
GLOBAL BUSINESS REPORTS

# UNITED STATES

## BIOPHARMACEUTICALS

**2019**

Pre-release Edition

# *Dear Readers,*

The United States' life sciences sector has experienced significant year-on-year growth and pronounced strength on a global scale for some time, and been resilient in the face of external pressures and shifting global dynamics. 2018 was a record year for generic drug approvals, exceeding the FDA's previous record set in 2017. Exciting discoveries are being made and milestones met in the biotech space, moving the industry further towards precision therapies and cures. However, whilst the U.S. life sciences industry will undoubtedly remain a powerhouse worldwide – particularly when it comes to innovation, as a high value market with a strong IP protection framework – several impacting factors have recently called the strength of its growth trajectory into question. Most pronounced at a national level is the U.S. government shutdown at the beginning of 2019, impeding upcoming biotech IPOs and impacting the FDA's ability to review applications, potentially leading to a complete approval gridlock. Meanwhile, the increasing scrutiny of CFIUS is causing trepidation amongst Chinese investors, which make up a large portion of VC investment into U.S. biotech companies. The financing landscape remains as competitive as ever, and it is crucial for companies and their home hubs to position themselves effectively to capture those investment dollars.

Within the United States, investors often turn their attention to the most prominent hubs of activity, with California's Bay Area and Massachusetts' Boston/Cambridge Area generally oscillating at first and second place depending on the assessment criteria. Interestingly, while California's vast land area is full of life sciences activity from top to bottom, the sheer size of the 163,696-square-mile Golden State has created the perception of fragmentation. As a result, San Francisco and its neighboring counties are often considered separately from other hubs in the state, including San Diego, Los Angeles and Orange County, which are all notable for life sciences employment and investment received year on year.

This publication seeks to shine a spotlight on California's less-recognized hubs, bringing them out of the shadow cast by the Bay Area's success onto an equal platform to be considered as investment destinations. The following pages present a snapshot of our research thus far, including insights from leading executives across the sector, in advance of the launch of the final report at the end of April, which will give a more holistic insight into the industry at a national level. Until then, our team continues to carry out on-the-ground research in top hubs in the United States to provide comprehensive coverage of the U.S. biopharmaceutical industry. We would like to warmly thank our association partners for their continued support, as well as all the executives and researchers who shared their valuable insights.

***Thank you – enjoy the read!***

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*Project Director*
**Global Business Reports**


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# A Solid Foundation for Success

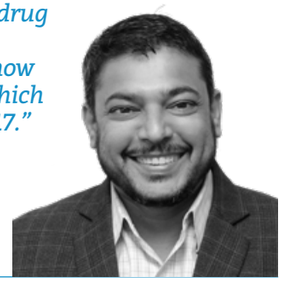
## *The U.S. Biopharmaceuticals Industry Remains Resolute*

From New Jersey - the historic base of large pharma and 'the medicine chest of the world' – to the biotech superclusters of the Bay Area and Boston-Cambridge, and the smaller biotech hubs strung across the country, stakeholders in the U.S. biopharmaceuticals industry have consistently shown a mutual desire to collaborate, evolve and innovate. However, following what was a dynamic and volatile 2018, domestic and international factors have led to an uncertain outlook for the U.S. economy, and raised questions over what advancements the biopharma industry can be expected to make this year.

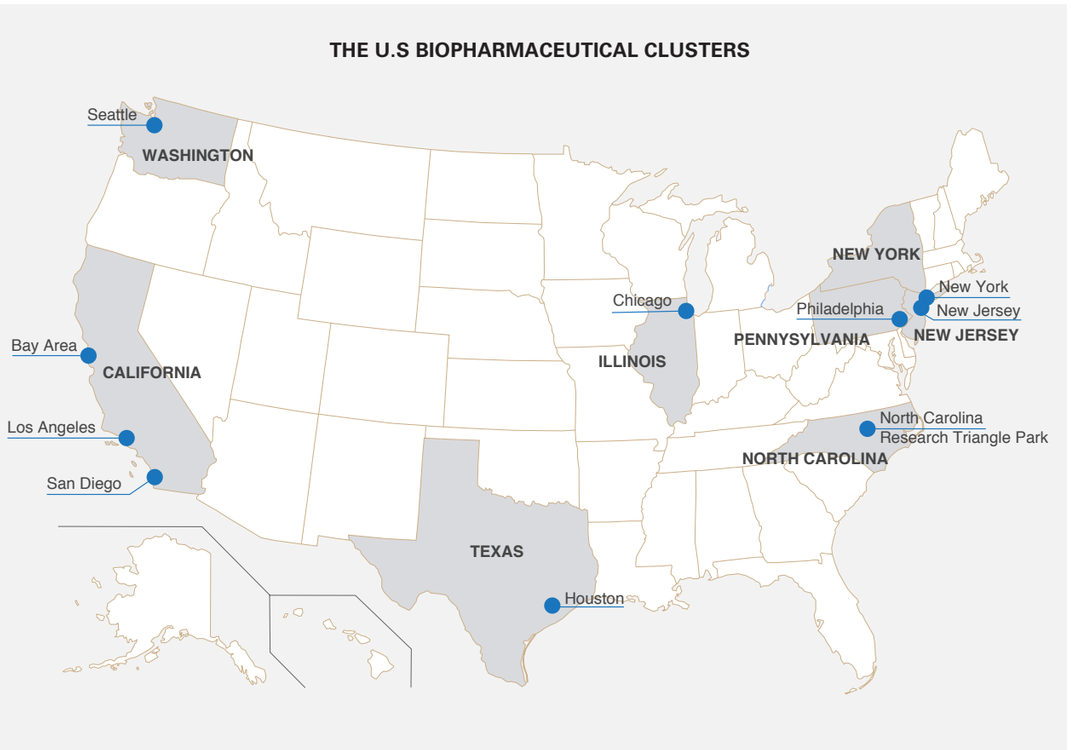
2019 was meant to be an exciting year for biotech IPOs, with Gossamer Bio and Allector amongst the larger names aiming to list on Nasdaq. However, the sidelining of the Securities and Exchange Commission (SEC) from the U.S. federal government shutdown of 2018-2019 has already placed doubts over the future of such deals due to the SEC's increased backlog. Pressure off the back of the Trump administration's concerted efforts to lower drug prices and a record year for FDA approved generics continues to trouble innovative companies. Of greater concern for smaller biotechs is a new regulation put in place by the U.S. Department of the Treasury in October 2018, which has meant that foreign investment resulting in a non-controlling equity stake in a biotech will be subject to review by the Committee on Foreign Investment (CFIUS). This could be bad news for U.S. biotechs, since over the first eight months of 2018, US$2.85 billion of investment came from Chinese investors, representing nearly a third of overall VC investment, according to Pitchbook. "Feedback indicates that Chinese investors are becoming tentative when deploying capital into the United States due to the current trade war and the future consequences U.S. investment may have for them," remarked Louis Lehot, managing partner at DLA Piper's Silicon Valley practice.

Despite growing concerns over the aforementioned political and geopolitical factors, the U.S. biopharmaceuticals industry's strong foundation and diverse base across multiple cities and states means it is unlikely to be shaken in the medium to long-term. The U.S. bioscience industry reached US$2 trillion in annual economic impact for the first time in 2018, according to the Biotechnology Innovation Organization (BIO), a figure larger than the entire GDP of all but eight countries. Other promising signs include accelerated venture capital investment and job growth in the life sciences industry across the nation.

*"The FDA has improved its timeline in terms of drug approval. Previously it could take up to 15 months for approval, which has now decreased to between eight to 11 months. Despite this, the FDA has increased the generic drug user fee amendments (GDUFA), maintenance fees, facilities fees and drug master file (DMF) fees. Accumulated fees are now almost US$200,000, which were US$80,000 in 2017."*



**-Jay Shukla, President and CEO, Nivagen**




*"Although the general market appears to be slowing down in some sectors and there are talks on Wall Street about a potential recession in the United States in the second half of 2019, I do not see it affecting the life sciences industry to a great degree. The life science and healthcare industry tends to be contra-cyclical, so I do not see a slowdown versus other industries or sectors."*

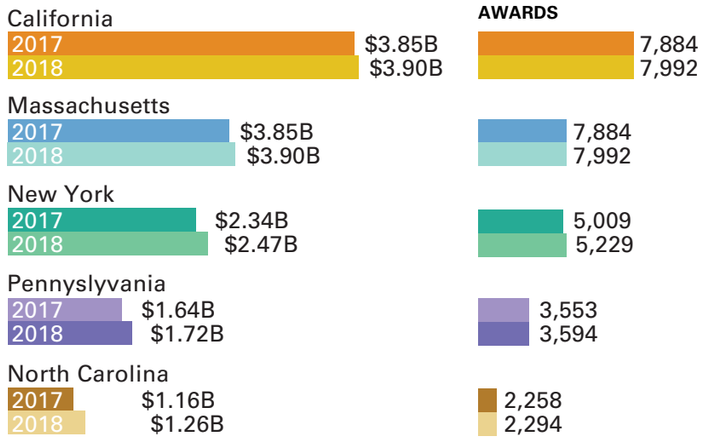
**-David H. Crean, Managing Director - Investment Banking, Objective Capital Partners**

Top academic and research institutions remain the key differentiator for developing a successful biotech hub, something that has increased in relevance as more opportunities – both through greater early-stage VC investment and an increasing number of incubators/accelerators - are being afforded to researchers and early-stage biotechs to help bridge the often problematic 'Valley of Death'. Boston-Cambridge - home to more than 500 biotech companies, five of the top six hospitals in the United States, and 48 colleges – continues to cement itself as one of the top biotech superclusters. The hub attracted US$2.155 billion in VC Investment in 2017, as well as attracting 48% of all US-based biotech IPOs the same year, according to MassBio. However, the Bay Area – the birthplace of biotechnology – continues to increase in influence, adding to the well-intentioned East –West rivalry between the two hubs

Although these superclusters often take the limelight, the U.S. biopharmaceuticals industry is by no means concentrated between the two. San Diego, where 48,430 people were employed in the life sciences sector in 2017, ranks third in VC investment in the United States according to Ernst & Young, garnering more investment than any other country, including China and the United Kingdom. "The key advancement I have noticed in San Diego's biotech hub is that there is more capital being attracted into Southern California," commented David H. Crean, managing director for investment banking at Objective Capital Partners. "We are also seeing more venture funds come down to San Diego. There is a lot of great technology in Southern California, across Los Angeles, Orange County and San Diego, and we are starting to see a little bit of that momentum picking up."

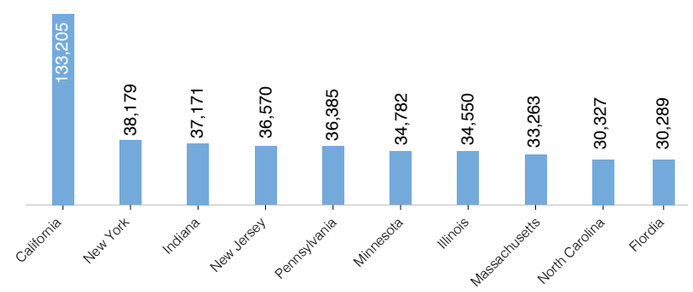
**TOP FIVE STATES RECEIVING NIH GRANTS**

Source: California Life Sciences Association (CLSA) 2019 California Life Sciences Industry Report



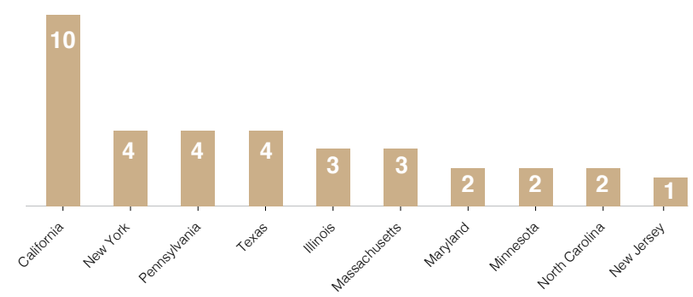

**EMPLOYMENT IN PHARMACEUTICAL AND MEDICAL DEVICE BY STATE 2017**

Source: California Life Sciences Association (CLSA) 2019 California Life Sciences Industry Report




**NUMBER OF UNIVERSITIES IN THE WORLD TOP 100**

Source: California Life Sciences Association (CLSA) 2019 California Life Sciences Industry Report




## RISING STARS OF THE U.S. BIOPHARMACEUTICALS INDUSTRY

Away from the traditional biotech hubs of California and Massachusetts, a number of cities are aiming to learn from the success of the superclusters. New York City has set plans to become a leader in life sciences innovation and R&D with a US$500 million investment plan. The De Blasio administration's Ten Point Plan, as part of LifeSci NYC, expects to create 16,000 new jobs, with a US$100 million new Applied Life Sciences Hub and US$300 million in tax incentives to attract investment in commercial lab space for life sciences businesses. Next door, New Jersey is also trying to reinvent itself. Long respected as the epicenter for the biopharmaceutical and medical device industry, as well as being home to 13 of the world's 20 largest pharmaceutical companies, a New Jersey Biotechnology Task Force has been set up to foster and evolve the New Jersey biotech ecosystem. North Carolina's life sciences industry, built around its Research Triangle Park – the largest research park in the United States with the highest density of Tier 1 universities in the country – continues to increase in relevance. Although unable to attract the same level of capital investment as the superclusters, the state is home to more than 700 bioscience companies that directly employ more than 63,000 people, according to NCBIO.

Los Angeles, historically known as the home for Hollywood entertainment and its previously established aerospace industry, has a burgeoning and ever-growing life sciences sector. In 2018, the University of California, Los Angeles (UCLA) and University of Southern California received a combined total of US$636 million in NIH funding and the county had the second largest employment numbers for life sciences in California. "L.A. County's bioscience industry currently generates more than US$40 billion in economic activity and supports more than 70,000 direct jobs and 160,000 indirect jobs, but it still has tremendous potential for growth," highlighted Mark Ridley-Thomas, supervisor on the Los Angeles County Board of Supervisors.

The United States has multiple biotech clusters that rival any across the globe. Its biopharmaceuticals industry has been built through its unparalleled research institutions, collaborative ecosystems, stream of domestic and international investment dollars, and an insatiable desire to keep innovating. Whilst other industries would be heavily affected by a potential slowdown in the economy this year, the U.S. biopharmaceuticals industry is unlikely to be held back in the interim.•

# A Special Focus on California

*The Golden State of Opportunity*

From the Gold Rush in 1848, to the creation of the motion picture industry in Hollywood in the early 1900s, and the tech boom of recent years, California has historically been an inventive state where dreams have been realized. Although some of the state's industries have declined in recent years, including aerospace, California's economy is now the equivalent of the world's fifth-largest country, with a GDP nearing US$3 trillion. California's life sciences industry has continued to evolve and is now incomparable across the globe. Home to 3,418 life sciences companies, including 1,570 biotech & pharma companies, the industry injects 958,000 direct, indirect and induced jobs into the state. Moreover, the state remains the national leader in NIH grants, attracting US$3.9 billion in 2018, as well as venture capital, which attracted US$7.6 billion the same year, US$1.5 billion higher than in 2017.

**CALIFORNIA IN NUMBERS**

Source: California Life Sciences Association (CLSA) 2019 California Life Sciences Industry Report

**Sacramento**
California's state capital

**40,017,007**
California population

**958,000**
Total direct, indirect and induced employment in life sciences (approx.)

**US$58,821**
California state GDP per capita

**US$164,123**
Average annual life sciences wages by cluster

**1,570**
Biotechnology & pharmaceutical companies in 2017

**US$177.7bn**
Total estimated revenue in life sciences sector (2017)

What remains key to the growth of the state's life sciences sector is its research and academic institutions. Driven by the University of California (UC) system, which is comprised of more than 238,000 students, the state is home to 10 of the world's top 100 universities (Shanghai Index, 2018 Rankings). Spread across the state from Davis to Irvine, the depth and breadth of the region's academic excellence is unparalleled, igniting ecosystems through a combination of talent, technology transfer and company spin outs. California's institutions are the entry point feeding into the largest biotech network globally. This is in part helped by having the largest number of doctoral recipients (4,954) in science and engineering in the United States, much higher than the second largest (New York with 3,050), according to CLSA.

Although attention is often reserved for the Bay Area, San Diego and more recently Los Angeles, it is California's entire network that contributes to an unsurpassable life sciences ecosystem. Sacramento - the state capital – which has 10,912 employees in life sciences, is an increasingly attractive choice for smaller biotechs and contract service providers due to its close proximity to the Bay Area and far lower living costs. Santa Cruz, roughly 70 miles south of downtown San Francisco, also offers similar opportunities. "Especially for young companies, setting up operations in Santa Cruz can be attractive as it is less expensive and with more square-footage available than most of the Bay Area," highlighted Andrea Pesce, industry alliances and licensing manager at UC Santa Cruz. With so many hubs in California competing for investment dollars and talent, one would assume that the competition would be harmful. In fact, California has made a concerted effort to increase collaboration between the different hubs so that their strengths can be shared. Joe Panetta, president and CEO of Biocom, sees any sort of rivalry as a positive motivator for the hubs and state overall: "The biotech industry is very collaborative, but it also enjoys great rivalry, especially in California. I would not say the hubs are in competition with each other, but are constantly chiding each other in a healthy manner. It serves to move everybody forward and to grow the industry overall. The bottom line for all these companies is to move across the goal line and improve the health of patients. We are all in it together, but we are constantly competing for investment capital and talent," said Panetta.•

## *Joe Panetta*

President and CEO,
Biocom

**Does rivalry reduce the opportunity for greater synergy between California's three major biotech hubs?**

Healthy rivalry is a positive thing for the industry. The biotech community is very collaborative, but it also enjoys great competition, especially in California. I would not say the hubs are in competition with each other, but are constantly challenging each other in a beneficial manner. It serves to move everybody forward and to grow the industry overall. The bottom line for all these companies is to launch products that improve human health. We are all in it together, and we compete for investment capital and talent – within California and across the country. One of the things Biocom aims to do is to communicate the vibrant message of California's life sciences industry whilst also underlining the individual strengths of each geographic hub. Moreover, we very much see ourselves as bridge builders not only in California, but also across the United States and the globe.

**What role is Biocom playing as lobbyist both in Sacramento and Washington D.C.?**

With the 5th largest GDP in the world, California is a large enough entity that we behave as a country. When you include Massachusetts, you are connecting the two most innovative states in the country with respect to life sciences. The greater question is how can we fuel the R&D pipeline of innovative products so that they can get through a very-efficient FDA process and into the hands of patients? When Gilead's first hepatitis drug came out a few years ago, we looked at the comparative cost of the drug versus maintaining a patient with Hepatitis C. When looking at the cost of healthcare, the cost of prescription drugs is just one component. What we realize is that we are not doing a good enough job communicating the true long-term value of drugs and therapeutics to the general public. We need to challenge insurers and other healthcare players more as an industry. We need to find a way to work collectively to make the system fairer and bring down the cost of healthcare across the board.•

# The Bay Area

## *The Innovation Capital of the World*

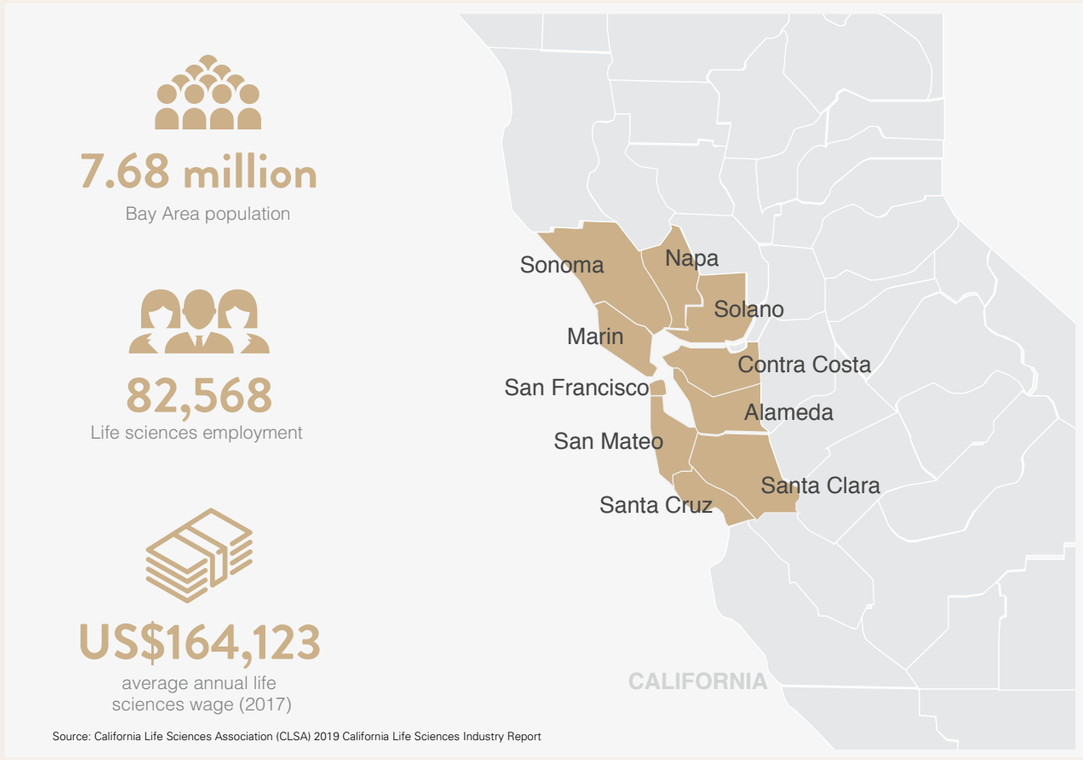
The Bay Area has become an epicenter for the global biopharma industry. As the birthplace of biotechnology, it boasts top academic institutions, a host of the leading biotech companies - including Gilead Sciences and Genentech – and a plethora of VC investment opportunities. For example, VC investment in digital health alone in the Bay Area was at US$3.6 billion in 2018 according to CLSA, far greater than overall life sciences VC investment in every U.S. state apart from Massachusetts – even exceeding that of every country globally. Furthermore, UC San Francisco (UCSF) and Stanford University received the largest amount of NIH funding - US$599 million and US$473 million respectively - across the state. However, what has really set the biopharma industry apart in the Bay Area is how it is able to leverage the different opportunities within the entire ecosystem. "The Bay Area is a hotbed of innovation and with the convergence of the Silicon Valley tech sector and the traditional biotech sector here, we are seeing amazing new technologies that leverage the strengths of both industries in digital health applications, computational biology, liquid biopsy technologies, and AI/ML therapeutic applications," highlighted Michelle Nemits, senior director for business development in the Bay Area at Biocom. "The advances in personalized medicines, cell and gene therapy and synthetic biology applications are also proliferating. The participation of non-traditional investors, like Jeff Bezos, Bill Gates and Richard Branson, speak for the potential some of these technologies may have to be disruptive forces as we move forward."

As a global epicenter for both the tech and life sciences industries, the Bay Area continues to position itself as a strategic center for precision medicine, with the overall aim of shortening drug development timelines. UCSF has made precision medicine central to its overarching institutional vision ever since President Obama's Precision Medicine Initiative and the California Initiative to Advance Precision Medicine, hosted by UCSF, has been designated US$30 million for the current fiscal year. Increasing numbers of companies, specializing in bioinformatics or diagnostic tools for precision medicine are finding their way to the Bay Area. DNAnexus - a spinout from Stanford University - has been developing a cloud-based data analysis and management platform for DNA sequence data, whilst Precision for Medicine's new Quartz Bio platform enables companies to manage biomarker data in a much more integrated way to help make sense of data in real time. Cytobank, located in Mountain View, has developed a SaaS platform for machine learning-based analysis of high-complexity life sciences data. It is furthering its technology by trying to better understand the needs of biotechs and pharma within the community. David Craford, president and CEO at Cytobank, highlighted: "Recently the field has seen remarkable success with immunotherapies, especially in the area of oncology. This has driven pharma to generate and analyze higher complexity data to understand the immune system and the host-immune response, as they attempt to maximize the value of the information they can get from every clinical trial patient sample. Especially in early phase trials, pharma will run very high complexity technologies on their samples."

*"The ability to identify well characterized – even rare – populations to demonstrate clinical proof of concept is paving the way for early approvals followed by expansion of indications. This approach is essentially replacing the "traditional" Phase 1/2/3. Contrast this with as recently as 10 years ago, where only a small handful of companies were proactively pursuing a personalized approach, or forced into it by regulators or payers. Then, the general holy grail was the $1B+ blockbuster, despite high failure rates. The incorporation of diagnostic tools for applications like patient stratification or efficacy monitoring has played a major role in this change in mindset."*

**-Rajiv Mahadevan, Managing Director, Precision For Medicine**





# San Diego

*Biopharma in Motion*

San Diego is home to one of the most collaborative and connected biotech hubs, not to mention the perfect climate and stunning scenery that attracts and retains talent. Although it has had to play second fiddle to the Bay Area for some time, the increased cost of living in the Bay Area and increased capital investment coming to San Diego - the city ranked third globally in venture investment according to EY – are slowly turning the tide. San Diego is able to offer a depth of life science managerial expertise, a pool of the top biotech companies, including Illumina and Gossamer Bio, and even the benefits of Tijuana, Mexico on its doorstep as a top destination for biomedical manufacturing. "San Diego continues to have a robust biotech ecosystem, both on the financing and research and development side," said Steve Worland, president and CEO at eFFECTOR Therapeutics. "While we have comparatively fewer investors here than Boston or the Bay Area, San Diego has a very strong reputation for its research and early product development prowess, so we can attract VCs that are located in other geographies, thereby importing capital to the region."

However, what remains key to San Diego's biotech ecosystem is its academic and research institutions. UC San Diego and Scripps Research received significantly higher NIH funding in 2018 at US$438 million and US$190 million respectively, and of the 50 to 60 startups UC San Diego produces each year, 66% are in the life sciences. "San Diego has the advantage of being more collaborative than anywhere else in the country," remarked Paul Roben, associate vice chancellor for innovation & technology commercialization at UC San Diego. "Across UCSD's scope of research, US$200 million is contributed annually by industry. We are the number one public institution in the country for industry dollars in research. We always try to understand what industry wants and we structure deals to meet their needs."

San Diego has been named in some quarters as the Silicon Valley for early-stage biotechs due to the nurturing ground offered to researchers and early startups. From biotechs like Abreos Biosciences - a precision medicine company dedicated to improving the development and commercialization process for biotechs with its proprietary Veritope platform - to Agilinx Therapeutics - a biotech founded last year that is acquiring immuno-oncology and infectious disease molecules and taking them through to proof of concept in humans – there is a consistent stream of new biotechs entering the ecosystem.•

*"The greater San Diego region offers access to highly skilled human resources, a collaborative culture, world-class research institutions, major hospital networks and a long history of entrepreneurship with repeated successful exits. Many organizations like BIOCOM, CONNECT, BioLabs, JLABS, and SDIC support Biotech growth providing resources and programs maximizing entrepreneurial success."*

**-Ruben Flores-Saaib,**
**Co-founder and Treasurer,**
**San Diego Innovation Council**

*"San Diego is a big innovation hub and one of the four major life sciences hubs in the United States. When the company evaluated these four hubs, in terms of cost, quality of resources and overall capability, San Diego County was the most affordable."*

**-Wayne Woodard,**
**CEO,**
**Argonaut Manufacturing Services**

**3.34 million**
San Diego population

**48,430**
Life sciences employment

**US$118,719**
average annual life sciences wage (2017)


Source: California Life Sciences Association (CLSA) 2019 California Life Sciences Industry Report

# Los Angeles

## *A New Phase of Growth*

Los Angeles' desire to move further into the life sciences industry should not come as a surprise to anyone on the West Coast. In fact, its influence in the biopharmaceuticals industry has been subtly increasing for some time now. The county has the second highest number of life sciences employment at 57,117 and NIH funding grants in the state, and is home to a number of the top performing academic institutions, including UC Los Angeles, University of Southern California (USC) and California Institute of Technology (Caltech). It also has one of the most proactive public boards – the Los Angeles County Board of Supervisors – in the United States that has identified the life sciences industry as a key growth industry for Los Angeles. "We are taking the concept of public-private partnership to new heights with the goal of making L.A. County a world leader in bioscience," said Mark Ridley-Thomas, supervisor for Los Angeles County. "We want to contribute to advances in global health, drive economic development and create jobs."

Over the past year, a number of initiatives have begun to help catalyze the county's growth. These have included the formation of BioLA - with Amgen as founding sponsors – a new bioscience organization that has been designed to strengthen the county's life sciences ecosystem and accelerate the pace of start-up activity. Moreover, L.A. County has allocated US$15 million to create the L.A. Bioscience Investment Fund for early-stage startups and the county is working with LA BioMed to build a 15-acre biotech park on the Harbor-UCLA Medical Campus. The key emphasis for these initiatives is to instigate greater collaboration within Los Angeles, something that has historically held the county back given the fragmented nature of the city. "The geographical dispersion of Los Angeles does impact UCLA as many technologies and startups have traditionally relocated to Boston or the Bay Area after the initial research is licensed," underlined Mark A. Wisniewski, senior director of biopharmaceuticals, business development and technology transfer at UCLA Technology Development Group. "Critical components for creating an integrated biotech hub in Los Angeles include attracting seasoned management and smart capital from biotech venture capital firms. We are moving in the right direction in Los Angeles but need to accelerate this positive trend."

*"Los Angeles has an enormous amount of unappreciated and hidden technology value as well as human talent, both on the research and the development side. There is great opportunity for investment in the area as there is currently little competition in what is a very dynamic space."*

**-Bassil Dahiyat, President and CEO, Xencor**

Bay Area and Boston-Cambridge-based companies have had the enviable benefit of not having to look elsewhere for venture investment, something not afforded to Los Angeles. However, in September 2018, Westlake Village BioPartners launched a US$320 million fund in committed capital to Los Angeles. With the funds set to be invested in pharma and biotechnology, especially around seed funding and series A funding, promising research at UCLA, Caltech and USC is set to receive a helping hand. Moreover, there has been a push by Mayor Eric Garcetti's office and the L.A. Economic Development Board to attract international investment from China and South Korea, especially given the city's strong Korean and Chinese communities.

For Los Angeles, trying to connect all stakeholders together so that the 4,751 $mi^2$ county can work more effectively as a single unit will be the main challenge. However, there is a clear concerted effort to make this happen and to create a life sciences hub to rival San Diego and the Bay Area.•



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**10.16 million**
Los Angeles County population

**57,117**
Life sciences employment

**US$88,523**
average annual life sciences wage (2017)


Source: California Life Sciences Association (CLSA) 2019 California Life Sciences Industry Report

## *Mark Ridley-Thomas*

Supervisor,
Los Angeles County Board of Supervisors

**Could you introduce us to L.A. County's bioscience industry and underline the catalyst behind the increase in life sciences jobs over the past year?**

L.A. County's bioscience industry currently generates more than US$40 billion dollars in economic activity and supports more than 70,000 direct jobs and 160,000 indirect jobs, but it still has tremendous potential for growth. Last year, L.A. County overtook San Diego and moved into second place in California in terms of its number of life science jobs and amount of grant awards from the NIH.

L.A. County is perfectly positioned to take the bioscience industry to the next level because it is the largest provider of public health services in California. As part of its Bioscience Initiative, L.A. County has invested in two bioscience incubators and is also working with LA BioMed to build a 15-acre biotech park on the Harbor-UCLA Medical Campus.

**How is the investment climate in L.A. currently set up to facilitate partnerships between investors and the biotech industry?**

After a 2014 Battelle Memorial Institute study affirmed L.A. County's potential to become a national bioscience leader, the L.A. County Economic Development Corporation released a Bioscience Industry Cluster Development Implementation Plan in 2016. Up until now, however, partnerships have happened organically due to interest from both investor and industry. With BioLA, we can ensure that the core elements of startup activity – infrastructure, capital and talent – exist in abundance for all early stage life science companies.

**What are your key objectives for the life sciences space in your final two years in office?**

Contrary to public perception, bioscience is not strictly a "lab coat" industry but one that provides well-paying jobs at all skill levels. In growing the industry, L.A. County is making a strategic investment to diversify the regional economy so that job losses can be kept at a minimum during economic downturns.•

# California's Biotechs Up Close

*"Alkahest's breakthrough research has interrogated the plasma proteome to understand which plasma proteins are most impactful to the aging process. To do this, we investigated plasma samples from a range of ages to understand if the protein signatures were in fact different. About 10% to 20% of proteins on either end of the spectrum either increase or decrease with age, with the majority of proteins preserving their function over time. The proteins which change with age, which we call chronokines, can be either beneficial or detrimental. We then target these chronokines for potential therapeutic effect."*

-Elizabeth Jeffords,
*Chief Commercial & Strategy Officer*, **Alkahest**

*"Agilinx's strategy is focused on acquiring assets that are nearing human trial. We then rapidly take them into the clinic and look for proof of concept in Phase I and Phase IIa to prove efficacy. By doing this, a whole new world of opportunities opens. There is a very high failure rate in clinical trials but with smarter medicine and new ways of genomic mapping we can be much more deliberate about which compound we are bringing to clinical trial and how we select our patient group."*

-Kevin Elliot,
*CEO*, **Agilinx Therapeutics** *&*
*Partner*, **Procela Consulting**

*"The company was developed for cancer patients who wanted effective, safe, and long-lasting treatment, without the use of drugs. But cancer is the smallest and first stage application of our approach, and Filtricine aims to be a next-generation therapy company for multiple diseases."*

-Xiyan Li,
*Co-Founder and CEO*, **Filtricine**

*"Rigel aims to discover key immune system processes, which we know are central to some diseases. IRAK, for example, is central to many immune-signaling processes. If we are able to block IRAK, we are able to block a large segment of downstream inflammatory cytokines that are activated. As a result, there are approximately 20 diseases where IRAK is potentially involved and we are excited to explore the broad potential of R835 in autoimmune and inflammatory diseases, such as psoriasis, lupus and others."*

-Raul Rodriguez,
*President and CEO*, **Rigel Pharmaceuticals**





# Standing Out in the Biotech Crowd

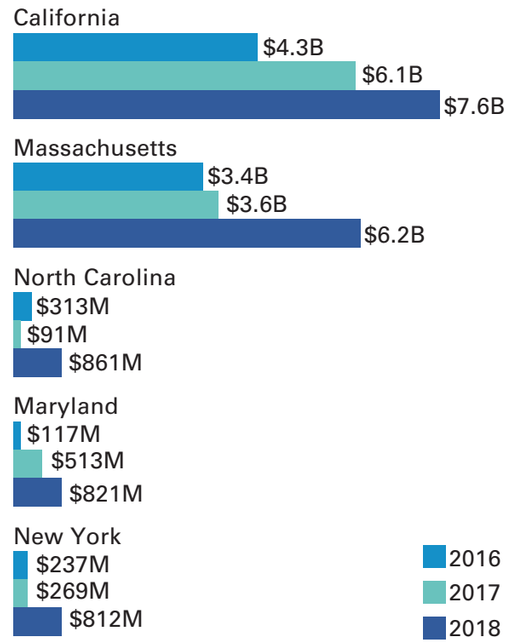
## *The VC Investment Climate*

The biopharmaceuticals industry has the highest percentage of R&D reinvestment in the United States. More recently, drug discovery has shifted away from large pharma, with biotechs now accounting for 70% of all clinical trials in the United States. Unlike large pharma, which will have commercialized products in the market and have a revenue stream, many biotechs do not. It is therefore less surprising that 90% of biopharmaceutical companies are currently not making a profit, according to BIO. For an academic researcher or recently-spun out start-up, initial funding will likely come through grants. The NIH, for example, provides US$37.3 billion funding per annum. However, given that a 2016 Tufts Center for the Study of Drug Development report put the cost of developing a drug at US$2.7 billion - which includes cost associated with failed drugs - if a biotech does not receive private investment, strike a partnership with a large pharmaceutical company or a big biotech, or have an IPO, they are unlikely to sustain themselves through the development period.

The beginning of 2018 featured a number of large M&A deals, including Celgene acquiring Juno Therapeutics for US$9 billion and Impact Biomedicines for US$7 billion, and Sanofi US acquiring Bioverativ for US$11.6 billion. However, it was VC private investment that took center stage, breaking numerous records, with US$13.5 billion in venture capital poured into biotechs in the first 10 months of 2018, far higher than all of 2017 (US$11 billion). Of note was Grail's oversubscribed US$300 million Series C round and Allogene Therapeutics – a biotech pioneering the development of allogeneic CAR T therapies for cancer – completing a US$120 million Series A, especially as both biotechs had substantial

**TOP FIVE STATES FOR LIFE SCIENCES VC INVESTMENTS**

Source: California Life Sciences Association (CLSA) 2019 California Life Sciences Industry Report




*"We like to focus on our differentiated approach – we believe we are one of the few companies focusing on controlling translation to control cancer – and our foundational science that comes out of some very strong labs at UCSF. In addition, we have an experienced team with a track record that many venture capitalists understand and respect."*

-Steve Worland,
President and CEO,
eFFECTOR Therapeutics

**TOP TEN BIOTECH VENTURE INVESTORS BY OVERALL ROUND TOTALS**

Source: DealForma

| INVESTOR | TOTAL ($M) |
|---|---|
| Arch Venture Partners | $3,919 |
| Fidelity | $3,386 |
| OrbiMed Advisors | $3,314 |
| Celgene | $2,671 |
| Comorant Asset Management | $2,571 |
| Alexandria Venture Investments | $2,507 |
| New Enterprise Associates | $2,368 |
| RA Capital Management | $2,306 |
| Foresite Capital Management | $2,210 |
| GV | $1,805 |

funding from Chinese VC firms. With CFIUS, as of October 2018, scrutinizing foreign transactions much more carefully, there could yet be implications for both biotechs and many other U.S. biotechs in the coming year.

## PERFECTING DUE DILIGENCE

Although there is increased capital pouring into biotechs across the nation, especially in California, which saw US$7.6 billion of VC investment in 2018 and Massachusetts, which saw US$6.2 billion, hundreds of biotechs will struggle to raise capital each year. For every investment a VC fund or private equity firm makes, it will always carry with it long odds, given that drug-approval rates have dipped to 9.6%, according to BIO. Despite the monetary risks associated with drug research and development, large pharma, big biotechs and VCs are increasingly looking to invest in early-stage biotechs to capitalize on technology before more significant value inflection points. "There is a trend of investment capital moving into the market earlier in the cycle," remarked Thomas W. Chalberg, partner at Heroic Ventures. "In the biotech space, early capital is a requirement. There is also the recognition of how much value can be created early on in the cycle, and investors now want to participate in this early stage value creation. Across the industry, we are definitely seeing a trend towards investment at earlier stages, which is often related to partnerships with academic institutions."

*"The Hong Kong stock exchange is more targeted towards Chinese companies – NASDAQ or the NYSE are still likely the better options for most U.S. companies to list on. However, there are some situations in which it does make sense for U.S. companies to consider Hong Kong as a listing venue; such as if they are targeting the Chinese market for their products and are looking to raise their brand profile in China and Hong Kong, or if they have Chinese or Hong Kong investors looking for an Asian exit"*

**-Alan Seem,**
**Partner,**
**Jones Day**

As investments are made earlier in the process, greater analysis will need to be undertaken to de-risk any transaction. "What is most important when doing a transaction with an early-stage company is that extensive due diligence is carried out as a result of higher potential risk. What we are seeing more of is a "build-to-buy" model, where companies put their money in with an option to purchase later," highlighted David H. Crean, managing director for investment banking at Objective Capital Partners.

Whilst certain early-stage biotech executives will travel the country searching for initial seed and Series A investment dollars, there are a handful of seasoned executives that understand exactly what investors are looking for. For example, Mirum Pharmaceuticals, a San Diego-based biotech, received US$120 million in its Series A funding round five weeks after its inception. "There are three key components for setting up a biotech: the science, which includes the technology or the molecule; the money; and the people," remarked Mike Grey, chairman and CEO at Mirum. "By far the most important component for any investor is the people. Mirum was a marriage between the previous leadership of Lumena and Tobira - a powerful group of minds. For the investors coming on board, the value proposition regarded the potential of getting to Phase III clinical data in a relatively short period of time."

Indeed, when considering successful acquisitions, there is usually an executive with a strong track record behind the scenes of the fledgling biotech being bought up.







## THERAPEUTIC FOCUS FOR 2019

Oncology continues to be the key area for VC focus, although many others are venturing into therapeutic areas that are less crowded. Given that a third of Californian companies' pipelines were focused on cancer in 2018 according to CLSA – 433 of the 1,332 total therapies in development – this should come as little surprise For Arch Venture Partners and OrbiMed Advisors, the first and third-largest venture investors, globally, cancer therapeutic investments from January 2015 to October 2018 came to 35% and 43% respectively as a percentage of their overall pipeline.

However, VCs are now looking to diversify their investment pipelines into other therapeutic areas and different technologies. Areas of considerable interest for investors include stem cell therapy, gene therapy, orphan drugs, neurodegenerative diseases, regenerative medicine, precision medicine and digital health. "Even though the bulk of venture dollars are flowing into oncology, there are in fact opportunities across multiple therapeutic areas," highlighted Carolyn Ng, managing director of Vertex Ventures HC. "Hence, there is no good rationale for us to be pigeonholed into only one area of interest as we would then be missing out on good opportunities within other segments of the industry."

For oncology, a vast amount of funding is reserved for immuno-oncology, whilst other approaches do not receive as much attention despite presenting many opportunities. "Though it was identified, along with immuno-oncology, as one of the 10 areas of emphasis by Vice President Biden's Cancer Moonshot panel, side effect reduction is an under-appreciated field," remarked Brian Frenzel, CEO of Tosk – a biotech developing a family of inexpensive, small molecule drugs designed to prevent the toxic side effects of common cancer treatments. "Side effects not only adversely affect patients' quality of life, but can be costly to treat and can limit the effectiveness of cancer therapy. Our small molecule drugs are inexpensive to produce and fit easily into existing treatment regimens. They are intended not only to reduce the cost of treatment but to improve outcomes for cancer patients."

As well as looking at short-term value creation, VC firms must always understand the ultimate commercial viability in the long run. This has meant that certain therapeutics, especially in immuno-oncology, have taken precedence over the past decade. The Bill & Melinda Gates Foundation – the largest private foundation in the United States – through its US$2 billion Strategic Investment Fund (SIF) has had the opportunity to really focus on meeting unmet patient needs that would not make monetary sense to a normal VC. The Foundation has had the key goal of managing and even eradicating infectious diseases in the developing world. To maximize on what is already being developed, the SIF has looked into the advancements being made in other therapeutic areas. "With so much investment going into areas like immuno-oncology, the Fund has looked to take advantage of this. Several companies in these spaces are focused on understanding the immune system and how we can manipulate it to fight such health conditions. Since the immune system is also critical in infectious diseases, a significant amount of the learnings and tools from other therapeutic areas can be applied to the foundation's priority diseases," highlighted Vidya Vasu-Devan, deputy director at the Bill & Melinda Gates Foundation's SIF. "As a result, the SIF team invests in these companies to leverage the products and technologies for diseases like HIV and TB. Additionally, we always look to support companies dedicated to eliminating infectious diseases."

## TIME TO PARTNER OR GO PUBLIC

2018 was a blockbuster year for IPOs, with US$8.2 billion raised on Nasdaq, breaking 2014's record of US$6.5 billion. The decision to go public or to stay private is not an easy one for any biotech. Forty Seven – a clinical-stage immuno-oncology company – completed its IPO in July 2018, raising US$116 million. "The decision for going public needs to be reflected on as it is easier to be private, but as we have six ongoing clinical trials, our expenditure is significant," highlighted Mark McCamish, president and CEO of Forty Seven. "We did not want to focus on one indication but to explore several simultaneously. Going public allowed for access to funds as well as maximizing the value of the company, not only to patients but to investors."

Although certain biotechs will be faced with the question of whether to go public in the near future, the decision may be taken out of their hands for 2019. The untimely United States federal government shutdown of 2018 to 2019 due to the United States Congress and President Donald Trump's disagreement over the latter's demand for US$5.6 billion in federal funds for a U.S.–Mexico border wall is set to have a lasting impact on the number of biotech IPOs expected this year. With the IPO market set to grind to a standstill, limited access to public capital will most likely mean another record year for VC funding, more partnerships and, with Eli Lilly acquiring Loxo Oncology for US$8 billion and Bristol-Myers Squibb acquiring Celgene for US$74 billion in the largest pharmaceutical-company acquisition ever, an increase in M&A activity.•

# Servicing Your Every Need

## *Opportunities Grow for Contract Service Providers*

The CDMO industry has been continuing on its path of exponential growth. Fueled by the redundancies of large pharma's manufacturing lines when drugs have failed before reaching the commercial stage, and the increased costs of developing and manufacturing new drugs, outsourcing manufacturing capabilities to CDMOs increasingly becomes the norm. In fact, the global contract manufacturing market is expected to grow at a CAGR of 7.2% between 2017 to 2023, according to Market Research Future, outpacing the overall growth of the pharmaceutical sector. Moreover, outsourcing penetration is set to increase from 30% in 2018 to 40% by 2020, according to Kurmann Partners.

There is a growing trend of CDMOs and CMOs looking to offer a one-stop-shop for the development and commercialization of drugs. In recent years, the CDMO space has consolidated as a result of large pharma wanting to work with fewer suppliers. As of late-2018, the top five CDMOS – Lonza, Catalent, Patheon (acquired by Thermo Scientific in August 2017 for US$7.2 billion), Recipharm and Siegfried – accounted for 15% of overall market share. However, this is far less than the top five CROs, which control 70% of market share, according to Kurmann Partners. Medium to large CDMOs are acquiring smaller companies to either complement their strengths, increase market access or fill any gaps they may have within their service offering. For example, Argonaut Manufacturing Services – a contract manufacturing provider based in San Diego – recently acquired LyoGen to expand its reagent lyophilization capabilities. Moreover, PCI Pharma Services acquired three companies – Millmount Healthcare, Pharmaceutical Packaging Professionals (PPP) and Sherpa Clinical Packaging – in three different geographies – Dublin, Ireland; Melbourne, Australia; and San Diego, California respectively – to gain more market access and strengthen its market position. "PCI has long desired to be geographically present in the West Coast of the United States, and Sherpa Clinical Packaging proved to be a very attractive opportunity," highlighted Justin Schroeder, senior executive director for global market and design at PCI Pharma Services. "Sherpa is a provider of clinical trial supply services and with efforts including supporting small and emerging clients. Our relationship with Sherpa strengthens the company's position as a leader in outsourced clinical support services and further offers our clients a rapid pathway to execute their early stage studies."

*"There is a demand for both one-stop services providers and niche service providers. The strategy that PCI has embarked on, in terms of providing a full-service offering, was based on feedback from our clients' demands. We have customers that will only require one particular service of our lifecycle portfolio of services, but we are definitely seeing an increase in demand for support across the product lifecycle, each phase of development and commercialization."*

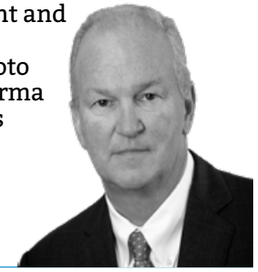
**-Justin Schroeder, Senior Executive Director – Global Marketing & Design, PCI Pharma Services**

Acquisitions are not the only path CDMOs are taking to enhance their service offering. CordenPharma has complemented its cGMP facilities in Europe and the United States with a new US$20 million commercial aseptic fill and finishing injectable plant in Caponago, Italy. Whilst some continue to grow organically, others are using this time to rebrand. The company formerly known as AGC Asahi Glass has integrated itself under the single AGC Biologics brand, following the acquisitions of CMC Biologics and Biomeva. Also following this trend is Ajinomoto Bio-Pharma Services, a CDMO headquartered in San Diego, which has rebranded itself to provide its large and small molecule clients access to a broader range of services. "Today, we offer small molecule API manufacturing in Europe, later-life-cycle small molecule API manufacturing through a 50/50 joint venture with Granules India, and large molecule biologic production in San Diego, California," highlighted David Enloe, president and CEO of Ajinomoto Bio-Pharma Services. "We have also added highly potent bio-conjugation and final fill and finish services in San Diego as this space is significantly growing. Moreover, in 2019, Ajinomoto aims to combine its oligonucleotide manufacturing entity – GeneDesign - with Ajinomoto Bio-Pharma Services."

One of the key shifts in the CRO and CDMO landscape is how contract service companies are offering more of a holistic service to biotechs and integrating themselves at earlier stages of their development timelines. With hundreds of biotechs looking to outsource their development and manufacturing in the key hubs of San Diego, San Francisco and Cambridge-Boston, contract service companies are looking at how best to serve them. More and more, contract service companies are offering quasi-consulting services and guidance in areas such as regulation and commercialization. Although there is a long-standing trend of contract service providers diversifying their service offering, CDMOs, and especially CROs, need to make sure they are not spreading themselves too thinly. For example, ProSciento, since inception in 2003, has solely focused on NASH and other related metabolic disease, believing that a science driven, deep expertise approach, is the most attractive to biotechs. AGC Biologics has found a niche in orphan drugs and biologics with small patient populations. CordenPharma, whose portfolio is split between biotech and pharma, has strengths in a number of therapeutic areas but particularly in oncology. "We have extensive manufacturing capacities combined with strong capabilities in highly potent and oncology manufacturing, both for Drug Substance and Drug Product, within four cGMP facilities – two in Boulder, Colorado for Drug Substance and two in Europe (Germany and Italy) focusing on Drug Product manufacturing for oral solid dosage and injectable sterile fill and finish respectively," remarked Michael

*"There is not necessarily an expectation on a CDMO to be disease knowledgeable. There is however benefit for a CDMO to understand the differing regulatory pathways across multiple geographies. A good example is the experience that Ajinomoto Bio-Pharma Services has had in San Diego with orphan diseases. Many of the commercial products manufactured or filled and finished in San Diego are orphan or hyper- orphan diseases, which necessitate unique regulatory strategies."*

**-David Enloe, President and CEO, Ajinomoto Bio-Pharma Services**



Quirmbach, chief business officer at CordenPharma. Although opportunities continue to come for contract service providers, their role is becoming more complex as well. They are increasingly having to deal with high-potency active pharmaceutical ingredients (HPAPIs) at their facilities, which is leading to greater risk assessments being carried out by their clients. SafeBridge Consultants - provider of the Potent Compound Safety Triangle™ of services in industrial hygiene, toxicology and industrial hygiene laboratory services – has evolved over time to become a product safety company due to the increasing need for toxicological risk assessments of contaminants. "We conduct assessments of capabilities of CMOs and pharma companies including due diligence assessments as part of M&A activities for companies to help them decipher between the 'contenders' and the 'pretenders' and our services have increased in relevance as compounds have become more potent," highlighted Allan Ader, co-managing director at SafeBridge Consultants. "Additionally, we have become a vital resource to quality programs in pharma and biotech to assess the potential for cross-contamination and we have become the experts in product safety and cross-contamination by developing Permitted Daily Exposure (PDE) values for determining cleaning limits."

As small biotechs, which will not have the capacity to upscale, and large pharma, which is tending to concentrate on its core expertise, continue to outsource their development and manufacturing, greater demands and expectations will be put on contract service providers. Despite this, the opportunities being afforded to them are enticing, especially given that more international biotechs are looking to CDMOs as a gateway to commercialize their products in the U.S. market.•

*"If a potent compound can be visibly seen in the workplace environment, then it is too much, both from an occupational and quality/product safety standpoint. As potent compounds are potentially toxic even if the compound cannot be seen, then it needs to be quantitatively assessed. Quantitative assessment needs to continue taking precedence as potent compounds become stronger and more potent. This is a message that all companies should take notice of."*

**-Allan Ader,**
**Co-Managing Director,**
**SafeBridge Consultants**





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# The Next Step

## *Shaping the Future of the U.S. Biopharmaceuticals Industry*

2019 is set to be a year of uncertainty for the United States, whether it is through a potential downturn in the economy, the lasting impact of the 2018 to 2019 government shutdown, increased trade tariffs with China, or a change in the makeup of NAFTA. However, while most industries will expect a slowdown, the biopharmaceuticals industry should remain resilient, driven by its unconditional desire to keep innovating. For example, embracing precision medicine could be a sure way for biotechs to reduce drug discovery and development time and therefore costs; increased innovation in the generics space may translate into a valued opportunity for CDMOs; and disruptive technologies, such as big data, artificial intelligence, and blockchain will eventually revolutionize the biopharma value chain. Although geopolitical factors will have an impact on certain players, it will not be enough to offset the overall industry. Due to this, the U.S. biopharmaceuticals value chain looks set to jump over any wall put in front of it.

*"[W]ith the convergence of technology, healthcare delivery is getting smarter. The traditional patterns of standardized care centered on hospitals and practitioner clinics are being complimented with a new philosophy of care delivered directly to the patient, tailored to individual patient needs. This evolution of sophisticated therapies and diagnostic models - think telehealth and personalized medicine - shows just how far healthcare has shifted to proactive wellness. This makes supply chain speed, agility, safety and compliance even more imperative."*

-Chris Cassidy,
*President, Global Healthcare Logistics Strategy,*
**UPS**

*"U.S.-based manufacturers will likely be more focused on complex, difficult to manufacture injectable products. There is still a lot of room for innovation in generics and I think this is where U.S.-based manufacturers will focus their attention."*

-Chris Rector,
*Vice President – Sourcing and Supplier Relations,*
**ClarusONE Sourcing Services**

*"We are evolving how translation is done at universities. The future of translation is going to be with startups, which will be aided by a more robust entrepreneurial ecosystem."*

-Richard Sudek,
*Chief Innovation Officer and Executive Director,*
**UC Irvine Applied Innovation**

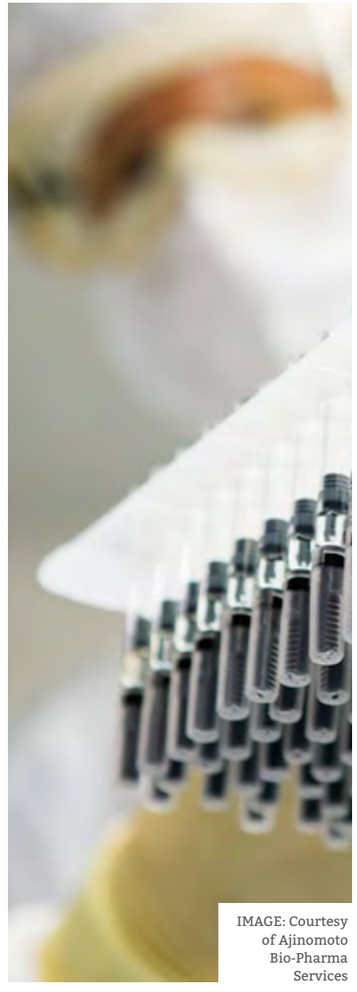

IMAGE: Courtesy of Ajinomoto Bio-Pharma Services

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