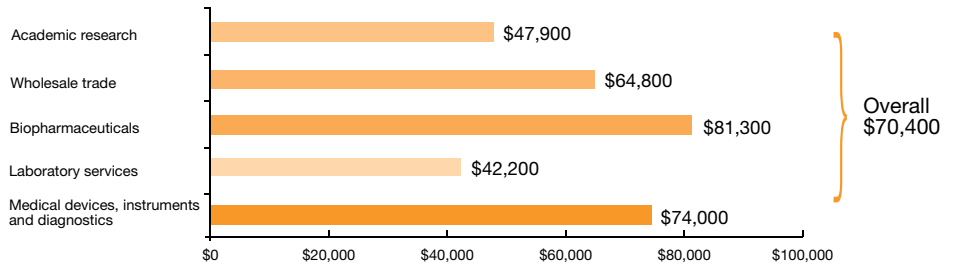
Total estimated employment 258,600

Source: CA Employment Development Division, BLS ES 202 data, company specific filings with the SEC

Robust wages in California's biomedical industry

Biomedical industry wages increased approximately 17.3% from 1997 to 2005, from an overall industry average annual wage of nearly \$60,000 to an overall wage of approximately \$70,400. Within the sector, biopharmaceutical companies paid the highest average annual wage – \$81,300.

Average wage by sector in California's biomedical industry 2005

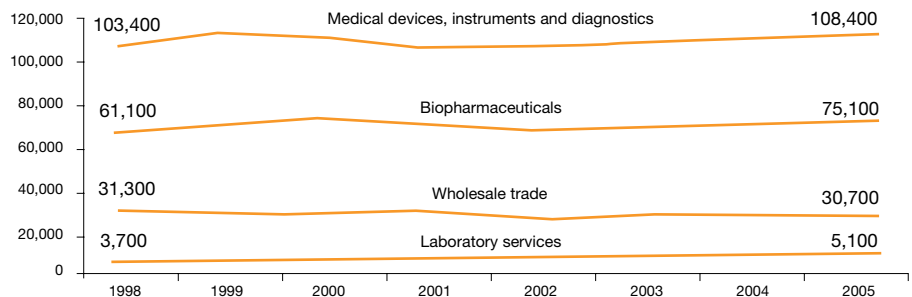


Source: Bureau of Labor Statistics, ES 202 data series; inflation-adjusted 2004

Employment in California's biomedical industry continues to expand

The commercial workforce in California's biomedical industry grew approximately 10% between 1998 and 2005. (Academic research numbers are collected separately and are not available in the same yearly increments.) Within the industry, however, some sectors experienced greater growth than others. For example, the wholesale trade sector experienced slight decline, while employment within biopharmaceuticals grew approximately 23%, and employment within laboratory services grew 36%.

Estimated biomedical industry employment in California 1998-2005

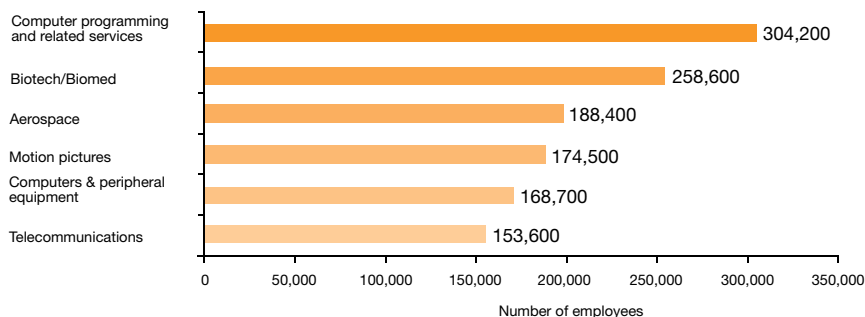


Source: CA Employment Development Division, Bureau of Labor Statistics ES 202 data

California's biomedical industry is a leading high-tech employer

Among California's high-tech industries, the biomedical sector employs significantly more people than aerospace and motion pictures and is second only to the general category of computer software and services (which includes consulting).

Estimated employment in California's high-tech industries, 2005



Source: CA Employment Development Division, Bureau of Labor Statistics ES 202 data

California's biomedical industry builds on entrepreneurial legacy

The Golden State has long served as an incubator for innovative ideas and fertile ground for the companies formed to bring those ideas to fruition. That approach appears to be thriving. Among companies responding to the CHI/PwC survey:

- 20% were founded since 2000, demonstrating ongoing inventions and discoveries with commercial promise.
- 57% have fewer than 100 employees, and 46% employ fewer than 50. In the biomedical industry, as in other sectors, small businesses help drive innovation, employment and the local economy.
- 53% have commercialized products, which is a significant milestone for biomedical ventures. At the same time, 41% stated their operations were focused on research (14%) or clinical development (27%). With all stages of the business lifecycle represented, the biomedical industry promises to continue generating products, employment and revenues for years to come.

California's biomedical industry remains committed to operating in the state

Despite well-publicized challenges to doing business in California, the biomedical industry remains committed to its operations in the state. Among companies responding to the CHI/PwC survey:

- 62% expanded their in-state R&D capacity in 2005, and 74% expect to expand their R&D activities here in the coming two years. 57% expect to increase their R&D staff in the coming two years.
- 71% expanded their in-state manufacturing capacity in 2005, and the same percentage intends to expand in-state manufacturing activities in the next two years. 55% expect to increase their California manufacturing workforce in the coming two years.
- 92% either expanded (45%) or maintained (47%) their in-state general and administrative (G&A) activities in 2005. 54% expect to expand their California G&A activities in the next two years, and 51% intend to expand their in-state G&A workforce.



California may be missing key opportunities within the biomedical industry

Even though a majority of the respondents to the CHI/PwC survey indicated they plan to grow their operations in California in the next couple of years, they are expanding operations, employment, revenues and tax dollars in other states and countries, too. In their responses, they indicated:

- 13% expanded their outside-California G&A activities in 2005, and 17% expect to expand those activities in the next two years.
- 32% expect to expand their out-of-state R&D capacity in the next two years.
- 74% expanded their out-of-state manufacturing capacity in 2005, and 97% intend to expand (76%) or hold steady (21%) those activities in the next two years.

The top five factors influencing decisions on where to locate facilities are 1) the ability to find talent; 2) proximity to R&D and cost of living (tied); 3) labor costs; 4) housing; and 5) taxation. These factors may not favor California as well in manufacturing decisions as they do for R&D and G&A.

More than half of firms surveyed expect to increase their workforces in California in the next two years.



MiraCosta College

Genentech funded the remodel of one of MiraCosta College's machine shops into a 3,500-square-foot bioprocessing facility that boasts over \$1 million in state-of-the-art equipment and provides hands-on learning opportunities for MiraCosta's biomedical students.

Developing the workforce: Industry and academia unite

A highly skilled workforce is key to the success of the biomedical industry in California. The state's clusters of life sciences companies have emerged around California's public and private colleges and universities.

In the biomedical industry's formative years, collaborations between start-up companies and local universities focused primarily on the technical skills of biologists, chemists, geneticists and engineers. As companies progressed from research to development and commercialization though, their hiring and partnering expanded to include process development, manufacturing, packaging, marketing, distribution and many other new job functions.

California's learning institutions responded with training programs for these new and vital roles. The state's companies stepped up to guide, shape and, in many instances, help fund faculty, develop curricula and provide hands-on training. The following sections describe just a few of the current collaborative efforts between industry and academia in developing the state's biomedical workforce.

Biomedical companies supporting education

Genentech. As a pioneer in the biotechnology industry, Genentech has sought ways to develop the industry's workforce in the communities where it resides. To assure its hiring success, the company sponsors biotech training programs around the state.

In Northern California, Genentech supports two programs at Skyline College in San Bruno. The first, a 12-week Biotechnology Manufacturing Certificate, prepares students for work in biologics manufacturing plants, such as those Genentech operates in Vacaville, San Francisco and Oceanside. Students who complete the certificate program – and 258 people have in the program's two-year history – are invited to interview for a follow-on "paid work experience" internship with potential for permanent employment.

The second program is a two-year AA of science degree with a biotechnology focus. The coursework concentrates on biology and chemistry (24 units) plus general academic requirements and prepares graduates for entry-level technician positions in R&D, quality assurance/quality control and manufacturing.

In Southern California, Genentech has worked closely with MiraCosta College to add a new bioprocessing track to their existing biotech career track, with emphasis on the needs of large-scale, FDA-regulated biopharmaceutical production. Offered in several certificate and degree options are: Biotechnology Laboratory Assistant, Research and Development, and Bioprocessing. The company also helps fund the school's faculty.

In addition to the community college support in San Diego County, Genentech has supported skills transfer programs for professionals downsized from the semiconductor and telecommunications industries. Together with the San Diego Workforce Partnership, Genentech sponsored a program that combined three months of training in biotech basics with five weeks of on-the-job work experience. The program has been open to applicants from any other industry. "One student used to be a supermarket manager," said Mary Schwalen, Education and Training Manager for Genentech in Oceanside. "Now he works in material services and he's been a great addition."

Invitrogen. Invitrogen works closely with the community college biotech and high school science programs throughout the state in addition to several programs supporting four-year and advanced biomedical degrees. The company, which provides products and services for life sciences R&D, donates hundreds of thousands of dollars in products to educators and researchers at all levels of California's educational system. Among beneficiaries of product donations is the Southern California Biotechnology Center housed at Miramar Community College and MiraCosta College, where Invitrogen helps develop curriculum suited to diagnostics manufacturing techniques.

"We feel it's important to reach out to young people, their teachers and mentors," said Lisa Peterson, Community Relations Manager for Invitrogen. "By showing young scientists that there is a viable career path that matches their interests, we expand their horizons while also ensuring that our industry will have vital new talent in the future." Peterson notes that Invitrogen guides hundreds of high school and community college students on tours of its manufacturing and distribution facilities – tours that include conversations with scientists and other staff. The company's outreach work has included sponsoring more than 50 summer internships for California undergraduate students and faculty over the past two years. The company also hosted a one-day "teacher externship" in conjunction with the Life Sciences Summer Institute in 2006, giving high school teachers and community college instructors an opportunity to talk with staff scientists and others about career opportunities in the life sciences industry.

Bayer HealthCare. Founded in 1993 as part of a 30-year development agreement between Bayer HealthCare and the City of Berkeley, Biotech Partners (formerly Berkeley Biotechnology Education, Inc./BBEI) is now also supported by more than 35 corporate, government, education and industry partners including the Genentech Foundation and Novartis AG (formerly Chiron).

Biotech Partners' unique multi-year program targets populations that are typically underrepresented in the sciences: students of color (97% of the students are minorities), young women (54% of the students) and those from low-income households. The career-focused, hands-on science and technology curriculum serves 125 to 150 students annually and is available from 11th grade through community college. Biotech Partners' program includes paid summer internships for high school students, year-long co-op jobs for community college participants and one-on-one support for its enrollees. Designed to build students' confidence, the program has been successful in every measure. For example, since 1993:

- Biotech Partners placed nearly 700 youth in internships and co-op work positions.
- Approximately 97% of students who complete at least one year of the high school component, including the summer internship, have gone on to graduate from high school, double the rate of the Oakland Unified School District.
- A full 97% of Biotech Partners' students pursue post-secondary education.
- Nearly all graduates seeking jobs in the bioscience arena have found employment within one month after graduation.

California programs fueling biomedical workforce

California Community Colleges. The U.S. Department of Labor has projected that U.S. employment in life sciences will grow 18% between 2002 and 2012. Among programs designed to help train those new workers – as well as support biotechnology-related economic development in California – is the Statewide Applied Biological Technologies Initiative (ABTI) launched by the California Community Colleges (CCCs) in 1997.

Today the initiative is comprised of six grant-funded centers serving different regions of the state. All have a common mission: to provide life sciences companies with appropriately educated and trained workers. To fulfill this mission – and tailor its programs to address its region's needs – each of the biotech centers relies on partnerships with local biomedical companies and biotech business incubators. The centers work with these partners, regional colleges, industry organizations, economic development boards and relevant government agencies to design state-of-the-art training opportunities for trainees at all levels in the community. The centers also work with regional high schools and state and private universities to offer joint curriculum, workshops, seminars and laboratory exercises as well as to secure federal, state and foundation grants.

All 110 of the CCCs offer the basic math and science courses required for employment in the state's biosciences industry. About one-third provide current and active hands-on skills courses toward employment or advancement within biotechnology fields. Examples of these highly varied programs include:

- San Diego Mesa College's chemistry technician certificate
- College of Marin's two-year program in biology with a biotechnology emphasis

- Ventura College’s certification in medical or plant biotechnology
- Solano College, City College of San Francisco, MiraCosta College and Moorpark College’s comprehensive curriculum in industrial biomanufacturing
- American River College’s associate’s degree in bioinformatics

A study published by the ABTI in January 2004 reported that the vast majority of the 1,100 students enrolled in biotech programs at that time had already earned at least a bachelor’s degree in a related field; some held a masters, doctorate, veterinary, pharmaceutical or medical degree. The average age of the students was 32. The programs do draw students in the 18- to 21-year-old range, many of whom use their two-year degrees to secure employment in the biomedical industry.

The ABTI estimates between 1,000 and 1,500 trainees per year from the CCCs attain employment in a company related to the education and hands-on skills they have learned. In FY2005-2006, more than 1,800 people participated in ABTI center activities. The demand from California’s life sciences industry for these well-trained and qualified employees is greater than current trainee numbers.

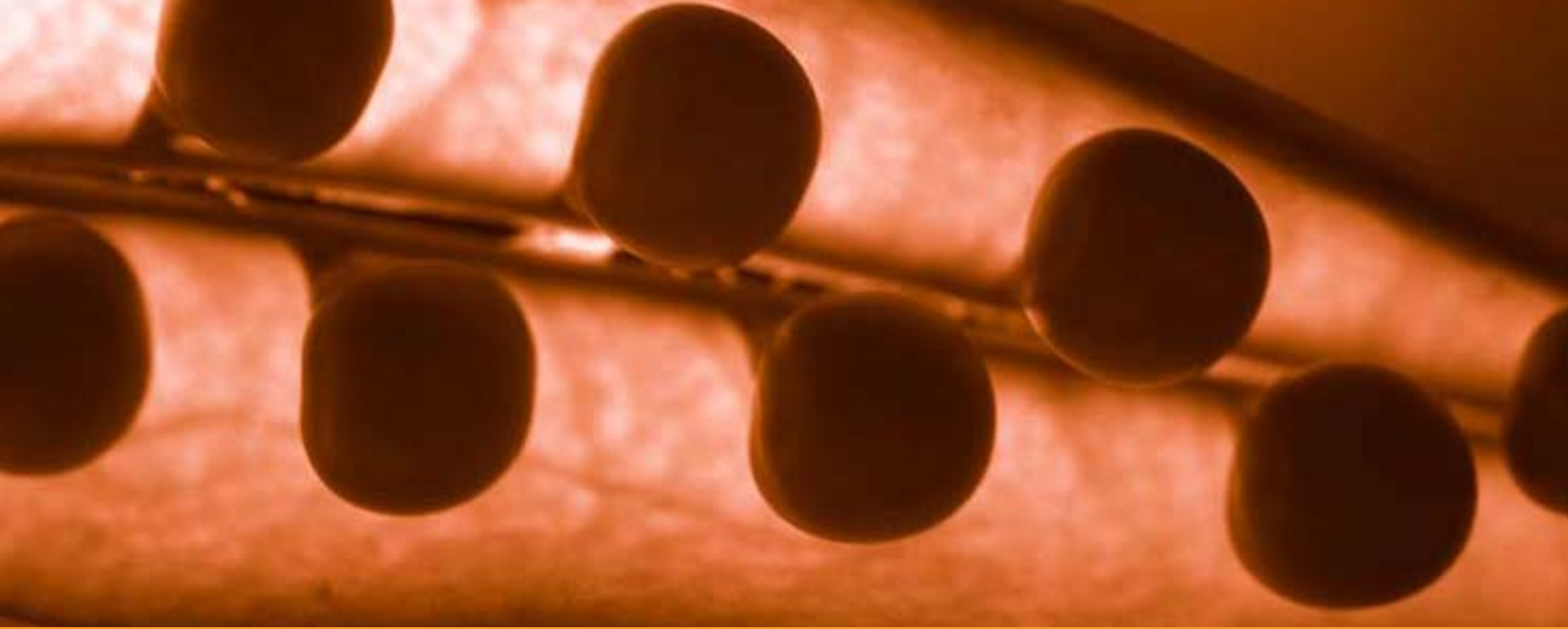
Donations of equipment, supplies, time and cash in FY 2005-2006 to ABTI centers totaled more than \$1.6 million. Among the program’s more than 270 company partners are Edwards Lifesciences, Inamed, Raven Biotechnology, Amgen, Genentech, Biosource, Ceres, Invitrogen, Biogen-Idec and Novartis AG.

California State University. The CSU is the largest state university system in the country and a vast resource for California’s technical workforce. It historically has created new and specific research and instructional programs in emerging areas critical to California’s economy, and the CSU system has kept pace with the evolution of the biomedical research and manufacturing industries.

Formed in 1987, the CSU Program for Education and Research in Biotechnology (CSUPERB) has worked as a liaison among CSU, industry, government and the public in the pursuit of six primary objectives: 1) foster economic development, workforce development and competitiveness; 2) facilitate training of bioscience technicians and scientists; 3) promote technology transfer and enhance intellectual property protection; 4) facilitate the acquisition and long-term maintenance of state-of-the-art biotechnology resource and research facilities; 5) facilitate joint research with industry in the biotechnology, biopharmaceutical and medical device arenas; and 6) promote the development of specialized biotechnology-focused graduate training programs.

CSUPERB manages multiple grant programs to support basic and applied research; entrepreneurial joint ventures; program development; faculty research; and student and faculty travel. Between 1999 and 2005, grants totaled \$3.9 million. At the same time, funds provided by CSUPERB are often matched from other sources, such as federal agencies, private foundations and industry. In some cases, and in particular with the Joint-Ventures Grant program, these matching funds would only come into the system because of the funding obtained from CSUPERB. In a recent survey, CSUPERB verified that faculty grants were matched at a ratio of greater than 2:1.

In addition to its grant programs, CSUPERB has implemented outreach programs to involve industrial, governmental and economic development organizations in its activities; workforce development programs to match curricula with industry needs; specialized symposia and workshops to promote learning and technology transfer; creation of specialized equipment facilities; and special recognition of faculty, students, legislators and corporate leaders.



UCSD Jacobs School of Engineering

The UC San Diego Jacobs School of Engineering's Bioengineering Department was established in 1994 as an outgrowth of the university's longstanding biomedical program. Today the school is consistently ranked among the top three biomedical programs in the nation and offers 11 degree programs (four undergraduate, four master's and Ph.D., and three dual degrees including MD/PhD, MD/MS and BS/MS) in bioengineering, biotechnology and bioinformatics.

The multidisciplinary bioinformatics and biotechnology programs were created, in part, to respond to the needs of the biotech and pharmaceutical industries just as the bioengineering program serves the needs of the biomedical device and instrumentation manufacturers. This responsiveness to the needs of local employers has made UCSD and the Jacobs School a prime source for highly trained and qualified biomedical personnel. In fact, many pre-med graduates who decide not to go into medicine elect to work in the biotech industry. A substantial percentage of the Jacobs School's mechanical engineering, electrical engineering, computer science and computer engineering students go on to work in the life sciences industry, with many staying in the San Diego area.

The school also maintains strong internship programs within the local biomedical industry. The Jacobs School has pioneered the team internship concept, which is especially relevant for life sciences companies. In this approach, engineering students are recruited from many disciplines to work together on an assigned project in companies such as Gen-Probe Incorporated, Invitrogen, ResMed and Celula. Beyond earning academic credit for their internship projects, the students have a high success rate (about 90%) of earning a permanent position at the sponsoring company. As students work on industrial internships or joint research projects with local companies, they see how the knowledge and theory learned in class is applied in the real world. At the same time, industry has access to talented students with fresh ideas – and benefit from an early look at the talent pool.

In addition to engineering training, the Jacobs School helps prepare students to become leaders in innovative companies through a course series offered by its von Liebig Center for Entrepreneurism & Technology Advancement. Students gain an insider's look at life sciences business from CEOs, venture capitalists and other professionals, and through readings, case studies and projects, they learn how entrepreneurial companies work. Most importantly, they gain insights into how to contribute to business discussions and decision-making. The von Liebig Center also partners with venture firms and corporations to advance the commercialization of Jacobs School discoveries, many of which are focused on software, devices and materials for the biomedical industry.

Investment

In 2005, California life sciences companies reported \$62 billion in worldwide revenues. On average, companies reinvested 42% of their revenues – whether from product sales, grants and contracts, or licensing technologies to other companies – back into R&D.

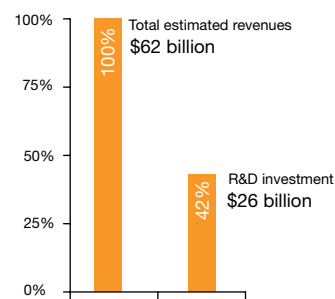
Highlights

- California life sciences firms accounted for approximately two-thirds of the market value of all NASDAQ-listed life sciences companies in 2006.
- 49% of the total \$5.9 billion biomedical venture capital dollars invested in the U.S. went to California companies – up from 43% in 2003.
 - 62% of those investment dollars went to fund biotechnology, and 33% were invested in medical device technology.
- Alliances between larger pharmaceutical and California life sciences companies in which the value of the agreements was disclosed totaled \$1.3 billion.
 - Only 16 (46%) of the 35 alliances announced the dollar value of their agreements.
- In 2005, 62% of firms surveyed expanded R&D in California and 71% expanded manufacturing in California.

The majority of firms responding to the CHI/PwC survey have fewer than 100 employees, indicating that most of California's biomedical firms are smaller firms with potential to grow. For those with proven management teams and solid scientific technologies, venture capital is available at historically high levels. And pressure on biomedical companies of all sizes to reduce the costs and risks of product development has been a catalyst for encouraging alliances and technology transfer agreements.

Biomedical product development is ever more expensive, difficult and tightly regulated. As the industry grows, it has become increasingly competitive. Companies compete not just with products, but for capital, employees, vendors and space. Rising healthcare costs are a matter of intense interest among politicians, the media and the public. Drug and device manufacturers have faced sustained criticism for the prices they charge. More than at any time in the past, inventors and producers of biomedical technology confront the dual challenge of generating profits to attract continued investment, on the one hand, and improving health access and affordability, on the other.

R&D investments as percentage of revenues



Source: CHI/PwC Survey, 2005

Venture capital (VC) investments continue at historic levels

Biomedical companies have long turned to venture capitalists (VCs) for funding. The relationships between companies and VCs peaked in 2000 with two market phenomena. The first was the general enthusiasm for investment in technology that accompanied the rise and early successes of Internet companies. The second was the mapping of the human genome and overly optimistic investor expectations about how quickly this knowledge could be translated into commercial therapies. After the investment dip in 2001-02, U.S. VC investment in life sciences companies has remained steady at an average of about \$3.7 billion, and at \$1.5 billion among European VCs.

What has changed, however, is how difficult it is for a start-up company to secure VC investment. The early phase of biotechnology saw VCs willing to invest in early-stage science whose commercial potential was speculative.

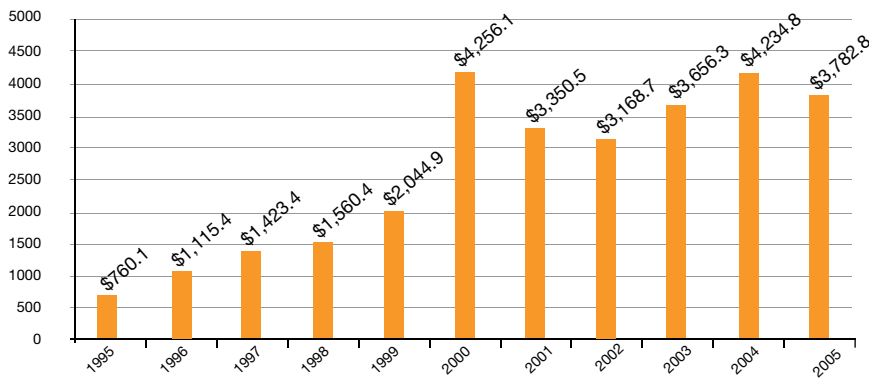
During the 1990s, however, after the failure of many start-ups, and substantial market cap reductions among others, VC investors grew more cautious. After the high-tech bubble burst in 2000-2001, VCs became more conservative yet, tending to make fewer investments, and those only in companies with solid

with evidence that payers would provide coverage and reimbursement for the new products. As initial public offerings (IPOs) have become harder to sell, VCs tend to delay an IPO until the company has product revenue or has achieved significant commercial milestones that attract higher valuations.

Still, California life sciences companies continue to capture a significant portion of available VC funding – 49% of the total \$5.9 billion invested in 2005. That is an increase from 43% in 2003. This funding level may reflect the numbers and quality of the biomedical companies in the state, but another trend among VCs is to direct their investment toward later and larger equity offerings for their existing portfolio companies. This enables the VCs to help advance their portfolio companies to a level of maturity that will attract a premium in the public market – either through an acquisition or an IPO – and to help ensure a higher return on their investments.

Ten-year U.S. biotech VC investments

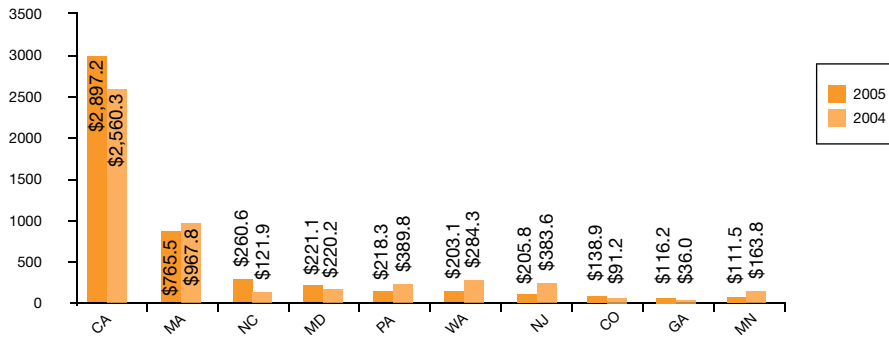
(dollars in millions)



Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree Report, Data: Thomson Financial

Life sciences investment by state Q1 2004 to Q4 2005

(dollars in millions)

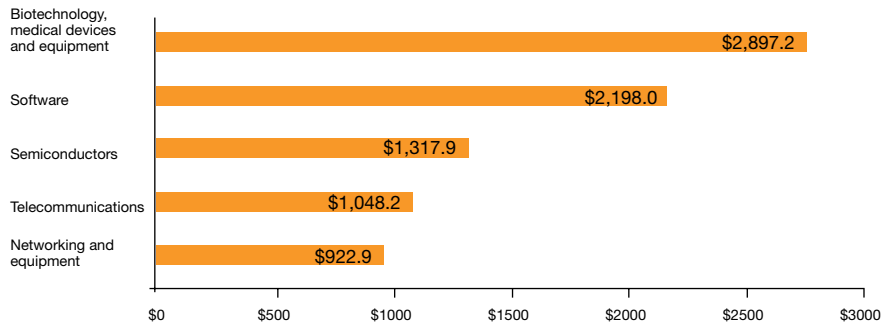


Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree Report, Data: Thomson Financial



Top five industry sectors in California 2005

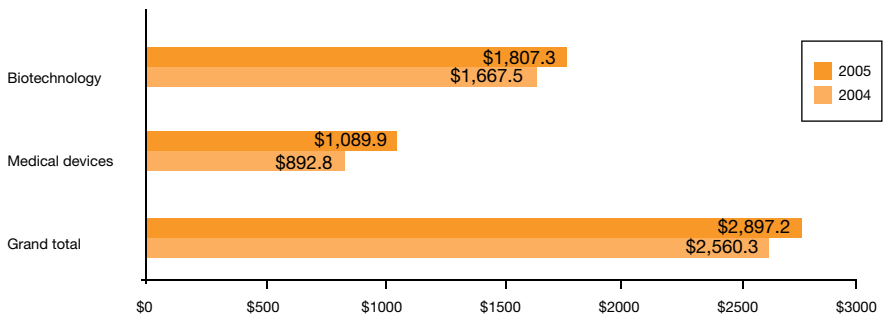
(dollars in millions)



Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree Report, Data: Thomson Financial

Life sciences investment in California Q1 2004 to Q4 2005

(dollars in millions)



Source: PricewaterhouseCoopers/National Venture Capital Association MoneyTree Report, Data: Thomson Financial

Industry alliances fuel innovation and growth while dispersing risk

California's biopharmaceutical and medical device and diagnostics industries entered into many research agreements, licensing deals and merger and acquisition (M&A) transactions with other companies in 2005 – to the sum of billions of dollars. Reported investments by larger pharmaceutical companies into promising projects within California's biotechnology sector alone totaled \$1.3 billion. And those numbers do not include acquisitions, usually made to strengthen a larger pharmaceutical company's product pipeline. Mergers and acquisitions are also a key development tool for the medical device sector (see page 23).

Companies invest in their own promising projects

California's biomedical companies also generate revenue through product sales. Of the respondents to the CHI/PwC survey, 36% said that all of their revenues came from product sales. Regardless of the funding vehicles they use, companies continue to make significant investments into their R&D and manufacturing capabilities. And they remain committed to doing business in California. However, the state may be missing opportunities to keep the manufacturing jobs and wages within California's borders.

Big pharma investment in California biotechnology industry 2005

Strategic alliances by therapeutic category	Number of alliances
Blood & coagulation disorders & products	1
Cancer	9
Cardiovascular	5
Gynecological/urological	2
Hepatic (Liver)	1
Infectious & viral diseases	1
Inflammation	2
Metabolic disorders	3
Musculoskeletal & connective tissue disorders	2
Neurology, nervous system	3
Ophthalmic	1
Renal system	1
Respiratory, pulmonary	2
Unspecified	10
Wound healing & tissue repair	1
Total number of alliances	35*
Total value	\$1.3 billion

Source: Windhover's *Strategic Transactions Database*

*Alliances that apply to more than one therapeutic category are counted multiple times.

CHI/PwC survey respondents claimed that in 2005:

- 62% expanded R&D in California, 28% held R&D within California steady and 10% reduced R&D or were not conducting research in the state.
- 71% expanded manufacturing in California, 25% held in-state manufacturing steady and 3% reduced manufacturing or were not conducting manufacturing in the state.
- 22% maintained at least some manufacturing facilities in another state and 28% had manufacturing capacity outside of the United States. 74% of the companies with out-of-state manufacturing expanded those activities in 2005.

In the next two years:

- 57% of California biomedical firms surveyed expect to expand R&D activities in California; 26% expect to hold R&D within California steady; and 32% expect to expand R&D outside of California.
- 57% expect to increase their California-based R&D staff by more than 50%.
- 71% expect to expand and 25% anticipate holding steady their manufacturing activities within the state.
- 55% plan to increase the number of manufacturing employees in California.
- 74% plan to establish or expand manufacturing capacities outside of California.



Personalized medicine and the transformation of healthcare

Pharmacogenomics, or “personalized medicine,” uses markers in individual patients’ genetic codes to pinpoint the underlying causes and mechanisms of disease and predict whether or not a drug will be effective.

In the clinic, pharmacogenomics will transform medicine from prescribing treatment based on a patient’s symptoms to therapies based on the patient’s personal DNA. By identifying genetic markers associated with specific conditions, pharmacogenomics will help physicians better define the long-term health risks patients face, more precisely diagnose the stage of patients’ diseases and more accurately predict their responsiveness or chances of experiencing side effects. Expected to be a part of mainstream medical practice within 10 years, pharmacogenomics products are already being used in patient care.

In drug development, genomics is enabling academic and industry researchers to better identify drug targets and the mechanisms of action of their investigational new drug candidates. Genomics-related technology facilitates the elimination of ineffective products at earlier stages of development than is currently possible. It also could guide companies in designing clinical trials that would more definitively prove drug efficacy, in turn decreasing the time, costs and risks of drug development.

California companies leading the way

The companies founded on genomics technologies are a diverse and specialized group. The majority of these offer genomic services, applications and products to help pharmaceutical and life sciences companies make their product pipelines more productive. Genomics companies’ capabilities, business models and strategies are as dynamic as the technologies on which they are founded.

Pharmacogenomics companies help pharmaceutical companies identify and use genotypes to recruit high responders for clinical trials. They are most useful in determining subsets of patients who may benefit from a drug or for helping pharmaceutical companies better define and/or expand markets for existing products. Among California-based pharmacogenomics companies are WaferGen, Inc. and Genomic Health. As the industry matures, more companies will build in-house drug discovery and development capabilities to become fully integrated pharmacogenomics businesses.

Target identification companies, by using proprietary reagents and instrumentation and/or high-throughput screening technologies, identify specific genes or gene expression, alleles, single nucleotide polymorphisms (SNPs) and/or haplotypes that may be of interest for drug development or drug rescue. Most of these companies, which include firms that are making research tools for researchers and pharmacogenomics companies, have incorporated bioinformatics capabilities and continue to build their own proprietary genomics databases. California-based firms include Affymetrix, Celera, Genomic Health, Callida Genomics, Illumina, ParAllele and Perlegen Sciences.

Diagnostics companies are actively developing tests to identify genetic markers. Whether these are assays to be run in commercial laboratories or simpler tools for use in hospitals and physicians' offices, molecular diagnostic tests are moving pharmacogenomics into mainstream use – and public awareness. With each added diagnostic tool, and the appropriate information and therapies to use with it, healthcare moves closer to truly “personalized medicine.” Current leading diagnostic developers in California include Celera Diagnostics, Genomic Health, Gen-Probe and Roche Molecular Systems.

Contract research organizations (CROs) manage clinical trials for drug sponsors. They have long been an important link in traditional drug development. CROs are available to support pharmacogenomics development by providing DNA sampling and regulatory submittal assistance to the clients that request these services.

The future of personalized medicine

Scientists, researchers and organizations – both private and public – are making strides in cross-referencing all that is known about the building blocks of human life. Ultimately, pharmacogenomics' contributions to R&D productivity will be evaluated on four measures: number of resulting products, revenue potential, time saved and costs-to-return ratios. By bridging the chasm between gene discovery and drug development, pharmacogenomics holds great potential in all four metrics.

As with the early examples of products like Herceptin®, the biggest impact initially will likely be in the treatment of cancer. Reasons for this include the heterogeneous and aggressive nature of the disease; the receptiveness of oncologists and cancer patients toward experimental and new therapies; the large unmet need; the obvious payoff in quality of life and cost-to-benefit ratios; and the large number of oncology drug candidates already in development.

Companies at the forefront of pharmacogenomics are generating product revenues that, while unlikely to reach the \$1 billion mark, have settled into the \$300 million to \$500 million per year range. They are finding that the genetic-based diagnostics that indicate which patients are most likely to benefit from a drug are creating instant target markets and helping to set premium pricing points. Further, using pharmacogenomics in clinical-trial design is expected to reduce the clinical development time from 10 to 12 years in traditional commercialization to just three to five years. These marketing and development advantages are making it much more viable for large biotechnology companies or collaborations to commercialize their own products.

Meeting societal dilemma

Despite the enormous potential for the industry and society, many challenges must be addressed to make pharmacogenomics a main part of medical and healthcare practices. In addition to the financial, technological and operational hurdles faced by any disruptive new technology, pharmacogenomics poses myriad societal dilemmas. Among these are impending intellectual property battles and the need for new regulatory and reimbursement policies.

Perhaps the most publicized, however, are the questions of privacy and ethics associated with the collection of DNA samples. In the hope of finding genetic links to various diseases, identifying new genetic markers for those diseases and locating possible targets for new drugs, Oakland-based Kaiser Permanente is one of a number of healthcare organizations around the country that are attempting to create large DNA databases. Kaiser is planning to ask for DNA samples from up to two million adults in Northern California, perhaps beginning yet this year. The plan has brought questions of privacy to the forefront. Concerns have also been raised on the validity of the data should large numbers of Kaiser enrollees decline to participate; the commercial value and use of the database; and insurance that genetic data will not be used to deny medical coverage to individuals whose genetic make-ups indicate susceptibility to serious conditions.



Genentech and Herceptin®

One early example of a successful pharmacogenomics product is San Francisco-based Genentech's breast cancer treatment, Herceptin®.

The drug was not effective for the general population of breast cancer patients, but a genetically based post-evaluation showed excellent results in women with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. Estimated at 25 to 30% of all breast cancer patients, these women have a more aggressive disease, greater likelihood of recurrence, poorer prognosis and approximately half the life expectancy of patients with HER2-negative breast cancer.

Genentech went to the Food and Drug Administration (FDA) with clinical data that showed the demonstrated benefit of Herceptin® to the HER2-positive subset of patients and the prototype of a diagnostic test that would clearly indicate which patients would benefit from the drug. The case was compelling. In the Phase 3 trial of Herceptin® in combination with chemotherapy, the median survival rate was increased to 25.1 months over the 20.3 months seen in the chemotherapy-only group. Herceptin® was shown to improve overall response rates from 29% in women treated with chemotherapy alone to 45% with the addition of Herceptin®. And the median time to disease progression was increased to 7.2 months in women treated with chemotherapy plus Herceptin® as compared to 4.5 months in women treated with chemotherapy alone.

Herceptin® received FDA Fast-Track designation as a product for the treatment of metastatic breast cancer in March 1998. To develop a diagnostic test that could reliably identify HER2-positive patients, Genentech collaborated with the Denmark-based diagnostics company Dako. The first combination pharmacogenomics products, Herceptin® and HercepTest® were approved in September.

In January 2002, the FDA approved a second diagnostic test to be used with Herceptin® that was developed by Vysis and acquired by Abbott Laboratories. This more accurate genotyping is available to physicians and patients. It is also being used in ongoing and future clinical trials to determine Herceptin®'s efficacy in cancer patients who over-express the HER2 protein – whether in different stages of breast cancer or in other tumor cancers.

Device M&A: Is the model broken?

By David Cassak, Managing Partner, Windhover Information Inc.,
Editor, Medical Devices, IN VIVO

Buoyed in part – but only in part – by Boston Scientific's (BSC) acquisition of Guidant, merger and acquisition (M&A) activity in medical devices in 2005 reached unprecedented levels. Overall deal activity, measured in number of transactions, continued its strong showing. And activity during the first six months of 2006 furthered the trend. Device company M&A remains a powerful industry dynamic and, even with Wall Street becoming more receptive to medical device company initial public offerings (IPOs), being acquired remains an attractive exit strategy for many medical device firms.

The BSC/Guidant deal was the largest device M&A transaction ever. In fact, the \$27 billion that BSC paid for Guidant, pre-spin off of any assets to Abbott, was more than total M&A dollar volume in devices for the two previous years combined. Clearly, its sheer magnitude has had a huge impact on market psychology.

Particularly among the small, venture-backed start-ups in areas like Orange County and around Palo Alto, concerns about the deal have much more to do with the appetite of the acquiring companies to continue to do deals than with any potential competitive impact of the acquisition. Think about that: Following the biggest deal in medical device history, the top-of-mind issue for most device executives is not how the marketplace landscape will change but, rather, how the deal-making landscape will.

Beyond taking Guidant off the table, however, the deal does not alter medical device industry deal-making appreciably – or immediately. Yes, Guidant will no longer be an acquirer, but as many industry executives point out, the company had not been a particularly active deal-maker for a number of years anyway. Boston Scientific may step back as it digests Guidant. But many large and mid-sized firms will continue to grow through acquisition. Industry executives are already looking to companies like Abbott, which acquired much of Guidant's vascular business as part of the BSC/Guidant deal and which has been an active acquirer of companies over the past half dozen years. Edwards Lifesciences is aggressively building its portfolio beyond heart valves into areas such as peripheral vascular disease and percutaneous valves. And others beyond cardiovascular devices – such as Cytoc in women's health and Stryker Corp. in orthopedics, to name just a few – are attracting attention.

Medical device M&A has long been characterized by a lot of small deals rather than a limited number of large consolidation moves. An analysis of transactions shows that the departure of two or three large players barely disrupts deal flow. Continued high M&A activity, however, continues to consolidate the industry. With consolidation will come a more limited pool of buyers – even if currently there are plenty of large companies left to deal.

Another dynamic likely to have an impact on device M&A is the ability of medical device companies to complete IPOs. Through the late 1990s and into the first years of this decade, public investors had all but turned away from small-cap device investments. After the disappointing performance of the companies that went public between 1994 and 1996, investors turned cold to devices. In 2003, there were no device IPOs at all. Small companies had little or no choice but to sell their firms when they chose to exit.

Beginning in 2004 and continuing through the first half of 2006, the IPO window opened somewhat, with several striking successes (most notably Fox Hollow Technologies). Yet the prior, weak IPO market fundamentally changed how VCs manage their investments in device start-ups. They now structure companies with acquisition in mind. This strategy is evident in capital structure, with different classes of stock, limited numbers of options and other tools. It is also reflected by the marketability of CEOs who have experience selling companies.

From the largest players – such as Johnson & Johnson (J&J), Medtronic, St. Jude Medical (itself the rumored takeover target of J&J) and General Electric – to small and mid-sized companies, M&A is a pragmatic way to fill pipelines, build critical mass or launch new strategic initiatives. Acquisition also is the most likely exit for investors in small device companies. The market remains robust.

Product pipeline

Drug research and development is a complicated and expensive process. On average, it takes 10 to 15 years and costs \$800 million to advance a potential new medicine from a research concept to a treatment approved by the U.S. FDA. Potential products being moved through the development process are said to be in the “product pipeline” or “pipeline.” The phases of drug development are:

Research and discovery (R&D) is the first stage of bringing a new medicine to market. It involves systematically identifying a process or protein causing a problem in the body and then identifying and engineering a compound to correct the problem.

Pre-clinical trials are the next stage, in which scientists conduct extensive testing of a molecule or compound in laboratory and animal studies to evaluate safety and biological activity in a targeted disease.

Clinical trials are those that test the molecule or compound in human volunteers. The first step is to file an Investigational New Drug Application (IND) with the FDA. With the Agency’s approval, the investigational new drug enters clinical testing. The three stages are:

PHASE I – Companies conduct studies on 20 to 100 volunteers to determine the safe dosage range of a drug in the body as well as how it is absorbed, distributed, metabolized and excreted.

PHASE II – Companies conduct studies on 100 to 500 volunteers who have the targeted disease to evaluate the drug’s effectiveness in treating the disease. Only therapies that show promising results in Phase II trials advance to Phase III trials.

PHASE III – Companies conduct studies on 1,000 to 5,000 volunteers who have the targeted disease to evaluate efficacy and long-term safety of the drug.

Filing or applying for FDA approval comes after, and only if, therapies show positive results in Phase III. Depending on the product type, companies file a Biologics License Application (BLA) or a New Drug Application (NDA).

FDA approval may come in months or years if the FDA agrees that the Phase III clinical data proves the safety and efficacy of the medicine. Drugs that survive into Phase III trials have only a 57% chance of making it through the FDA approval process and to patients. California currently has approximately 802 drugs in the R&D pipeline, with nearly half being tested in patients.

Product development

Innovation in California’s biopharmaceutical pipeline

By Sheldon Ng, Senior Consultant, and Roberta Pinheiro, Analyst, IMS Emerging Biopharma

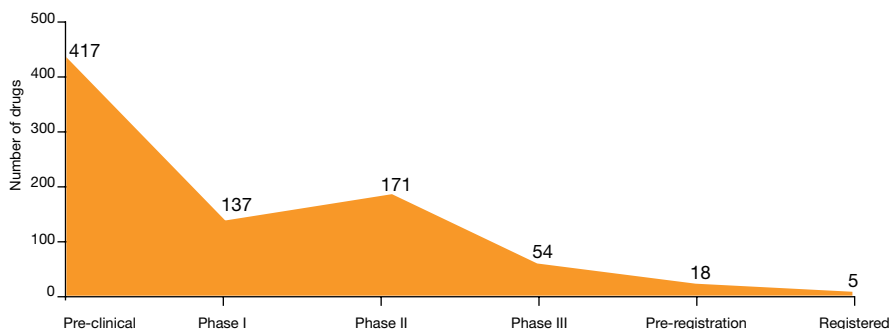
In 2005, global sales of biotechnology and pharmaceutical products surpassed \$600 billion for the first time. The direct product revenues also generated enormous additional economic value as they circulated through the operational chain that includes the discovery, development and marketing of prescription medicines, as well as associated supply and support activities and services adjacent to the biopharmaceutical industry.

The launch of new products – innovative new chemical and biological products, improved formulations and means of delivering existing products, and newly introduced generics – was a significant driver of revenue growth. While the total number of new product launches in the United States (20) was relatively low in historical terms, it is notable that 25% were from companies based in California.

Looking toward the products of tomorrow, it is encouraging to note that the biopharmaceutical and pharmaceutical industries are in a period of intensified pipeline activity. Globally, about 5,955 active products are in pre-clinical testing or clinical development. Of those, 2,352 (39%) are being evaluated in clinical, or human, testing. These numbers show a 31% increase of product candidates in clinical trials over the past three years. Companies in California account for approximately 13% and 16% of the total pipeline and the molecules in the clinic, respectively – impressive numbers that reflect the state’s leading role in global biopharmaceutical innovation.

California’s biopharmaceutical pipeline is robust, further attesting to the state’s contributions to therapy development. California companies have 802 products in the full pipeline (pre-clinical and clinical stages), of which 385 (48%) are in clinical testing.

California drugs in the pipeline



Source: IMS R&D Focus, April 2006

Top disease focus areas of California's product pipeline

Pipeline rank	Disease focus	# of products in development
1	Oncology	255
2	Immune system and inflammation	163
3	Central nervous system	116
4	Infectious disease	101
5	Diabetes and metabolics	58
6	Cardiovascular and blood diseases*	53

*Diseases or conditions that center on blood, blood forming agents or the cardiovascular system

Source: IMS R&D Focus, April 2006

Oncology R&D is a major focus area that has begun to deliver on its great promise. Breakthrough therapies such as Avastin® (Genentech) for colorectal cancer have helped fuel growth, and cancer therapies accounted for \$28.6 billion in global sales in 2005. Nearly a third (32%) of the products in California companies' pipelines target cancer, and they include a wide array of new types of therapies that could offer more effective means of treating disease than do currently available products.

The second largest disease focus in the state is **broad range immunological and inflammatory** disorders that include arthritis, psoriasis, asthma, pain, inflammation and chronic obstructive pulmonary disease (COPD). The aggregation of molecules focused on this category of ailments make up fully one-fifth of the California pipeline. Previous successful launches in this class include Enbrel® (Amgen) for rheumatoid arthritis (RA) and other indications, and Rituxan® (Genentech, Biogen-Idec) for RA and non-Hodgkin's lymphoma.

Therapies in the **central nervous system (CNS)** market address a large number of diseases and produced global sales of over \$93 billion in 2005. Above-average industry growth in CNS is attributed to sub-categories such as antidepressants, antiepileptics and antipsychotics that affect a wide range of age groups. CNS products in development (14% of the California pipeline) offer great promise and the potential for fewer side effects than seen in current therapies. As the populations of the world's largest pharmaceutical markets grow older, the clinical need for treatments of age-related CNS disorders will become more acute. A number of California companies are committed to developing new treatments for such debilitating conditions as Alzheimer's disease (19 products in development), and Parkinson's disease (8 products in development).

Infectious diseases span a wide range of disorders and are a key area of focus for the California pipeline, comprising 13% of all active programs. An array of clinical development programs are targeting unmet needs with novel therapies for HIV and AIDS (27 products in development), hepatitis and other transmittable diseases. These programs build on advances already made by companies such as Gilead Sciences' Atripla™, the first once-daily single tablet regimen for adults with HIV-1 infection, and Peninsula Pharmaceuticals' (acquired in 2005 by Ortho-McNeil) work toward new antibiotics for life-threatening infections.

Diabetes and other metabolic disorders (see page 27) are the target of at least 58 different development programs in California, or 7% of the total. Spurred by a combination of societal changes in diet, physical activity, obesity and aging,



diabetes mellitus is on the rise and will potentially affect nearly 300 million people worldwide over the next 20 years. Biopharmaceutical companies are making continued scientific breakthroughs in discovering novel therapies and delivery mechanisms to manage the disease. By 2007, five new product classes are expected to reshape the market. These include new hormonal treatments aimed at improving insulin production and secretion, enhancing cellular metabolism of carbohydrates (sugars) and targeting other potential key mechanisms. Companies also are developing inhaled insulins, the first of which was launched last year by Nektar Therapeutics in collaboration with Pfizer.

The sixth largest focus of the California pipeline is **cardiovascular disease**. While this market is already well developed (cholesterol-lowering statins saw \$28.2 billion in 2005 global sales), promising therapeutic advances for a large number of diseases are being moved through the pipeline. Therapeutic classes such as anticoagulants and antithrombotics are expected to see increased utilization, partially through successful development of potential therapies like Nuvelo's alfiameprase for stroke and Sangart's oxygen-carrying agent, Hemospan®.

California's role in healthcare innovation continues in the biologics segment which was, after all, created here. Biologics, complex products developed from recombinant DNA, have provided significant advances in the ability to treat and manage many diseases. The potential for future breakthrough biologics developed in California appears good: About 31% of the pipeline consists of biologics, compared to a global average of 27%. The state's academic and R&D environments have supported strong growth in this area over the past 25 years – in fact, biologic agents marketed by California companies in 2005 generated over \$17.5 billion in annual revenue, 33% of the global total.

Confronting an epidemic: California biomed and diabetes

Diabetes is a serious disease that has become a public health crisis, placing a growing burden on California's – and the nation's – healthcare system. Nearly 1.7 million or 6.6% of California adults (age 18 and over) had been diagnosed with diabetes as of 2003, similar to the overall national prevalence. At least 12.8 million more Californians are at significant risk for developing diabetes from being overweight or obese. Nationally, an estimated 14.6 million people have been diagnosed with diabetes, and an additional 6.2 million are unaware that they have the disease.

When diabetes is undiagnosed or poorly controlled, the risk of serious and preventable complications, such as blindness, kidney failure, heart disease and amputation, is greatly increased. Yet managing the disease can be complex and challenging: patients must be aware of their blood glucose levels and keep them under control through monitoring, diet and exercise. Some management plans include oral medications or insulin, and patients' needs for medication change with age and other factors that affect their health. Keeping a patient's diabetes management plan current requires frequent interaction with healthcare professionals.

Combined, the costs for controlling diabetes and treating complications from its poor management account for one out of every 10 healthcare dollars spent in the United States. The per capita annual costs of healthcare for people with diabetes rose from \$10,071 in 1997 to \$13,243 in 2002, an increase of more than 30%. Assuming diabetes spending followed the national healthcare expenditure trends from 2002, the average American with diabetes would have spent \$16,852 last year for treatment. In comparison, the average healthcare cost for individuals without diabetes was \$3,258.

California institutes and diabetes research

California researchers are working to reverse current trends and to improve medical measures for preventing and controlling the disease. Among academic research centers with that mission is The Larry L. Hillblom Center for Diabetes. This inter-institutional center coordinates the resources and expertise of researchers at the Salk Institute and University of California, San Diego, with the express goal of advancing understanding of the molecular mechanisms causing Type 2 diabetes.

Inder Verma, Ph.D., the center's director, said, "By analyzing and comparing data samples with experimental data, Jerry Olefsky, M.D. and Shankar Subramaniam, Ph.D. at UC San Diego have already identified several dozen genes that play a role in insulin resistance. Now we are in the process of whittling down the list." Through innovative technologies developed at the Salk Institute and UC San Diego, he added, he and his colleagues hope to select the most promising targets for therapeutic interventions.

Diabetes is a topic of intense focus at other of the Golden State's academic and research centers, too. These include the Diabetes Center at the University of California, San Francisco; the Joslin Diabetes Center at the University of California, Irvine; the Leslie and Susan Gonda (Goldschmied) Diabetes and Genetic Research Center at the City of Hope and Beckman Research Institute; the Sansum Diabetes Research Institute in Santa Barbara; The Whittier Institute for Diabetes Research in San Diego and others.

Biomedical products for diabetes management

Therapeutics. The state's commercial biotechnology companies also are seeking promising genetic targets for therapeutic interventions. For example, scientists at Hayward-based Metabolex believe they have created the largest database of genes involved in diabetes and have screened that database to generate a group of promising targets for new drugs.

"Our lead drug candidate, metaglidasen, is a novel, oral insulin sensitizer," said Harold E. Van Wart, Ph.D., president and chief executive officer, Metabolex. "The compound is designed to improve the treatment of Type 2 diabetes by lowering blood glucose without the edema and weight gain of currently marketed products" – products, he added, that currently command a more than \$2 billion market.

Metaglidasen currently is in a head-to-head comparison, Phase II/III trial with one of the approved products. Given FDA approval for Type 2 diabetes treatment, the compound may also have potential as a preventive treatment for patients identified as pre-diabetic. "These patients are converting to diabetes at a rate of 800,000 per year," said Dr. Van Wart. "Diabetes is a real epidemic. We hope our product will one day prevent people from progressing into full-blown disease."

Amylin Pharmaceuticals, based in San Diego, is named for a hormone that is co-secreted with insulin from the beta cells in the pancreas. (Company co-founder Garth Cooper, Ph.D., discovered the hormone in his postgraduate research work at Oxford University.) Amylin has developed and, in 2005, gained approval for two first-in-class medicines for diabetes. SYMLIN® is a self-administered injection given before meals that helps patients achieve lower blood glucose after meals, leading to less fluctuation during the day, and better long-term glucose control compared to patients taking insulin alone. Similarly, Amylin's BYETTA® improves blood sugar control by lowering both post-meal and fasting glucose levels, leading to better long-term control. The product stimulates insulin secretion only when blood sugar is high and restores the first-phase insulin response, an activity of the insulin-producing cells in the pancreas that is lost in patients who have Type 2 diabetes.

Medical devices. To manage diabetes, and to forestall the debilitating consequences of the disease, diabetes patients have one primary objective: maintaining steady blood glucose levels. Diet, exercise, stress management and regular eating and sleeping routines all help, as does taking medications as prescribed.

Among recent advances in diabetes management has been the introduction of innovative medical devices for quick, accurate and virtually pain-free glucose monitoring. Abbott Diabetes Care, an Alameda, California-based division of Abbott, offers a full line of monitoring systems and test strips for both home and hospital use. The company also continues to develop next-generation products. Edward Fiorentino, president of Abbott Diabetes Care, said the company currently has a glucose monitoring system in development that measures glucose levels in the interstitial fluid and transmits the results every minute to a wireless, pager-seized receiver.

"The receiver may be worn on a belt or easily carried in a pocket or purse," he said, "and is designed to display glucose values, glucose trends and the rate of change." He added that the receiver will emit high- and low-glucose alarms, giving the patient advance warnings. It also can store glucose data for analysis by users or their healthcare providers.

Alerted to a change in blood glucose outside the safe range, a diabetic patient may need to take insulin. To make the dosing easier and less disruptive than a self-administered shot, the medical device industry has developed insulin pumps. California manufacturers include Abbott Diabetes, as mentioned above, and LifeScan, Inc., a Johnson & Johnson Company located in Milpitas.

If current trends continue, the American Diabetes Association predicts that 33% of all children – and half of minority children – born in 2000 will develop diabetes in their lifetimes.



Another is Medtronic, maker of the MiniMed line of continuous glucose monitoring and insulin pump devices. The company's MiniMed Paradigm® REAL-Time System has been approved for insulin-dependent patients 18 years and older and is being tested in younger patients. (Type 1 and some Type 2 diabetes patients are insulin-dependent.)

Claudia Graham, Medtronic's Vice President of Global Therapy Access, explained, "The Paradigm® REAL-Time system is a continuous glucose monitoring device that communicates directly to the pump, establishing the first step toward a closed-loop system." The monitor signals the patient and the pump when glucose levels are out of the safety range. It tells the patient to take action, and wirelessly transmits the glucose value directly to the pump. The user then does a confirmatory finger stick test and then administers insulin. "In a closed-loop system, the monitor would signal the pump to automatically administer insulin based on these glucose values," Graham said. She added that no product does that — yet. But Medtronic and other biomedical device companies are working toward that goal.

Biomedical manufacturing

Beyond research, the
biopharmaceutical,

medical device,

instrumentation and

diagnostics sectors

manufacture products,

and each sector offers

California the potential

for hundreds to

thousands of new and

highly paid jobs.

Manufacturing within the biomedical industry encompasses a wide array of activities. Making genetically engineered proteins involves the world's most complex and costly production facilities. Increasingly medical devices include microprocessors and advanced information technology. Life sciences manufacturing thus depends on workers with highly technical skills and specialized training.

The industry's sectors have differing timelines and regulatory requirements for obtaining product approval, yet all are commercializing new products at an impressive rate. Today the state's biopharmaceutical companies have 385 drugs in clinical trials with 20% of those products in Phase III or the filing stages of development. Another 417 compounds are being tested in preclinical settings. Among all biomedical companies responding to the CHI/PwC survey, 53% categorize their stage of development as commercialization; another 41% say they are research-oriented or in clinical development.

New life sciences businesses, as well as California's existing company base, will need increased manufacturing capacity as they grow. Because many companies originated in California, the state is in a strong position to keep a large share of future manufacturing. Respondents to the CHI/PwC survey indicated that 68% of their manufacturing capacity was located in California, and 71% intend to expand that capacity in the next two years. Naturally they will need skilled workers. As part of their strategic and financial planning, companies within the industry are working closely with the state's universities and community colleges to design and provide workforce-development curricula (see page 12).

Another incentive companies have for building manufacturing capabilities in the state is Governor Schwarzenegger's commitment to bolstering the state's infrastructure. Several infrastructure components are critical to the life sciences industry's success. These include water and energy, which are both essential to all laboratory and manufacturing processes. In addition, roads, schools and housing are integral to the industry's ability to recruit and retain a sufficient workforce. CHI/PwC survey respondents said that the ability to attract talent was the top factor influencing their decisions to expand within California; cost of living (tied with proximity to R&D), cost of labor, housing and taxation completed the list of top five factors.

A third potential advantage in California's bid to encourage companies to build manufacturing facilities here is the improvement in the state's fiscal condition. After a period of alarming budget deficits, California has regained its balance. The current improvement in state finances may provide an opportunity to implement incentives key to stimulating investment and job creation within the life sciences industry. Other states and foreign countries offer a rich array of enticements for California companies to locate operations elsewhere, ranging from tax credits and abatements to free land. In contrast, California's incentives have been limited to a modest research and development tax credit and net operating loss carry-forward. And even these have come under attack from legislators skeptical about the power of tax incentives to increase corporate investment.



Of the companies responding to the CHI/PwC survey:

- 60% currently manufacture products in California; 22% do at least some manufacturing in other states; and 28% have manufacturing capacities in other countries.
- 71% expanded and 25% held steady their manufacturing inside California.
- 71% expect to expand their in-state manufacturing in the next two years, and only 2% anticipate decreasing their California manufacturing capacity in that timeframe.
- 55% plan to increase the number of manufacturing employees in California in the next two years.

While these responses promise continuation of the manufacturing growth trends in California's biomedical industry – and in California – there are signs that the state is missing additional opportunities. The CHI/PwC survey respondents said:

- Only 68% of their manufacturing capacity is located in California.
- 74% expanded and 21% held steady their manufacturing beyond California's borders in 2005.
- 76% expect to expand their out-of-state manufacturing in the next two years.



Public health crisis: Preparation, prevention and response

California – given the size, density, diversity and mobility of its population – is vulnerable to public health crises. Citizens and agencies alike understand the probabilities of such natural disasters as earthquakes, fires and floods. The state’s residents, in both their professional capacities and personal lives, have assembled “earthquake kits,” devised escape routes and created emergency response plans. They have encountered and managed agricultural and bacterial pests imported via the state’s ports, international airports and major freeways. And they have assimilated the heightened security measures warranted by the threat of terrorism.

Today California’s healthcare leaders, policy makers and biomedical industry experts are working together to understand and prepare for another public health crisis: pandemic flu.

According to Howard Backer, M.D., Chief Medical Consultant for Emergency Preparedness with the California Department of Health Services (CDHS), pandemic influenza has the potential to severely disrupt every sector of society and to cause more death than any other public health threat. Epidemiologists around the world agree and would add that any future pandemic is likely to have devastating consequences on global health and economies.

Statistics for seasonal influenza hint at the potential casualties of a pandemic. Seasonal flu infects an estimated 17 million to 50 million people in the United States each flu season. On average each year, it causes 36,000 deaths and 200,000 hospitalizations in the United States. According to the American Society for Microbiology, influenza and pneumonia are the leading infectious causes of death in the United States and rank seventh among all causes of death worldwide. Three recent pandemics were exceptionally deadly: the Spanish influenza in 1918 caused more than 50 million deaths worldwide; Asian influenza in 1957 killed up to two million people; and Hong Kong influenza in 1968 left 700,000 dead.

Flu pandemics occur after a new influenza virus emerges. Because people have little or no immunity to the virus, and because it takes time to develop vaccines, the disease spreads easily person-to-person, causes serious illness and can sweep across the country and around the world in a very short time. It is difficult to predict when the next influenza pandemic will occur or which strain will be involved. However, health professionals are most concerned about the highly pathogenic avian H5N1 virus that continues to spread across eastern Asia and other countries. The H5N1 virus is especially virulent, is being spread by migratory birds, can be transmitted from birds to mammals and, in some limited circumstances, to humans. Like other influenza viruses, it continues to evolve, raising the fear that it will become adept at spreading from human-to-human.

The World Health Organization (WHO) has placed the H5N1 virus on alert status, and California policy- and decision-makers are preparing for the worst. Backer was responsible for outlining the state’s “Pandemic Preparedness and

Response Plan” (www.dhs.ca.gov), which defines seven measures to enhance the ability of CDHS and local health departments to respond to a pandemic outbreak. In the enacted 2006-07 budget, Governor Schwarzenegger has allocated more than \$88 million in public health preparedness funds that could be directed toward pandemic flu preparations and response.

California biomed and crisis preparedness

The sense of urgency regarding pandemics extends beyond agency conference rooms into California’s biomedical industry’s laboratories and manufacturing plants. Researchers and companies are focused on six key junctures in preparing for an infectious disease outbreak.

Vaccines. It takes months or years to develop, produce and distribute new vaccines, so vaccination is not expected to be the first line of defense in a rapidly spreading pandemic. Yet better formulations and use of currently available vaccines could increase immunity and improve outcomes, especially for the more vulnerable pediatric and geriatric populations. Toward that end, researchers are working to improve current flu vaccines, which may only be 30% to 40% effective in high-risk populations. MedImmune, Inc., a Maryland-based company with R&D facilities in Mountain View, California, in 2003 launched FluMist®: the first intranasal vaccine approved in the United States. Delivered as a nasal mist, FluMist is a live virus vaccine that uses a modified attenuated – or weakened – form of the influenza virus to stimulate a protective immune response in the body. (Attenuated, live virus vaccines have been successful in the prevention of diseases such as measles, mumps, rubella, polio and chickenpox.)

More effective vaccines for seasonal influenza can deliver immediate health and economic benefits. Depending on the year, flu accounts for as much as \$3 billion to \$15 billion in direct and indirect costs, including approximately 70 million missed workdays and approximately 38 million missed school days. Beyond protecting against seasonal flu, better vaccines may lessen the impact of pandemic flu.

Still, a vaccine for the specific pandemic strain would be ideal, and several projects are aimed at developing such a tool. MedImmune and the National Institutes of Health’s (NIH) National Institute of Allergy and Infectious Diseases (NIAID) – through a Cooperative Research and Development Agreement (CRADA) – are working to produce versions of MedImmune’s live, attenuated intranasal influenza vaccine for use against different subtypes of potential pandemic influenza strains. The NIH has begun enrolling participants in a Phase 1 study of an intranasal H5N1 influenza vaccine candidate. Investigators at MedImmune and Johns Hopkins Bloomberg School of Public Health Center for Immunization Research, where the study will be conducted, are hopeful that a live, attenuated intranasal influenza vaccine would be as effective against potential pandemic A strains as it has been shown to be against seasonal A strains of influenza.

Antiviral medications. Antiviral drugs could reduce the death toll in an influenza pandemic. One class of antivirals, neuraminidase inhibitors, do not eliminate the virus, but they do decrease its release from infected cells by blocking a key viral enzyme. By limiting the severity of symptoms in infected patients, antivirals could be used to protect vulnerable groups.

The World Health Organization (WHO) has recommended that governments stockpile neuraminidase inhibitors to treat 25% of their populations in case of a pandemic. One leading neuraminidase inhibitor, Tamiflu® was discovered by Gilead Sciences and brought to market in partnership with Hoffmann-La Roche. Roche and GlaxoSmithKline, maker of Relenza® are working with the WHO and governments around the world to establish rapid response stockpiling.

Another key way to prepare for a pandemic, according to Frederick Hayden, M.D., professor of Internal Medicine and Pathology at the University of Virginia Health System, would be to conduct additional clinical studies to define the proper antiviral dosages for critically ill patients. Because of the potential for influenza viruses to become resistant to existing drugs, Hayden recommends developing alternative therapies and routes of administration for the currently marketed medicines.

Diagnostics. In the face of a pandemic, point-of-care professionals would need to quickly determine the cause of their patients’ symptoms. “To make sure the patient has flu A, and not another respiratory illness, you would need to be able to run diagnostics,” said Noel Harvey, Ph.D., director of Research and External Relations at BD Technologies, a medical device and diagnostics company with facilities in San Jose and Oceanside. “Some could provide results in 15 minutes or less — ensuring valuable anti-virals are used on appropriate patients.”

Carlsbad-based Invitrogen is another company on the forefront of pandemic planning. Willem Folkerts, director of Invitrogen’s Federal Systems subsidiary, noted that myriad tools, tests and technologies that the company is developing

for protection against bioterrorism could be well suited for point-of-care professionals during a pandemic. One prime example is the company's work with the U.S. Defense Threat Reduction Agency to develop a handheld instrument for detecting the presence of biological agents. "From a single sample," he said, "we can detect six different pathogens within a 15-minute analysis time."

Portable diagnostic tools could enable public health officials to more quickly identify, contain and control a pandemic. "When you live in a global village," James Meegan, Senior Director of R&D for Invitrogen Federal Systems said, "you have the opportunity to take a global approach to diseases like SARS and avian flu."

Cepheid, headquartered in Sunnyvale, is adapting technologies it has developed to combat bioterrorism and to provide clinical diagnostics for pandemic influenza. Cepheid produces automated systems that enable any-skill-leveled technicians to perform complex DNA and RNA analyses in a matter of minutes. Best known for its products and performance around the 2001 anthrax bioterrorism scare, the company is in the R&D phase for genetic tests to detect the presence of clinical and pandemic organisms. Cepheid CEO John Bishop explains that the most accurate way to detect these organisms is to identify their unique DNA, a task that starts with understanding the genome of the specific virus.

Delivery technologies. Vaccines and, in some cases, antiviral medications are administered via injections. Beyond making plans for increasing syringe production in case of an outbreak, medical device companies also are developing technologies to reduce the impact of a pandemic. In addition to the dose-sparing, safety engineered syringes it currently offers, BD Technologies is developing a "micro-needle" that delivers vaccine into the skin instead of the muscle – an approach that may require less vaccine for more effective immunity.

Capacity for stockpiling. Imagine if millions of people were infected. The medical device supply chain could break down under pressure if adequate planning and partnership between medical supplies companies and governments are not undertaken well in advance. The avian flu vaccine is "currently a two-dose regimen. That would require approximately 600 million syringes to immunize the United States alone," according to BD's Dr. Harvey. "Governments around the world are approaching the medical device industry requesting hundreds of millions of syringe units even without a vaccine currently on hand," he said.

Harvey warns that other front-line supplies needed to fight infectious outbreaks will include masks, ventilators and hospital beds, which are currently in short supply. The acquisition and stockpiling of such supplies is part of the ongoing preparedness planning at all levels of government globally. According to infectious disease experts, however, stockpiles of antiviral medications and flu vaccines are inadequate, and necessary vaccine surge capacity does not currently exist in the United States or in the world.

Plans for surveillance and containment

On November 1, 2005, the U. S. Department of Health and Human Services (HHS) released the National Strategy for Pandemic Influenza, making the United States one of about 50 countries that have drafted pandemic-preparedness plans. In the following month, federal lawmakers followed up with legislation providing \$3.8 billion for state and local pandemic planning, vaccine development and antiviral and supplies stockpiling.

The California Department of Health Services (CDHS) issued its draft preparedness plan in 2005 and continues to update the public on pandemic flu via its Web site – www.dhs.ca.gov. The site features links to municipal and county health agencies, basic information on avian flu and notices of meetings, conferences and publications. The state’s plan focuses on measures to enhance state and local health departments’ response to a pandemic outbreak or other public health emergency. These measures include expanding the capacity to investigate disease outbreaks and increase surveillance and response to communicable diseases; increasing California’s antiviral drug supply and capacity to manage antiviral drugs and vaccines; developing a program for preventing and controlling infections in healthcare facilities; strengthening the state’s laboratory infrastructure and surge capacity and mounting an aggressive public health education campaign.

Public education campaigns and communications would stress such simple measures as frequent hand washing and covering one’s mouth when sneezing – tactics effective in stemming the spread of seasonal flu. Public health preparedness campaigns to discourage going to work or school with upper respiratory virus will be important, according to Alloy Venture’s Leighton Read. And up-to-the-minute instructions during a pandemic would be vital to containing and controlling the crisis.

Plan globally protect locally

As Carol Brosgart, M.D., Gilead Sciences’ vice president of Public Health and Policy, noted, “Crises such as the AIDS epidemic, the Katrina disaster and a possible pandemic, in some ways are like a torchlight illuminating problems in our healthcare system, in society and how we work together. Let’s use pandemic preparations as an opportunity to examine and improve our more routine operations.”

By improving its prevention and treatment of seasonal influenza, California will be better prepared for pandemic influenza. Being prepared for pandemic influenza will enhance the state’s ability to respond to other emerging infectious diseases, the threat of bioterrorism and natural disasters.

Crises such as the AIDS epidemic, the Katrina disaster and a possible pandemic, in some ways are like a torchlight illuminating problems in our healthcare system, in society and how we work together.



Academic research

California's academic research centers lead the nation in grant funding and commercial licensing agreements. Breakthrough science forms the foundation of the state's biomedical industry.

Translational research – the process of rapidly advancing basic science from the laboratory into treatments for patients – has gained traction within California's biomedical industry.

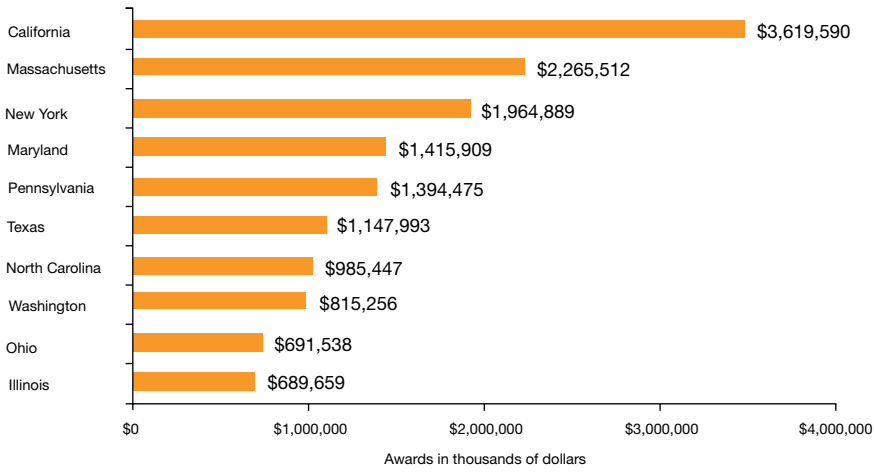
Long before there was a term for this process, California's academic research centers were making biomedical-related discoveries that ultimately yielded life-saving medicines, diagnostic tools, drug delivery systems and medical devices. The state's community of academic research centers includes 100 institutions – among them the 10-campus University of California, the 23-campus California State University, Stanford University, University of Southern California, Caltech and private research institutes such as the Salk Institute, The Burnham Institute and The Scripps Research Institute. Research at the three UC-managed national laboratories (Lawrence Berkeley, Lawrence Livermore and Los Alamos) advances human health by using scientific and engineering capabilities to focus on the areas of genomics, disease susceptibility and prevention, and improved healthcare and medical biotechnology. Researchers in the state's schools – faculty, post-docs, graduate students and undergrads alike – continue to pioneer research that enlarges the body of scientific knowledge and presents opportunities for making new therapies for patients around the world.

Academic research and the National Institutes of Health

Researchers in company labs rely on product sales and investment capital to fund their work (see Investment section, page 16). Academic researchers, in contrast, depend mainly on government grants and philanthropy to support their research. By far the largest supporter of health-related research in academic laboratories is the National Institutes of Health (NIH). The NIH grant application process is highly structured and extremely competitive. Applications are peer reviewed, and even those that are eventually funded are frequently returned to the applicant for additional clarifications.

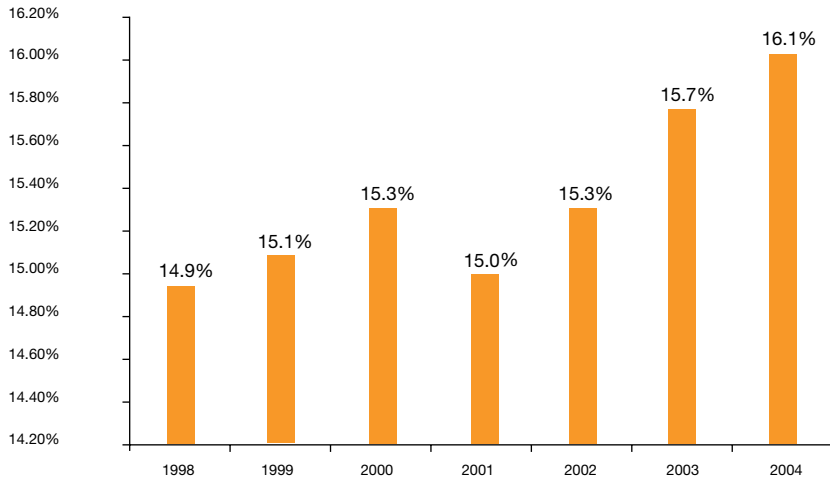
Since the program's founding in 1946, California's academic researchers have consistently received more NIH funds than any other state. In 2004, California received 7,788 grants and contracts totaling \$3.6 billion in NIH funding, approximately 37.4% more than the second largest grantee (Massachusetts). As the top recipient of NIH funding, California received 16.1% of all NIH funds distributed nationwide in fiscal year 2004. Between 2000 and 2004, funding to California increased approximately 31.9%, comparable to the overall increase in NIH funding distributed nationally (28.4%).

Top ten NIH grantee states FY2004



Source: NIH award data at <http://www.silk.nih.gov/public.cbz2zoz@www.states.fy9604>

California's share of total NIH grants 1998-2004

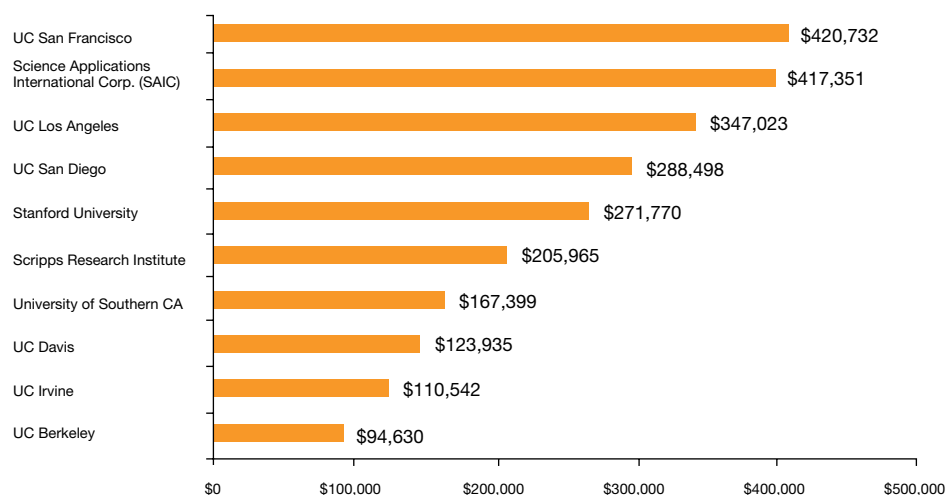


Source: NIH award data at <http://www.silk.nih.gov/public.cbz2zoz@www.states.fy9604>

For fiscal year 2003 (the most recent year for which data for grantees was available) eight of the 10 California institutions receiving the largest amount of NIH funding were universities. The two non-university institutions receiving substantial NIH grants in 2003 were the Science Applications International Corporation (SAIC) and The Scripps Research Institute (TSRI).

Ten largest NIH grantee institutions in California in FY 2003

(in millions of constant USD)



Source: NIH award data at <http://silk.nih.gov/public/cbz2zoz/www.fy2004.californ.dsnc>

Government funding for small businesses and start-up companies

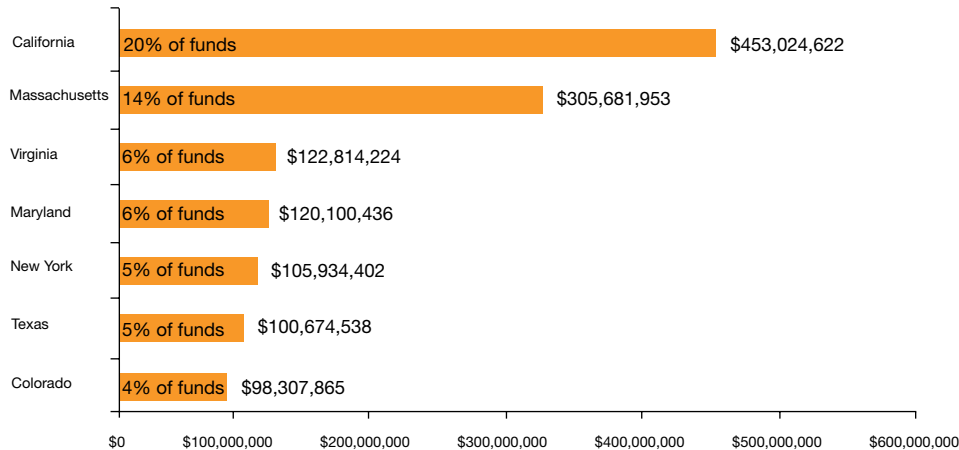
The U.S. Small Business Administration's (SBA's) Office of Technology uses two grant programs to increase the competitiveness of small, high-technology firms: the Small Business Innovation Research (SBIR) and the Small Business Technology Transfer (STTR) programs. Attracting SBIR and STTR dollars is important for the development of new products. The federal SBIR program is a critical provider of seed capital for biomedical entrepreneurs and often provides initial funding for start-up companies.

Under the SBIR program, federal departments and agencies with annual extramural R&D budgets exceeding \$100 million must reserve at least 2.5% of those budgets for awards to small U.S. high-tech firms. For 2004, such agencies included the Departments of Agriculture, Commerce, Defense, Education, Energy, Health and Human Services, and Transportation, as well as the Environmental Protection Agency, National Aeronautics and Space Administration, and the National Science Foundation.

Under the STTR Program, federal departments and agencies with annual extramural research budgets exceeding \$1 billion must reserve 0.30% of such funds for award to small U.S. high-tech firms. The set-aside percentage was increased from 0.15% to 0.30% in fiscal year 2004. These awards are smaller than the SBIR grants and fund cooperative R&D projects involving small business and a non-profit research institution. These include the U.S. Departments of Defense, Energy, and Health and Human Services, as well as the National Aeronautics and Space Administration and the National Science Foundation.

California companies have been particularly successful at attracting SBIR and STTR money. In 2004 (the year for which most recent data is available), the state received the largest number of SBIR and STTR awards (1,463) and the largest amount of total funding (\$453 million) in the United States. The bulk of SBIR and STTR awards to California come from the Department of Health and Human Services via the NIH.

Distribution of SBIR and STTR awards to selected states FY2004



Source: Small Business Administration

Technology transfer: Where academic and industry researchers meet

California's biomedical research institutions often produce inventions that spark private sector interest, resulting in agreements to transfer novel technologies from academic institutions to commercial companies who, in turn, conduct the applied research and development necessary to turn basic science into a product for patients. One key source of innovation for the state's biotechnology, pharmaceutical, medical device, drug delivery, diagnostic and genomics companies is licensing agreements with California's academic research centers.

Research collaborations continue

Among the companies responding to the CHI/PwC survey:

- 51% have at least one clinical research agreement with a California academic research institution.
- 54% may broaden their research agreements, and nearly half (45%) plan to establish new research agreements with a California research institution in the next two years.
- 35% have at least one patent license agreement with a public or private California academic institution.
- 29% anticipate establishing at least one patent license agreement in the next two years.

The top two factors influencing biomedical companies' decisions to expand within California are 1) the ability to find talent and 2) proximity to R&D. Active and leading research institutions within all of California's biomedical centers affect those decisions favorably.

Basic research and education in California: The road ahead

In 2006, California's academic research community continued to flourish, thanks to the deep pools of scientific talent in public and private institutions around the state. The outlook for the years ahead, however, is far from clear, with challenges and opportunities in almost equal measure.

Federal funding. In his budget request for 2007, NIH Director Elias B. Zerhouni, M.D., explained how research discoveries are transforming medicine.

- **Coronary heart disease:** Since 1970, owing largely to new drugs and devices, mortality from cardiovascular disease has decreased 63%, averting one million early deaths a year.
- **Cancer:** For the first time in history, annual cancer deaths in the United States have fallen. Discoveries based on NIH-funded research have produced improved screening and detection, along with innovative drug therapies for cancers that were untreatable. Today there are 10 million American cancer survivors.

Dr. Zerhouni also explained how NIH has expanded the scope of its mission to encompass biodefense, vaccine research, pandemic flu preparedness as well as new fields of research: genomics, bioinformatics, bioengineering and biomedical imaging.

Despite these accomplishments – and after doubling the NIH budget between 1998 and 2003 – federal support for biomedical research has weakened. In fact, current funding has fallen below the rate of inflation, resulting in a net decrease. Meanwhile, with large federal budget deficits pressuring all discretionary spending, the near-term prospects for increased federal funding appear dim.

Troubling as well are severe restrictions on NIH funding for embryonic stem cell research. Leading scientists have described stem cells as a field with as much, or more, potential to unlock the mysteries of disease as the discovery a generation ago of recombinant DNA and genetic engineering. But President Bush decided in 2001 to permit federal funding only for research on a small number of existing stem cell lines, far fewer lines than the scientific community considers adequate. In July 2006, the president vetoed legislation that would have expanded funding for embryonic stem cell research. It was his first use of the veto power. To circumvent federal limitations, in 2004 California voters passed Proposition 71, creating a new embryonic stem cell research initiative funded by \$3 billion in state bonds (see page 42).

University of California initiatives. The University of California is a public resource unique in the world of higher education and academic research. In recent years, UC has increasingly encouraged research faculty to collaborate with industry in order to translate basic discoveries into practical technologies for patients. Examples:

- **UC Discovery Grants.** Matching grants are provided through UC Discovery Grants, offered by the Industry University Cooperative Research Program (IUCRP), which promote academic excellence while fueling entrepreneurship, job creation and economic growth. Partner companies have engaged more than 730 UC faculty and 1,600 students since 1996 in research relevant to industry R&D and the California economy. Through July 2006, 795 UC Discovery Grants involving 447 partner companies have been awarded, for a total of nearly \$2.7 million in joint industry, state, and university funding. Life sciences grants represent 54% of that total.

The majority of these life sciences research projects have focused on using molecular biology and information technology research and development in all life sciences-related disciplines to identify new approaches for diagnosing or treating patients or on developing new technologies to advance drug discovery. To extend that research, the program has launched a one-year Pilot Project to draw new multi-disciplinary ideas for advances engaging the IUCRP's five scientific fields and identify emerging opportunities in related technology areas, focusing on: health and wellness, energy and environment, and rapid application of nanotechnologies.

- **California Institutes for Science and Innovation.** To create partnerships among UC, the state and industry, the four interdisciplinary California institutes focus on quantitative biology, nanotechnology and information technology. Taken together, these four institutes represent a billion-dollar, multidisciplinary effort that focuses public/private resources and expertise on research areas that are critical to sustaining California's economic growth and competitiveness – while bringing the benefits of innovation more quickly into the lives of people everywhere. The program encourages company scientists and engineers to participate in and support institute research programs. It also provides an accelerated path for technology transfer designed to enable the founding of new companies and to attract new cycles of private investment to young entrepreneurial firms. The Institutes helps participating companies better leverage their R&D investment, providing society with a rate of return that economists have shown averages roughly 50%. Companies involved in research projects through the California Institute for Quantitative Biomedical Research have included GlaxoSmithKline, Gryphon Sciences, Merck, Mitsubishi, Scios and others.



The California Institute for Regenerative Medicine

By Christopher Thomas Scott, Ph.D., Executive Director
Program on Stem Cells in Society, Stanford Center for Biomedical Ethics

November 2004: The Voters Speak

Scientific and political winds met in a perfect storm on November 2, 2004 when California voters approved Proposition 71, a bond measure authorizing the release of \$3 billion to support stem cell research. First came groundbreaking advances in stem cell biology – including the discovery of human embryonic stem cells – that predicted a bold new future of medicine. The next event was just as momentous. On August 9, 2001, President George W. Bush announced that funding from the National Institutes of Health (NIH) could no longer be used to derive new stem cell lines made from donated embryos. His decision was driven by his moral opposition to using human embryos for medical research, in step with his social conservative supporters. In an apparent concession, the president said that funds could be used for research on lines made prior to his address. If researchers wanted to make new lines, they would have to find private funding.

Since the president's proclamation in 2001, Congress introduced a welter of stem cell and cloning legislation. While politicians and scientists are unanimous that the experiment that produced Dolly the Sheep should never be used to clone humans, legislators remain divided about whether a powerful technique called nuclear transfer, which uses human eggs, can be permitted to make new lines of embryonic stem cells, along with lines made with unwanted donated frozen embryos. Congress considered a dozen or more measures in 2006, including an act (HR 810) that would overturn the Bush policy and laws that would impose severe criminal penalties on researchers, caregivers and patients using embryonic stem cells or their therapeutic derivatives. In a watershed event, HR 810 passed the Senate in late July, but not with enough votes to override Bush's first-ever presidential veto.

The funding restrictions, political uncertainty and fears that the U.S. would lag behind other countries prompted California, long accustomed to its position at the forefront of medical research, to ensure that this promising area of biomedical research had a future. Advocates of stem cell research knew the endorsement of top scientists was required for the vote to carry, especially on the eve of the 2004 presidential election. Two weeks before the election, Governor Arnold Schwarzenegger officially endorsed the measure. Proposition 71 easily passed by a vote of 59% to 41%. It would provide an average of \$300 million a year for ten years to academic institutions and corporations, with most of the money targeting embryonic stem cell research.

The California Institute for Regenerative Medicine

The measure created the California Institute for Regenerative Medicine (CIRM). The institute is presided over by a 29-member board, the Independent Citizens Oversight Committee (ICOC) and three working groups comprised of university officials, stem cell scientists, commercial life sciences professionals, disease advocacy representatives and real estate specialists. Among its powers, CIRM has the ability to obtain money from bonds sold by – and repaid to – the state, using the funds to finance research, new laboratories and to support its own costs.

The architects of Proposition 71 designed it to create an independent scientific institute not subject to the shifting interests of elected officials, Washington politics or annual state budgets. Other potential – but indirect – positive effects include luring researchers to the state, increasing investment in companies that develop therapies and tools and increasing employment and tax recovery. The measure's economic upsides are expected to emerge only over long time horizons, ten years or more. The sheer size of CIRM – with an annual budget about the size of a smaller, new institute at the NIH – sends a message about the promise of stem cells, underscoring how expensive biomedical research can be and how distant therapies are from human use. Things begin in the laboratory and, with the bond money, California aims to compete alongside those nations who support embryo research and the full spectrum of stem cell biology.

Legal challenges

In practice, however, it proved impossible to build a state-funded organization of that magnitude without involving the California legislature. After all, California lawmakers, as the representatives of voters, reasoned that the CIRM as a state agency deserved the same level of oversight and accountability as, for example, the University of California. State lawmakers introduced bills that included a constitutional amendment requiring more transparency of the CIRM deliberations and meetings, public input into policy-making and the disclosure of financial conflicts-of-interests of members of working groups and anyone else associated with the institute. Though these bills failed, the legislature is likely to take an ongoing interest in CIRM for years to come.

Along with the action in Sacramento, two lawsuits challenged the constitutional authority of the CIRM and ICOC to spend money and, as a result, no General Obligation bonds have been sold. The suits turn on claims that the act would not be applied in a socially or economically reasonable fashion, does not have sufficient state oversight and that CIRM governance is fraught with conflicts-of-interest. On March 2, the Alameda County superior court heard the plaintiff's arguments and on April 21, its decision ruled in favor of the CIRM, upholding the constitutionality of Proposition 71.

The superior court's strongly worded opinion said plaintiffs could not argue to invalidate the act based on how the statute might be applied in the future. On the matter of state oversight, the ruling states that state entities not exclusively under state control could indeed expend funds for legitimate purposes. It further found sufficient controls over CIRM, citing independent audits, public reports and conflicts-of-interest requirements, and noted that most members of the ICOC are nominated or appointed officials. Because the plaintiffs oppose stem cell research, they will likely exhaust all possible legal avenues and plan to appeal the ruling. In light of the verdict they are unlikely to prevail.

Near-term progress

The downside for CIRM is legal limbo. In the intervening months, the institute has aggressively moved to address legislative challenges and criticism from Sacramento lawmakers. It launched its organization and found money to survive, raising \$45 million in bond anticipation notes to provide much-needed bridge funding for the first round of training grants. One day after the Bush veto, Governor Arnold Schwarzenegger directed the state to issue a loan of \$150 million to launch the research programs. The response from California laboratories was swift and immediate: CIRM received 350 letters of intent from scientists who say they will apply for funds. It drafted a set of medical and ethical regulations for research institutions, building upon guidelines written by the National Academies of Sciences. CIRM requires that research oversight committees must review and approve the experiments. Grantee institutions must ensure that women who donate eggs for stem cell research be given time to consider their donation and be fully informed of the medical risks involved. No money can be exchanged for eggs, other than reimbursement of reasonable donor expenses.

Another concern centers on how benefits from CIRM-funded discoveries will flow back to California taxpayers. CIRM's proposed intellectual property (IP) policy for non-profits addresses some of the return-on-investment concerns. Under the federal 1980 Bayh-Dole Act, academic institutions may patent inventions that arise from government grants. Negotiating licenses with companies that commercialize the discoveries generates royalties for basic research institutions. Under the

CIRM policy, non-profits that patent and license inventions must return 25 cents of every dollar made above \$500,000 to the state's coffers.

Following NIH policy, grantees are instructed to negotiate non-exclusive licenses when possible; in practice this means that a fair number of exclusive licenses will be executed because the start-up is the only entity that can reasonably commercialize the product and/or because the fees, milestone and royalty terms make sense for both parties. If an exclusive license is negotiated, then a commercial development plan is required. If the plan isn't followed or is slow to develop, CIRM reserves the right to "march in" and take back the technology.

Biotech executives and CIRM supporters alike worry that the dominant holder of embryonic stem cell patents, the Wisconsin Alumni Research Foundation, will make good on its demand to extract payments from the state. This, coupled with march-in rights, revenue payments and state-mandated price controls of therapies, has the biotechnology industry concerned about how California companies can stay competitive in a CIRM-funded environment.

Setting the stage

Though CIRM won't be fully funded for a year or more, Californians have reasons to be encouraged. CIRM executives are experienced in "big science" administration, the nuts-and-bolts of a research granting enterprise. The draft Grants Administration Policy, or GAP, has clear mechanisms for submissions, approvals and oversight. The leadership is formulating a long-term strategic plan, a requirement if CIRM hopes to be responsive to changes in national and international regulatory policy. The grant review committees, comprised of leading scientists, are exceptionally strong. Ethical policies, though evolving, have been carefully considered. California was the first state to write improved ethical rules by iterating on national guidelines.

The move towards open meetings has been good for the CIRM, particularly with respect to informed policy-making. Inviting public comment reinforces the notion that the research and its benefits belong to all citizens. But open meetings aren't appropriate for scientific peer-review, where anonymity of expert reviewers ensures the integrity of the process. Finally, CIRM must address the challenge of communicating effectively with the public, calibrating expectations when basic and clinical science – and the policy that guides them – is rapidly changing.

Voters stated in clear terms how important stem cell research is to California. But time is of the essence: Countries where embryonic stem cell research is encouraged are moving quickly to discover and develop treatments and cures, and American investment will likely follow. Once the lawsuits are over, CIRM looks to be primed and ready to get on with the business at hand, keeping California at the edge of a promising new biotechnology, where it belongs.



Methodology

Survey

CHI partnered with PricewaterhouseCoopers LLP to collect and administer the data for the 2006 CHI/PwC California Biomedical Industry Survey. The survey was conducted in the spring of 2006 and targeted approximately 1,500 companies that conduct business in California in the areas of pharmaceuticals, biotechnology, medical devices, diagnostics or medical equipment. PricewaterhouseCoopers provided a secure and confidential Web-enabled questionnaire. Participants' data was captured by the Web site and loaded into a database, which was then downloaded for formatting and analysis by PwC staff.

Questions to which PricewaterhouseCoopers did not receive a valid rate of response were dropped from the final report. The response rate to the survey, after deducting invalid or obsolete contacts, was 5.8%.

Employment

The data used to estimate biomedical industry employment in California was provided by the California Employment Development Department. This data is collected from employers in the Current Employment Survey (CES). It does not include the self-employed, unpaid family workers and private household employees. Jobs located in the county are counted in the county, although workers may live outside the area. Jobs are counted regardless of full-time or part-time status. Individuals who hold more than one job may be counted more than once.

Wages were computed using ES 202 Covered Employment and Wage data from the Bureau of Labor Statistics. As 2004 is the most recent year for which wage data is available, computed wages were inflated using the Consumer Price Index to generate estimates of these wages for 2005. Additionally, Securities and Exchange Commission EDGAR data were used to determine in-state employment numbers for large medical device manufacturing companies headquartered elsewhere yet maintaining significant California operations.

The college and university portion of academic research employment was calculated using the Bureau of Labor Statistics ES 202 Covered Employment and Wage data. 2004 is the most recent year for which data was available from BLS. Therefore, the 2005 employment number for college and university employment is equal to the 2004 number. Private education services employment was calculated in the same manner and with the same data source as the rest of the industries.

Investment

Descriptions of venture capital investments in California life sciences companies were derived from the PricewaterhouseCoopers/National Venture Capital Association MoneyTree™ Report with data from Thomson Financial. Information about the market value of California biomedical firms in 2005 was provided by NASDAQ.

Strategic alliances were estimated using data on California companies in Windhover's Pharmaceutical Strategic Transactions Database.

Personalized medicine

This section was excerpted from *Personalized Medicine: The Emerging Pharmacogenomics Revolution*, a white paper published by PricewaterhouseCoopers in February 2005. The description of Kaiser Permanente's planned DNA database was derived from the San Francisco Business Times' June 18, 2006 edition and the Chris Rauber and Daniel S. Levine article, "Kaiser seeks deposits into bank of DNA." That information is gratefully used by permission of the *San Francisco Business Times*.

Product development

Data characterizing the California biopharmaceutical pipeline were compiled by cross-referencing California biopharmaceutical companies and their reported development products from proprietary IMS databases, including IMS Lifecycle: R&D Focus. Biopharmaceutical products were categorized into therapy areas based on Anatomical Therapeutic Chemical (ATC) codes, used by the World Health Organization since 1976. Biologics pipeline summaries were taken from the IMS R&D Focus database, and biologics sales figures were derived from the IMS National Sales Perspective Database. The data capture R&D activities in California, regardless of the location of the companies' headquarters.

Public health crisis

This section was excerpted from *Strategies for Prevention and Response to Public Health Crises*, a white paper published by the California Healthcare Institute in May 2006. The information was updated and expanded through interviews with companies with California operations that are focused on pandemic and other health crises preparedness.

Academic research

Data used in the NIH grants analysis come from the National Institutes of Health Office of Extramural Research. The data include all awards to California from NIH, some of which do not necessarily fund basic biomedical science. For example, a number of grants were used for training programs and projects that are designed to support the research training of scientists for careers in the biomedical and behavioral sciences, as well as to help professional schools to establish, expand and improve programs of continuing professional education. Other grants were used to fund health policy or behavioral science research. Despite these caveats, overall the NIH data does demonstrate the federal commitment to health sciences research in California.

Monetary time series data were adjusted for inflation using the Consumer Price Index. Nominal dollars were inflated to real, either 2004 or 2003 depending on the availability of data, dollars.

Data for the SBIR and STTR grants analysis comes from the U.S. Small Business Administration (SBA). SBIR and STTR data include awards distributed by all federal agencies participating in these two programs. As such, some of the funding described here overlaps with funds distributed by NIH to California.

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