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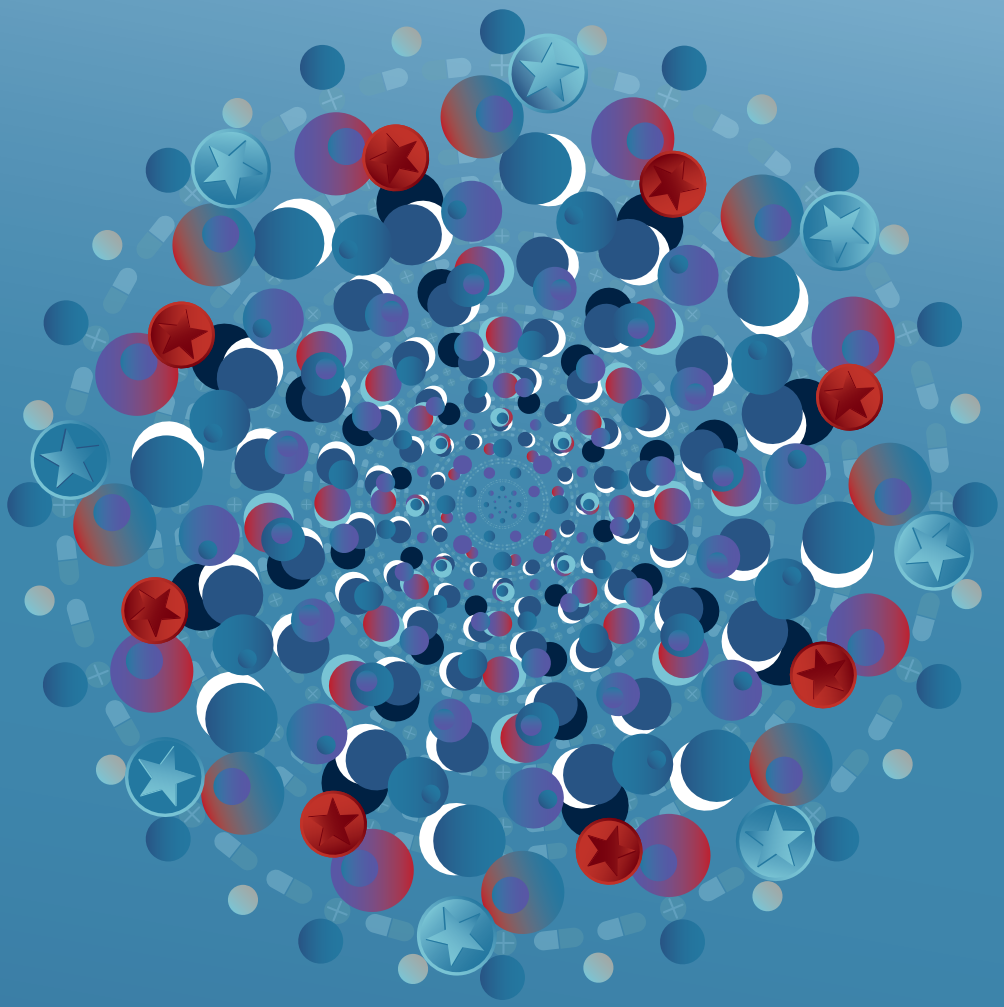

UNITED STATES BIOPHARMACEUTICALS

2018

Biopharma Superclusters - Massachusetts - San Francisco Bay Area - New Jersey
Research and Development - Contract Services - Drug Discovery
Academic Research - Regulations and Compliance - Logistics and Distribution

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Dear Reader,

Welcome to the 2018 edition of the United States Biopharmaceutical Industry Report, a joint CPhI-GBR analysis launched at CPhI North America.

The United States is broadly recognized as the global leader in drug discovery and innovation, producing more than half of the world's new molecules in the last decade. Improving patient outcomes through a deeper understanding of disease areas and better-defined addressable patient populations is revolutionizing drug discovery approaches. By not only developing more effective treatments but also matching the right drug to the right patient, companies are driving a new phase of medical progress.

Arguably the most competitive destinations within the United States in terms of attractiveness, our 2018 research has focused on Massachusetts and California, notably the Boston/Cambridge Area and the San Francisco Bay Area, and also New Jersey as the historic center of pharmaceutical activity. While Massachusetts is lauded for its culture of collaboration, in part attributable to the extreme density of activity, the Bay Area is often cited as the top biotech supercluster due to the sheer volume of activity and high investment figures, both in terms of NIH funding and venture capital.

Running adjacently to CPhI Worldwide, which takes place in October, bioLIVE is a new focused proposition that establishes premium-class, global leadership in Bioprocessing and Manufacturing. CPhI's strong position in the small molecule space, experience with developing professional events for the complete value chain, and the natural convergence between small and large molecule markets presents a unique opportunity for CPhI to ensure sustainable growth in the long-term by moving with market developments in bio Pharmaceutical Processing & Manufacturing.

The following pages bring together insights collected from interviews conducted with over 100 of the biopharmaceutical industry's most insightful and authoritative industry associations, academic institutions, research organizations, consultants and analysts.

We would like to warmly thank our association partners at MassBio, Biocom and BioNJ for their continued support, as well as to all the executives and researchers who shared their valuable insights.

Rutger Oudejans
Brand Director
CPhI

Alice Pascoletti
General Manager
Global Business Reports (GBR)

Editorial Analysis

GBR journalists provide unique and first hand analysis and insights into all aspects of the USA biopharma industry after months on the ground

8, 14, 30, 44, 51, 82...

Exclusive Interviews

Leading industry figures from the East to West coast biopharma hubs share their insights and their pipelines with GBR

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Data, Maps and Infographics

Maps, charts and graphs illustrate industry trends

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UNITED STATES BIOPHARMACEUTICALS 2018
Industry Explorations
CPhI & Global Business Reports

This research has been conducted by
Catherine Howe, Neha Premjee
& Emma Johannes

Edited by Mungo Smith
Graphic design by Gonzalo Da Cunha

Image courtesy of Batavia

Introducing the U.S. Biopharmaceutical Industry

"A curative therapy that costs a lot to develop is likely to be expensive, so we need to think of novel financing models and identify mechanisms whereby the innovators will still be rewarded but the healthcare system can still afford to make the investment to treat the patients. We are seeing innovation in biology and the lab, but we also need to see innovation in processes for healthcare financing."

- Thomas Goss,
Senior Vice President,
Boston Healthcare

Introducing the U.S. Biopharmaceutical Industry

Countries around the globe have long placed great emphasis on fostering a competitive life sciences industry. India's focus on generics reflects a need for affordable, accessible medicine and aptitude for low-cost chemistry, whilst China's growing biotech industry highlights a government focus on driving its technology sectors and meeting the needs of its growing population. The United States, however, has garnered particular attention from overseas as a high value market and the leader in innovation and drug discovery. Well supported by its favorable IP framework and investment climate, the U.S. biopharmaceutical industry accounts for a huge portion of global innovation, producing more than half of the world's new molecules in the last decade.

The U.S. biopharmaceutical ecosystem is diverse; from the large, vertically-integrated companies, to the rising number of biotech start-ups and university spin-outs that are yet to reach commercialization. Whilst on the one hand companies are expanding capabilities both through organic and inorganic growth, outsourcing trends are also on the rise – larger companies are increasingly seeking to streamline development timelines, while small companies at the opposite end of the spectrum require reliable partners to bridge gaps in expertise, financing and infrastructure.

Collaboration is broadly recognized as key in driving development pipelines, especially as large pharma companies increasingly look to universities and small biotechs for cutting-edge research to bolster their own pipelines. Conversely, universities and start-ups take advantage of funding and expertise from larger companies to translate science into real-world applications and drive development pipelines through to commercialization. The industry landscape is continuously morphing by extension – just as university spin-outs and start-ups are entering the market with increasing frequency, large pharma companies are acquiring innovative companies pursuing novel targets and therapies with significant differentiators from current standard of care in different therapeutic areas. More broadly, companies are refocusing their strategies around growth after years of cost-cutting and restructuring. This uptick follows a period of relatively low M&A activity, in part attributable to the growth gap created by patent cliffs, coupled with a dearth of FDA approvals, which caused a period in which companies did not grow. Big pharma companies are now catching up and seemingly making up for lost time.

The strategies of the biotech start-ups entering the market are also shifting in focus, with many more companies setting their sights on acquisition and earlier market exits. "M&A used to be much more infrequent in this industry, but large pharmaceutical companies' greater dependency on M&A has infused more of a "build it to sell" mentality into the culture of entrepreneurship," highlighted Robert Blum, CEO at Cytokinetics, a Bay Area biotech company. "This is not unlike what has happened in the technology sector over the years and is what venture capitalists are much more inclined towards these days. This means there will be fewer long-term sustainable biopharmaceutical companies because we will see more aggregation into the large pharma and biopharma companies."

A significant amount of M&A activity has also come from portfolio divestitures involving adjacent businesses such as consumer, animal health and vaccines among

Source: drugcostfacts.org

THE ROLE OF COMPETITION AND LOW-COST GENERIC DRUGS IN THE HEALTH CARE SYSTEM

Generic Share of Total Prescriptions Dispensed in the U.S.

89%

Source: 2017 Association for Accessible Medicines
Generic Drug Access & Savings in the U.S. report

UK	83%
Canada	73%
France	30%
Germany	81%
OEDC	52%
Japan	34%

Source: OECD Health Statistics 2017

other assets. Equally notably, many larger companies are focusing their portfolios around particular therapeutic areas, stepping away from disease areas that are not perceived as a core strength or the strongest market opportunity. The neurodegenerative space has seen particular setbacks, for example, with Pfizer exiting its research in both Alzheimer's and Parkinson's in January 2018.

In the services segment, companies are making acquisitions to build out their capabilities with the goal of becoming an integrated solutions provider. Nevertheless, many still recognize the importance of being selective in their areas of focus, rather than attempting to be all things to all customers.

Affordable alternatives: facilitating patient access

Whilst the United States is certainly the global hotbed for innovation, producing more than half of the world's new molecules in the last decade, generics are an important component of the marketplace. According to the Association for Accessi-

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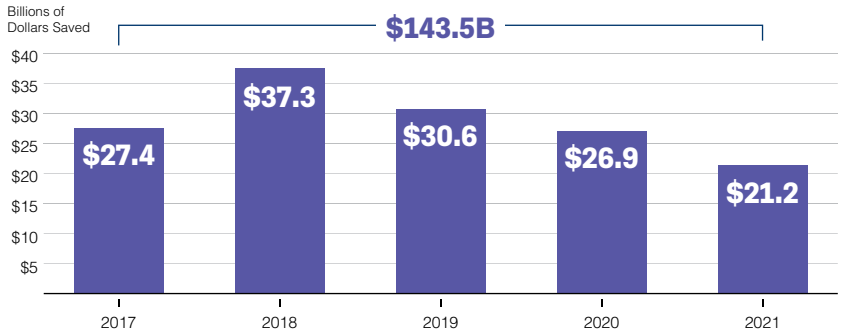
Increasing Competition Leads to Consumer Savings

Competition in the market and expiring patents produce substantial savings on prescription drugs. In fact, new competition from generic and biosimilar drugs will reduce prescription drug spending by $143.5 billion (between 2017 and 2021).

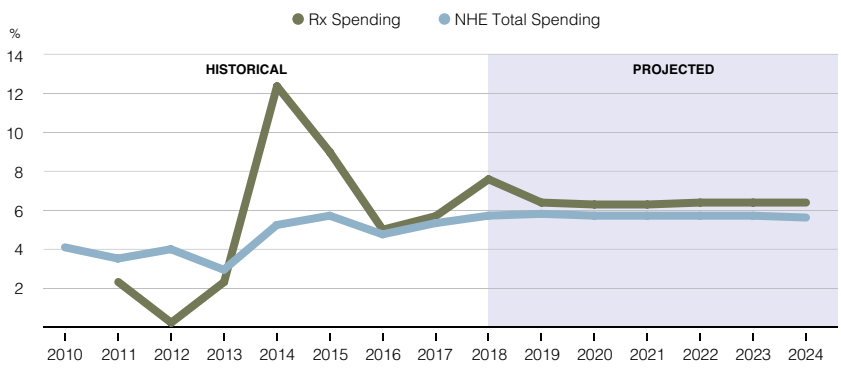
Patent Expirations Driving Savings in Prescription Drugs Over Next Five Years

Source: IQVIA, "Outlook for Global Medicines through 2021



RX DRUG SPENDING: ANNUAL PERCENTAGE CHANGE

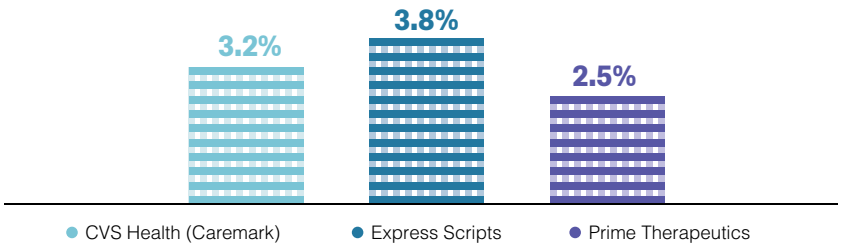
Source: CMS/OACT NHE projections



2016

Leading pharmacy benefit managers all report drug spending increases by commercial payers in the low single digits for 2016.

Source: Adapted from "Which PBM Best Managed Drug Spending in 2016: CVS Health, Express Scripts, or Prime?" Drug Channels. March 2017



John Patrick Oroho

Executive Vice President & Chief Strategy Officer
PORZIO LIFE SCIENCES

Established in 2004 as a subsidiary of Porzio, Bromberg & Newman, Porzio Life Sciences specializes in compliance with a particular focus at the state level.

What are the primary focus areas across Porzio Life Sciences' offices in Morristown, NJ, Washington DC and Boston, MA?

Morristown remains our headquarters, but we have a large office in DC and we are expanding our Boston office. Across the firm, we undertake a lot of work in compliance monitoring and auditing, but are probably best known for how to operationalize compliance with legal and regulatory requirements. Over the years, we have developed online databases on a subscription basis, through which we track the laws, regulations and pending legislation across all 50 States to show how to sell, market and distribute products in every State. We now also handle federal and international laws and regulations.

In 2013, the Federal government commenced the Open Payments program, which necessitates the disclosure of financial relationships with physicians and teaching hospitals. States are precluded from asking for this same information. However, States have approached this in different ways and now require disclosure of different types of information from different types of practitioners. A growing number of States have enacted disclosure requirements for people other than physicians; nurse practitioners, physician's assistants, other types of what we call mid-level practitioners. In some instances, we also see fragmentation at the city level. Companies will have to study the individual state, city and local regulations. Porzio Life Sciences is well positioned to support them.

How have States acted to address concerns surrounding drug price transparency?

Until now, transparency has always related to financial interactions between companies and doctors and hospitals. We are now seeing a major push towards transparency for drug pricing at a State level. At least nine States have actually enacted legislation around price transparency and about 16 more have pending legislation. However, not every State is asking for the same information and not every State covers all types of products. How companies price their products has always been confidential – it is part of the IP – so pricing transparency is problematic. We are beginning to see some legal challenges arise around this. From an operational standpoint, it remains unclear which department will be responsible for reporting the information to States. In some companies it will be the HCP Transparency Team and in others it will be the government price reporting department.

As a company that has carved out its niche specializing at a State level, where do you see the biggest gravitation of activity?

Cambridge and California have become research hubs – many States want to follow suit, but it is a long process. New Jersey is also following this path, and benefits from the presence of strong academic institutions. However, it will take a while for New Jersey to catch up to the Bay Area, San Diego or Boston/Cambridge. Where New Jersey really stands out is the high concentration of individuals with significant experience leading life science companies. We are increasingly seeing companies deciding to set up commercial operations in New Jersey. Together with economic development groups we are seeking to establish New Jersey as a hub and incubator for companies that are ready to commercialize.

One area on which we are focusing is the facilitation of licensing deals. Many major companies have products on the shelf that are still prescribed by doctors but in volumes that are too low to warrant a sales force behind them. A smaller company, often made up of executives from big pharma, will license a product that fits this description and put a smaller sales force on it. Smaller companies are thereby able to introduce themselves to key opinion leaders and healthcare practitioners in a particular therapeutic area, getting their foot in the door for when their future independently-developed candidates are ready for commercial launch. New Jersey fits that model perfectly and can develop an ecosystem within which larger companies will continue to manufacture mature products, which are a great lifeline for start-up companies. This also introduces the startups to larger companies and can lead to JV agreements, licensing deals and faster commercialization pathways. ■

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ble Medicines (AAM), the generic share of total prescriptions dispensed in the United States in 2017 sits at 89%, whilst accounting for only 26% of total U.S. drug costs. Small-molecule generics remain the favored lower-cost prescription option due to increased patient access and perceived healthcare savings. According to North Carolina-headquartered IQVIA (previously IMS Health and Quintiles), expiring patents and competition from generic and biosimilar drugs will reduce prescription drug spending by US$143.5 billion between 2017 and 2021. Propagating similar savings figures, the AAM estimates US$253 billion in total healthcare savings in 2016, with Medicare savings amounting to US$77 billion (US$1,883 per enrollee) and Medicaid savings of US$37.9 billion (US$512 per enrollee). “Doctors will continue to prescribe the white tablet before they start prescribing other treatments due to the lower cost,” noted Stephan Kutzer at Alcami Corporation, a CDMO with executive offices in North Carolina. “Whilst new emerging areas such as gene therapy and cell therapy are extremely exciting and we are very much a part of that, it is important to keep an eye on the real overarching drivers of the pharmaceutical industry. Rather than biologics, it is the white pill that is being prescribed and subsidized and supported by the insurance companies.”

For those companies with a focus on export markets, price sensitivity is even more pertinent. “Supplying biologics to many emerging markets is also almost impossible – it is still small-molecule drugs that support probably 85% of the world’s population in its fight against diseases,” added Kutzer.

The importance of generic drugs is unquestionable in the United States as in other parts of the world. Nevertheless, research into new targets and development of novel therapies are also hugely important in understanding and addressing the underlying causes of diseases. The potential for cures and vast improvement in quality of life is a worthwhile driver for novel drug development. However, new therapies must be able to demonstrate economic viability in order for companies to embark on the lengthy and costly development process, with all its associated risks.

> **The number of post-grant proceedings (mainly inter-partes reviews (IPRs)) continues to grow in the biopharmaceutical space. Within the Hatch-Waxman framework, where big brand companies may sue generic companies over certain drugs, generic companies use IPRs as a strategy not only to invalidate patents but also as a strategy to achieve better settlements. For example, a generic company can either file or inform a company that they will file, and those actions influence whether the brand wants to settle with the generic before entering the litigation process. This is handled on a case-by-case basis, but is certainly used as a strategic tool.**
>
> **- Vishal Gupta, Partner, Steptoe & Johnson**

Image courtesy of Aragen Bioscience Inc.

Cost vs. value

The rhetoric around drug prices remains a challenge for the industry and pivots on striking a balance between patient accessibility and commercial reimbursement. While companies tend to advocate a message of social responsibility, they operate as commercial enterprises – the market opportunity still has to make economic sense. Beyond the immediate effect on companies' profits, lowering drug prices would greatly reduce incentives to innovate. PhRMA estimates the average cost to develop a new medicine, including the cost of failures, as US$2.6 billion. It follows that market-entry prices will of course be substantially higher than generic alternatives with likely indirectly-proportional development costs.

Equally challenging is that, whilst the biopharmaceutical industry is making great strides in medical progress, the U.S. healthcare system has not kept pace; it is not yet designed to properly absorb and measure the cost of curative therapies. This means that the potential savings sustained by actually keeping patients out of hospitals are often overlooked. "Currently, we do not have a healthcare system; we have a sick-care system," commented Bob Coughlin, president and CEO at MassBio, Massachusetts' first state biotech trade association. "It is designed to treat chronic sickness with therapies over the life of a patient. If we are going to live in an age of cures, we need a healthcare system and a payer system that can ensure access to these breakthroughs. The way to save money in a healthcare system is by keeping people healthy and out of hospitals and having an accounting system that tracks costs avoided when new drugs come to market. The clock is ticking, and we need to continue to work together as an industry to come up with a new system, or the government will do it for us and get it wrong. We need the payer system to innovate at the same rate at which we innovate on the discovery and manufacturing side."

Flagged by many as a potential solution to reimbursement, the industry has seen a rapid increase in value-based contracts between drug-developing companies and payers. Risk-based contracting requires the interaction of many stakeholders, from providers and insurers to entities like CMS, to ensure that appropriate policies are pushed forward to create a framework in which these types of contracts are supported. MassBio has formed working groups, connecting payers and market access representatives from its member companies to encourage these partnerships and other innovative methods of paying for new therapies. "We are taking the argument of drugs being too expensive off the table; drugs save money by keeping people out of the hospital and actually only account for 12% of the total cost of healthcare," said Coughlin. "Restricting access to patients is not an option, so the only solution is to find new ways to cover the costs of these drugs."

Innovation Capital

One of the most R&D-intensive industries in the United States, the pharmaceutical sector is responsible for a huge portion of global innovation and new medicine, accounting for 17% of all domestic R&D funded by U.S. businesses. In contrast, R&D investment into software, automotive and aerospace sits at 13%, 5% and 4% respectively.

Drug development is currently characterized by a trend towards precision medicine, broadly translating to more targeted treatments for patients. In tandem, the growing number of diagnostic companies are supporting more specific treatment pathways and even enabling more targeted patient selection for clinical trials. Alongside the clear benefit of finding the right drug for the right patient, finding the right patient for the trial – in other words, the patients likely to have the highest response rates – could vastly improve trial success rates, leading to a higher number of approvals. Improving trial success rates also greatly reduces average drug development timelines and costs as a result, which will enable reduced drug pricing in the longer run due to lower reimbursement costs. ■

> "A curative therapy that costs a lot to develop is likely to be expensive, so we need to think of novel financing models and identify mechanisms whereby the innovators will still be rewarded but the healthcare system can still afford to make the investment to treat the patients. We are seeing innovation in biology and the lab, but we also need to see innovation in processes for healthcare financing."
>
> **- Thomas Goss, Vice President, Boston Healthcare**

Vishal Gupta

Partner
STEPTOE & JOHNSON

Steptoe and Johnson is a 600-attorney international law firm specializing across all areas of IP, with U.S. offices located in New York City, San Francisco, Los Angeles, Washington, Chicago and Phoenix.

Steptoe & Johnson has an extensive U.S. presence, with good proximity to the major biopharma hubs. How great a focus is life sciences within the firm's portfolio?

Life sciences continues to be an important focus area for Steptoe & Johnson and its IP department. We are an approximately 600-attorney firm with offices in New York, Washington D.C., Chicago, Phoenix, San Francisco, London and Brussels.

A crucial component of successful firms in life sciences is a strong technical background to compliment a strong legal background. We are one of the few firms with robust and stable of attorneys who also have advanced life sciences degrees – 19 of the 60 attorneys in IP have advanced life sciences degrees, such as PhDs or masters. A thorough understanding of the technical basis of cases enables our lawyers to argue trial cases better, repackaging information from scientists and companies so it can be better understood by a lay jury or judge. Similarly beneficial is an understanding of the technical intricacies of an invention and ability to argue back and forth with the patent office in an appropriate way. Overall, Steptoe is comprised of vigorous advocates devoted to its clients and their objectives.

How does the United States' strong IP protection framework affect the dynamics between branded and generic drugs?

Going forward, brand companies will create more of a thicket of patents, which is what we see in the biologics space. Companies will file for patents around a number of processes and methods of use as well as the compounds themselves. This requires the generic company to invalidate a greater number of patents in order to enter the market or free themselves of patent litigation, also helping the brand company to get around IPRs, creating higher entry barriers for the opposing company.

On the generic side, a larger volume of invalidation-related filings will have to be pursued. It is almost malpractice not to pursue a post-grant proceeding at this point, because the rules are somewhat favorable towards those trying to invalidate the patent. It makes sense for these companies to go for post-grant proceedings in conjunction with whatever the district court litigation is. With concurrent strategies, certain invalidity arguments can be pursued in Federal Courts while others can be pursued before the Patent Trials and Appeals Board.

As patents continue to be challenged more and more aggressively and brand companies strengthen their patent positions, how could the validity of these patents be affected?

Patentability, 'Section 101', is very important in the biologics space. These arguments, which say that even the patenting of a particular subject matter is not allowed, have appeared increasingly in the last few years in life sciences, especially in the biologics space. The test for patentability is firstly whether the claim is directed at something that is not allowed to be patented. In biologics, this would be a natural phenomenon or something that is naturally occurring. Pure products of nature cannot be patented – something must be done to it or it must be changed in some way. Examples of patentable subject matter includes novel processes, new compounds or novel antibodies, or an alteration of a naturally-occurring substance. The law is evolving in this area and increasing in clarity..

In patent invalidation strategies, this might be brought up very early on in the case, even in the pleading stage, summary judgement or at trial. In the pleading stage, it can be argued that the patent by law should not have been granted to win the case. We are seeing these 101 arguments being made at earlier stages of cases, in addition to later on in the case.

Have there been any major developments in biosimilars guidelines?

Some of the biosimilars guidelines have become more finalized. Interchangeability guidelines continue to become more developed, providing greater incentive to develop interchangeable biosimilars as opposed to just biosimilars. Unlike a non-interchangeable biosimilar, an interchangeable biosimilar can be auto-substituted. As those guidelines develop, the exact tests needed to satisfy interchangeability will be continue to crystallize.

What will be the next efforts in bolstering in-house capabilities at the firm?

While we will always do the small molecule work, we are very focused on biologics for the future, whether in antibody therapy, DNA-related technologies or gene technologies. There have only been a handful of biologics trials so far, and Steptoe is one of the few firms to have argued one of these big antibody trials. We continue to expand our team and continue to take on cutting-edge cases. We maintain a very focused support base between our attorneys who can understand the science as well as act as effective litigators and counselors. ■

Success factors: Introducing the hubs

Within the United States, as innovation has increasingly found its roots in academic institutions and small biotech start-ups, the epicenter of medical progress has shifted away from regions with a historically strong presence of large pharma companies. The tables have in fact turned – it is now the big pharma companies that gravitate towards the fledgling innovative startups and academic institutions with spin-off potential. With the influx of new technology-driven companies into the market, large pharma companies are able to bolster their pipelines through partnership with small biotech companies, whilst themselves bringing additional resources and later-stage development expertise to the table. New Jersey remains notable as the birthplace of several large pharma companies and strong commercialization capabilities, but where cutting-edge innovation is concerned, it is California and Massachusetts that today take center stage.

The growth of Massachusetts' life sciences industry has been particularly pronounced in recent years, lessening California's lead as the number one biotech supercluster. The two are now arguably neck-and-neck in terms of attractiveness, with the Boston/Cambridge area often cited as the most conducive to innovation due to its high concentration of companies and culture of collaboration. While different segments of the industry are well-represented, the presence of large research centers of companies such as Sanofi, Pfizer, Biogen and Novartis, alongside a plethora of biotech start-ups, has resulted in a skew towards drug discovery in the Massachusetts area. Shire's current consolidation of its many sites across the state into two main campuses at Cambridge and Lexington will also involve the addition of 100 research jobs as part of the move to root its center of excellence for biopharma research and U.S. business operations in Cambridge.

California still undoubtedly boasts the larger industry by numbers and investment, with employment also more spread out across different disciplines – the California Life Sciences Association's 2018 Report indicates that there are currently 3,249 life sciences companies in the state, with US$6.7 billion in venture capital attracted and US$3.8 billion in NIH grants in 2017. Genentech, part of the Roche Group, is often ranked first across the fields of biotechnology, oncology and in-vitro diagnostics, and sits in good company with the likes of Amgen and Gilead, which also have their headquarters in the Bay Area.

> **The primary component for a sustainable innovation hub is the ability to generate new start-ups and for them to take hold and thrive. As well as elements such as great science and scientists, funding is also integral. Although the financing aspect is out of our control, we hope that by being present and supporting the community with the necessary infrastructure that investors will take more notice.**
>
> **- Lesley Stolz, Head, JLABS Bay Area**

California is spread expansively over 163,696 square miles and can be subdivided into several clusters, the most prominent being the San Francisco Bay Area, San Diego, Orange County and Los Angeles. "As the birthplace of biotechnology, the Bay Area provides a very strong anchor for the state's life sciences community," commented Joe Panetta, president and CEO at Biocom. "The San Diego cluster is as old as the Bay Area's but has differentiated itself as a leader in cutting-edge technology in therapeutics and research. When the companies grow to a certain size, they increase in attractiveness to larger pharma companies… Because the technology is so attractive, companies tend to be acquired before they have a chance to grow. Every large pharma company has some sort of research outpost in San Diego as a result of acquisitions. San Diego is also the center of the genetic sequencing industry."

Meanwhile, Orange County has its core strength in medical devices and diagnostics and L.A.'s industry is in its very early stages.

By comparison, Massachusetts received US$2.6 billion in NIH funding and US$2.9 billion in venture investment in 2016 but, in terms of drug discovery, Massachusetts-based companies have demonstrated remarkable efficiency with funds received – whilst California companies currently have 1,274 new therapies in the pipeline, Massachusetts-headquartered companies boasted 1,896 drug candidates in 2017, accounting for 19% of the U.S. pipeline and 9% of the

global pipeline. Massachusetts' relatively small geographic area of 10,565 square miles is a key component of its primary advantage, namely the high concentration of companies to be found in the region. The sheer density of activity is greatly conducive to collaboration and by extension innovation, whether through knowledge-based partnerships or from a financial perspective. "In the same 10 to 15 square miles, 16 of the top 20 leading biopharma companies, the top 10 leading medical device manufacturers, and the top diagnostics manufacturers can all be found," commented Travis McCready, president and CEO at the Massachusetts Life Sciences Center. "This is truly quite rare. On top of this, we now have all of these companies starting to work with each other which will be very important going forward."

Just slightly further up the East Coast, New Jersey has placed great importance in its life sciences industry ever since Johnson & Johnson set up shop in New Brunswick in 1886. The state is home to 14 of the world's 20 largest pharmaceutical, medical technology and diagnostics companies, including Bristol-Myers Squibb, Merck, Novartis, Pfizer, Sanofi, Novo Nordisk and Bayer Healthcare. As the industry continues to generate huge economic impact, the state government and associations maintain a supportive framework through which the industry can continue to thrive. Although Massachusetts and California carry the torch for biotech, New Jersey's incentives for small companies and startups have also attracted a number of biotechnology companies.

According to the New Jersey Economic Development Authority, the state boasts the highest concentration of scientists and engineers per square mile anywhere in the world, at around 225,000 in total. Augmented by 13 teaching hospitals and four medical schools, New Jersey is a prime location for clinical trials, with about 2,300 active trials currently underway. In 2017, 23 new FDA drug approvals came from companies with a New Jersey footprint, which is about 50% of the total number of FDA approvals. "One recent trend is that New Jersey has become a growing hub for companies looking to commercialize products in the United States," emphasized Michele Brown, president and CEO at Choose New Jersey, a privately-funded non-profit corporation founded to market the state as a premier business location to both domestic and international businesses. "As a result of our high concentration of biopharmaceutical companies, we have a highly-educated workforce that understands and has the experience to bring products to market. In fact, New Jersey's roots in life sciences commercialization dates back to 1886 when Johnson & Johnson was founded in New Brunswick and became the first commercial manufacturer of sterile surgical dressings."

Across the Hudson River, New York is also garnering attention as a growing cluster. As a prime financial hub, it seems an obvious match. "We have been very excited about New York as a hub for a long time," commented Lesley Stolz, head at JLABS Bay Area, the San Francisco location within the network of Johnson & Johnson incubators across the country and overseas. "The cost and availability of space are a primary challenge, and the state and city have only recently recognized that a lot of the scientists coming out of academic institutions want to stay there. It takes a concerted effort to create a cluster. Very few have emerged naturally. With the new incubators that are opening up around NYC, including a new JLABS facility, we are very optimistic that we will see an uptick in activity."

The potential of New York as a life sciences hub has translated into increasing attention from Empire State Development, which focuses on supporting the State of New York's economy across a number of industry sectors. As well as the 9% corporate tax credit and three-year job creation credit offered by the state, Empire State Development offers the Innovate NY Fund, which supports innovation and job creation, offering US$47 million in total. "Boston deployed an effective strategy a few years ago, which has played out very successfully," referenced Loretta Beine, Empire State Development's director of industry development for life sciences. "We are looking to follow in their footsteps and replicate elements of that strategy, focusing on workforce and infrastructure development. We plan to work closely with established partners, drawing on historical successes to decide on the best ways to utilize our funds."

As the life sciences industry incorporates high technology to a greater extent, New York could be in a strong position to drive innovation across a number of areas. "In the early 1990s, New York State put together centers of excellence in high technology areas relating to bioinformatics, the human genome, wireless technology and biotechnology," highlighted Beine. "Having this infrastructure in place allows people to connect within a collaborative environment across many areas. We will respond to the needs of these environments as they continue to progress."

Over the next eight to ten years, New York State will allocate US$620 million through its life sciences investment funding initiative towards strategic areas of focus in fostering growth and developing the industry.

While geography is by no means prohibitive in an increasingly globalized environment, proximity still holds major advantages for the time being. For this reason, although pockets of activity will continue to flourish and germinate across the country, the so-called "biotech superclusters" will continue to garner the most attention both nationally and internationally as destinations for investment and partnership. ■

> "Many of the large pharma companies have felt the need to increase their presence in the Boston/Cambridge area in order to be a part of the innovation activity. Proximity brings a lot of benefits. This industry is highly collaborative with partnership across companies being common and a big driver of success."
>
> **- Lain Anderson, Managing Director and Partner, L.E.K. Consulting**

Travis McCready

President & CEO
MASSACHUSETTS LIFE SCIENCES CENTER

The Massachusetts Life Sciences Center was established with a mandate to deploy US$1 billion over 10 years in three major capital categories.

Massachusetts is the second-largest recipient of NIH funding within the United States. Taking into account the high volume of companies in the region, how does this translate into availability of funding?

An interesting dynamic is taking place: on a per capita basis, we lead the United States in the amount of venture capital being invested into early stage companies. Last year it was US$3 billion. However, unlike in years past, those venture capital dollars are going in larger tranches to a smaller number of companies. The ecosystem has managed to maintain equilibrium because the large pharma and medical device companies have their own investment funds, which amounts to about a billion dollars going into early stage companies. This deployment of investment funds in young companies is not done in any other ecosystem. Equally important, funding dollars are not in excess, which keeps up the standard and competition. Each company still has to produce great science in order to compete. Massachusetts is particularly efficient with its money. A company can complete an IPO in Massachusetts 2.5 times faster than any other state in the country with the exception of California, which sits at the same ratio. This speed is a sign of efficiency and proof that we are investing in great companies.

What are the main objectives for the Massachusetts Life Sciences Center in the near future and longer term?

For the near future, we are currently in dialogue to secure more funding, as we are publicly funded. Part of this process is to take our story directly to the taxpayers and engage our elected officials and communicate our impact with the first round of funding. We are very confident in that communication and the results from that initial round. We are hopeful that these conversations will culminate with a bill getting signed by our governer around the second quarter of 2018. ■

Massachusetts

CAPITAL
Boston

POPULATION
6,895,917 (United States Census Bureau, 2017)

AREA
10,565 mi²

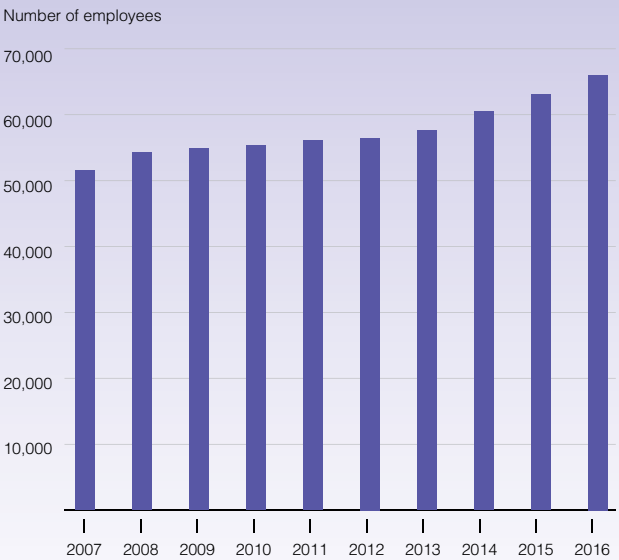
GDP 2016
$505.8 billion and ranked 11th in the United States (U.S. Department of Commerce)

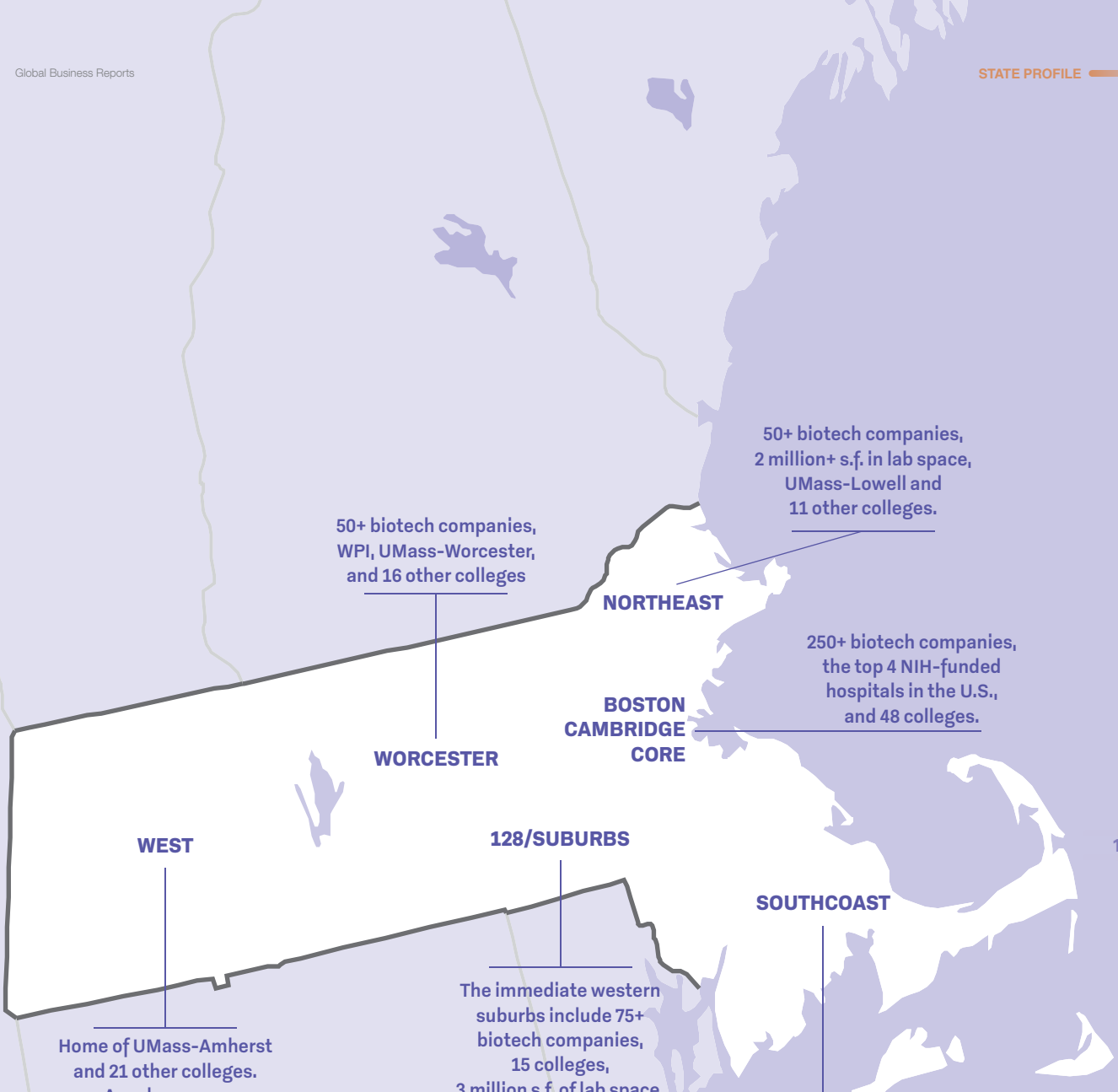
Life Sciences employees

66,414

MASSACHUSETTS BIOPHARMA INDUSTRY EMPLOYMENT

Source: Privately owned companies, U.S. Bureau of Labor Statistics, Quarterly Census of Employment and Wages (QCEW); MassBio





500+

Biopharmaceutical businesses

1,896

Drug candidates in development:
19% of US Pipeline
9% of Global Pipeline

28.2 million

Area of lab space in square feet

Robert K. Coughlin

President & CEO
MASSACHUSETTS BIOTECHNOLOGY COUNCIL

Founded in 1985, MassBio's mission is to advance Massachusetts' leadership in life sciences to grow the industry, add value to the healthcare system and improve patient lives.

Could you briefly introduce MassBio and outline its role in Massachusetts' life sciences industry?
MassBio was the first state biotech trade association and is now the largest with over 1,100 members. Our role is to ensure our members have the best possible environment to operate in so they can improve lives of patients around the world. To do so, we provide a range of services including state and federal advocacy, professional development and networking, and our own purchasing consortium. More broadly, we act as an intermediary among all segments of our sector and across academia and government to help facilitate communications and partnerships, and to support innovation within Massachusetts.

How essential is the role of universities not just in training a skilled workforce, but in contributing to early-stage research?
Massachusetts did not become the top life sciences hub in the world by chance. There would be no biotechnology or life sciences industry in Massachusetts were it not for the world-class academic institutions and academic medical centers. We have the best and brightest scientists in the world working to develop new, breakthrough cures and treatments. Together with a thriving life sciences industry, there is no unmet medical need known to humankind that somebody in this market is not trying to solve.

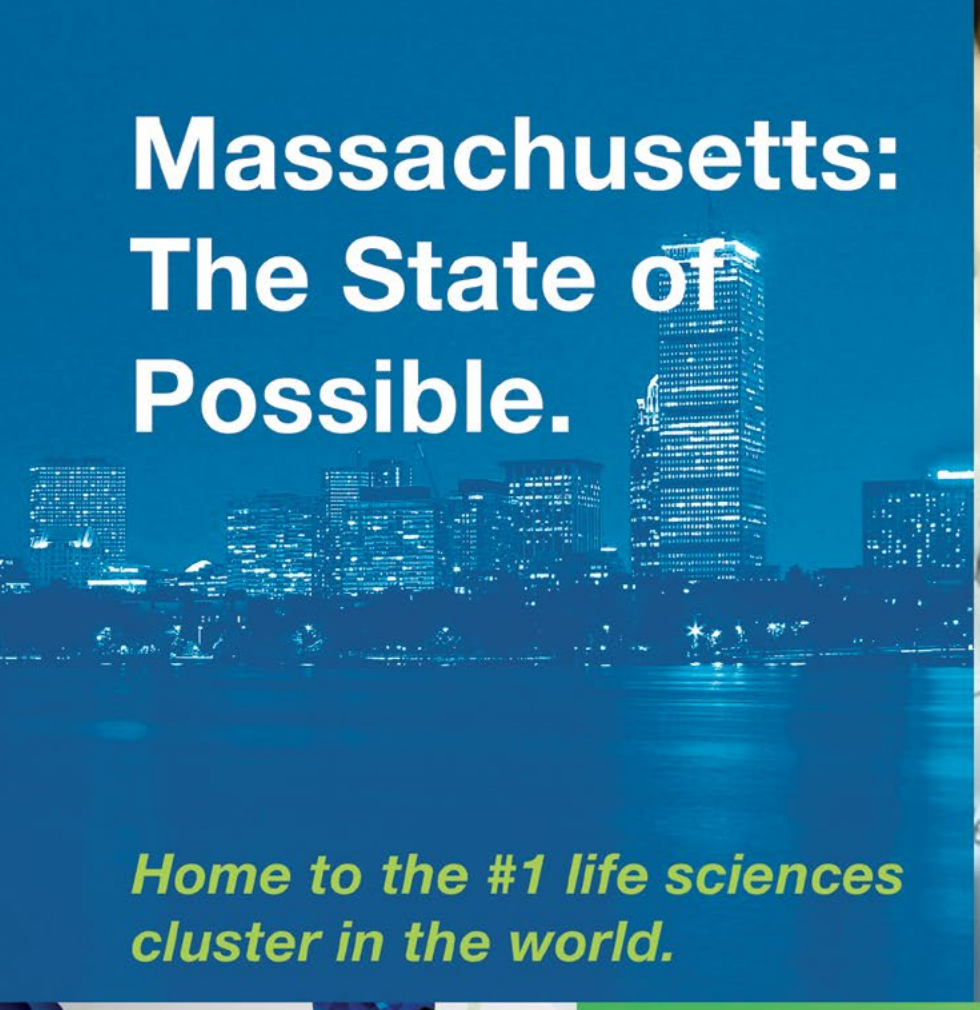
Is new activity stemming primarily from the relocation of companies to the state, or from new companies forming from university spin-offs and other sources?
New activity stems from both company relocation and from new companies formed from tech transfers and other sources. MassBio's economic development team has done an incredible job recruiting large pharmaceutical companies to Massachusetts. They have come mainly for two reasons. First is to tap into the R&D and second is to carry out business development and licensing deals. The drug discovery model has changed in the past decade; big pharma companies have taken the money they may have previously invested into vast campuses and instead invested in partnering and licensing deals. This is called external innovation. It is cheaper, more efficient and has helped pharma companies secure a higher likelihood of success with new breakthrough therapies through partnerships with small companies. 18 of the top 20 pharma companies now have a significant presence here in Massachusetts.

Are there any particular gaps in the market or trends shaping the industry?
There is a significant opportunity around convergence. Today, unlike ten years ago, the lines between different industry segments such as biotechnology, pharmaceuticals and medical devices are becoming much more blurred. A decade from now, we hope to be the best location in the world for all things life sciences across areas such as drug discovery, cures, combination therapies and companion diagnostics.
We are also seeing huge growth in the diagnostics field. Ultimately, many believe that drugs will not be approved in the future without a companion diagnostic. We want to be able to supply all the components so that precision medicine can become a reality. In addition, we are very excited about digital health. Following on from 2008's ten-year US$1 billion life sciences initiative, the current state government is rolling out a five-year half-a-billion life sciences initiative with some focus on digital health, contract manufacturing and workforce development.

Which areas of the industry specifically will the new life sciences initiative be targeting?
The initiative will be focused on early stage funding, because company creation is a priority; workforce development, because we need to maintain that world-class pipeline of talent; biomanufacturing, of which we have seen growth but not to the degree of success we believe we can achieve; and there will also be a component to help us capitalize on convergence and advancements in digital health.

What are the areas of focus for MassBio going forward?
Drugs and therapies invented in Massachusetts are being used by a patient population of close to two billion worldwide. MassBio's primary focus is ensuring Massachusetts continues to be the best home for the life sciences industry and that we have the resources to continue to innovate and serve patients. In Massachusetts, we do not do "me-too" drugs – we pride ourselves on trying to invent what is next. ■

Massachusetts: The State of Possible.



Home to the #1 life sciences cluster in the world.

MassBio represents 1100+ organizations in the life sciences industry, supporting members through professional development and networking, visibility and advocacy, savings, rewards, and purchasing power.

MassBio
MASSACHUSETTS BIOTECHNOLOGY COUNCIL

Visit us at the Massachusetts pavilion at BIO 2018 to learn what's possible.

MassBio.org

California

CAPITAL
Sacramento

POPULATION
39,536,653 (United States Census Bureau, 2017)

AREA
163,696 mi²

GDP 2016
$2,622.7 billion and ranked 1st in the United States (U.S. Department of Commerce)

Source: PwC, California Life Sciences Association

Research and lab services

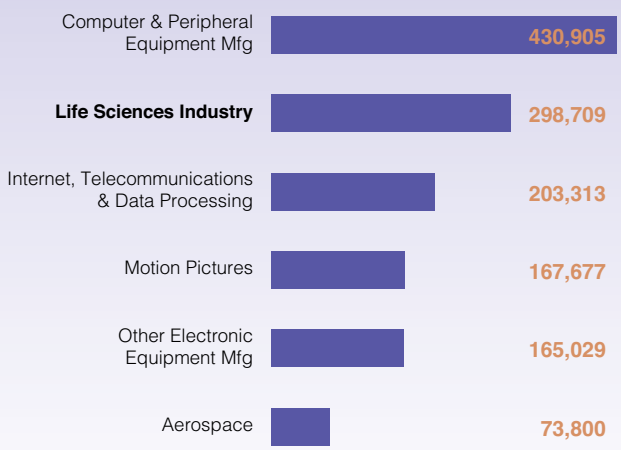
4,316

Life Sciences employees

298,709

CALIFORNIA: LIFE SCIENCES EMPLOYMENT VS. OTHER HIGH-TECH SECTORS, 2016

Source: Bureau of Labor Statistics Quarterly Census of Employment and Wages; 2012 Economic Census



Source: PwC, California Life Sciences Association

$113,674

Average Wage

1,274

New Therapies in the Pipeline

$3.8 Billion

NIH Grants Attracted in 2017, Leading Nation

$7.8 Billion

Venture Capital Attracted in 2017, #1 in the Nation

$34 Billion

Wages Paid

4,800

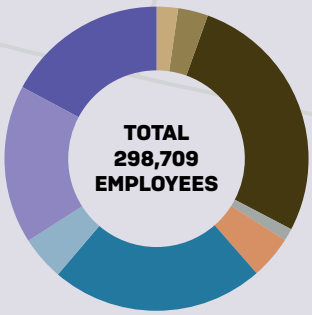
Science and Engineering PhDs Graduated from California Institutions

919,700

Total Direct, Indirect & Induced Jobs

TOTAL LIFE SCIENCES EMPLOYMENT BY CLUSTER

Source: PwC



Other Northern California
2%
6,231

Sacramento Area
3%
9,096

Bay Area
24%
72,663

Other Southern California
1%
2,659

Santa Barbara & Riverside Counties
4%
12,116

Los Angeles County
20%
58,414

San Bernardino & Riverside Counties
4%
10,881

Orange County
15%
45,089

San Diego County
15%
45,949

Joe Panetta

President & CEO
BIOCOM

Representing over 1,000 members, Biocom seeks to accelerate success for California's life science companies in their quest to improve the human condition.

Could you give a brief introduction to Biocom and its role in California's life sciences industry?

Biocom is the state's largest and most experienced leader and advocate for California's life science sector. We work on behalf of more than 1,000 members to drive public policy, build an enviable network of industry leaders, create access to capital, introduce cutting-edge workforce development and STEM education programs, and create robust value-driven purchasing programs. Biocom was founded nearly 25 years ago in San Diego to provide the strongest public voice for research institutions and companies that fuel the California economy.

Biocom has locations throughout California and Washington, D.C, 50 people on our staff and a 60-member board of directors representing all segments of the industry, from pharmaceuticals to medical devices and diagnostics, service providers, and leaders within the academic and research community. Our presence is global, with an office in Tokyo and significant agreements with leading life science associations in Europe and Asia.

We are in the middle of our five-year strategic plan to position California as the worldwide center for precision medicine. Our focus is to build California's individual life sciences clusters, which primarily include the San Francisco Bay Area, San Diego, Orange County and the greater Los Angeles area, and build bridges between these clusters and others around the world. We have placed a significant emphasis on strategic partnerships in Japan, Australia and France. We also care deeply about access to capital for our earlier-stage companies. Every year, we hold a highly-regarded global partnering and investor conference, which attracts about 300 life sciences leaders and venture capitalists from around the world for two days of meetings, panels, and partnering.

What are the defining characteristics and dynamics of California's primary life sciences clusters?

For the most part, they are rich with promise, deeply connected to academic centers of excellence and renowned research institutes, and also quite diverse. The San Francisco Bay Area can be divided into five micro clusters, each with differing specializations. As the birthplace of biotechnology, the Bay Area provides a very strong anchor for the state's life sciences community. Our 200 members in the Bay Area reflect the growing demand for an organization with powerful advocacy and transformative programs to help them grow and thrive. Biocom offers customized events, services, and products unique to the Bay Area's needs.

What are the primary contributing factors to the success of these clusters?

The latest generation of new technologies and the convergence of these technologies is a big driver in attracting companies to California. Big data, artificial intelligence, virtual reality, and precision medicine, along with immuno-oncology, stem-cell start-ups, and digital health all take advantage of the collective power found in these innovative clusters. Another factor that contributes to successful clusters is the wealth of business and research talent. Companies are attracted by the sheer magnitude of talent, funding, relationships, and experience available here. According to Biocom's latest Economic Impact Report, life science companies in California generate nearly US$317 billion in annual economic impact, support more than 1.1 million jobs, and our organizations received nearly US3.6 billion funding from the National Institutes of Health, the most of any state. Equally important is the spirit of community and collaboration that is the hallmark of our industry and something that Biocom is known for encouraging and developing wherever we have a presence.

One challenge across California is that the industry has had to support its own growth without many incentives provided by state government. The situation is very different from other hubs, such as Massachusetts. State investment in California is generally only through research universities such as UC Berkeley, UC San Francisco, UCLA, UC Irvine, UC Riverside and UC San Diego. I can point to one fine state program that is 13 years old and very successful: we passed a citizens' initiative, which created a US$3-billion Stem Cell Agency to provide grant funding to academic researchers and small companies within that field.

Are there any particular areas of opportunity for foreign companies in California?

Our effort to attract companies from overseas to settle in California really centers around the fact that most large pharma and biotech companies have gaps in their product pipeline and can benefit from a partnership with our local biotech companies. At the same time as we introduce our companies to counterparts abroad, such as Japan, we also seek to attract these international companies to create a presence here in California.

What are the main objectives for Biocom in progressing the industry?

The life science industry, with its near-philanthropic commitment to improving human health, is distinctly important to our economy and quality of life in California. It is our vision at Biocom to empower all people in California – and across the country, frankly – to understand the important role of the life sciences in our state and to help the industry continue to prosper. As a unifying force for our state, Biocom is uniquely qualified to provide the tools to help each of California's life science hubs expand, excel, and thrive. ■

WE SPEAK

FOR CALIFORNIA'S LIFE SCIENCES.

Biocom is the largest, most experienced leader and advocate for California's life science sector.

We work on behalf of more than 1,000 members to drive public policy, build an enviable network of industry leaders, create access to capital, introduce cutting-edge STEM education programs, and create robust, value-driven purchasing programs.

Our business model is driven by our unique understanding of the distinctive strengths of local clusters across the state and the power and opportunities that arise when they work together.

Learn more about how Biocom can help your company achieve success: **www.biocom.org**

BIOCOM
accelerating life science

Michele Brown

President & CEO
CHOOSE NEW JERSEY

What are some of the specific characteristics of New Jersey's pharmaceutical industry?

New Jersey is the only state where a high degree of life sciences specialization spans four of five major industry subsectors: drugs and pharmaceuticals; research, testing and medical labs; bioscience-related distribution; and medical devices. One recent trend is that New Jersey has become a growing hub for companies looking to commercialize products in the United States. As a result of our high concentration of biopharmaceutical companies, we have a highly educated workforce that understands and has the experience to bring products to market. In fact, New Jersey's roots in life sciences commercialization dates back to 1886 when Johnson & Johnson was founded in New Brunswick and became the first commercial manufacturer of sterile surgical dressings.

Whilst New Jersey is certainly a life sciences hub, there are higher-ranking U.S. states. In what ways could New Jersey increase its competitiveness?

Part of our mission is to promote the State's extraordinary strengths and assets to the life sciences industry. With nearly 3,300 facilities operating across all sectors, New Jersey continues to be a leader in life sciences. Our State was ranked number one for biotechnology growth potential, ranked number two for biotechnology strength and is in the number one region for biopharmaceutical jobs. In 2017, 50% of FDA approvals came from companies with a footprint in New Jersey and 12 of the top research companies have facilities here.

New Jersey has more than 8.3 million square feet of laboratory space, including incubator space for early-stage biotech companies. Our incubators, located in North, Central and South Jersey, also offer companies a variety of support services and technical services to help them grow. The Commercialization Center for Innovative Technologies (CCIT) in North Brunswick, at the heart of the State's "Research Corridor", for example, is one of the most significant incubation facilities in the United States. Other New Jersey incubators include the Enterprise Development Center (EDC) at New Jersey Institute of Technology (NJIT) in Newark, the South Jersey Technology Park (SJTP) at Rowan University in Mullica Hill, and Princeton Innovation Center, just minutes from Princeton University. ■

New Jersey

CAPITAL
Trenton

POPULATION
9,005,644

AREA
8,723 mi²

GDP 2016
$575.3 billion and ranked 8th in the United States (U.S. Department of Commerce)

Life Sciences employees

117,260

#1

Region for NIH Funding (NIH Report Database, 2016)

50%

of 2017 FDA approvals came from companies with a footprint in NJ

312,000

Biopharma Patents from 2010 to 2014

PHARMACEUTICAL AND BIOTECH CLUSTERS

#1

Largest Seaport on the East Coast

#3

Busiest Seaport in North America

22 million

Consumers within a two-hour drive (with $800 billion in income)

418

Academic patents from 2010 to 2014

27,000

Life science students graduated every year

225,000

Highest Concentration of scientists and engineers in the world

Debbie Hart

President & CEO
BIONJ

Founded in 1994, BioNJ's mission is to enhance the climate for the life sciences industry in the state.

What role does BioNJ play as a support system to its members?

BioNJ's member base covers every category of the life sciences industry, from innovators both large and small to service providers and academic institutions. We have really broadened our reach in terms of what we are doing and our approach. In particular, we have expanded our work in raising awareness of the value of medical innovation and what exactly our member companies are doing to make a difference for patients, reducing healthcare costs and growing the economy in New Jersey and beyond. The impact of New Jersey companies is global, and it is critical that BioNJ plays a role in telling its story.

The second category of increased focus is patient advocacy. We make sure that BioNJ acts as a conduit for patients to communicate with our members. We also engage patients in our advocacy work to ensure that government at the state and federal levels is doing things that help provide access for patients and help advance the therapies and cures that they need. We have a particular opportunity here in New Jersey with the change in Administration – Governor Phil Murphy was sworn in earlier this year and understands the impact of the industry on the economy, as well as on patients.

Could you elaborate on the factors playing into New Jersey's attractiveness for life sciences companies?

New Jersey is a robust life sciences ecosystem where science is supported, companies are created, drugs are developed and patients are paramount. The policy framework has played an important part in attracting some of the earlier-stage companies here and in keeping some of the larger companies. However, potentially our strongest asset is our location. It is possible to fly almost anywhere in the world on a direct flight from one of five airports within a 60-minute drive. The time zone is also favorable for business, allowing communication with California and the United Kingdom in the same business day. Wall Street is also right across the river; the NIH and the FDA a train ride away. New Jersey's talent is second to none, especially when it comes to bringing a drug to market. Rent is also far more competitive than in any of our competing geographies. Coupled with cultural benefits and quality of life, the combination is powerful.

How does BioNJ ensure a supportive ecosystem for drug discovery and novel therapies?

Since the industry first began to take shape, commercialization has been a very important part of what New Jersey offers. Nevertheless, we also have a strong opportunity in new company creation. In addition, our academic institutions are also being more creative and thoughtful about the way they are bringing technologies and research to market. One of the most exciting things that happened in the last year has been the announcement and opening of several new incubators. There is one at Princeton University in conjunction with BioLabs, as well as one recently opened at Celgene, which will be accepting applications from all around the world. The Seton Hall Hackensack Meridian Medical School, which will offe in the fall, offers a wealth of new opportunities.

Many large pharma companies are building their R&D capabilities in hubs such as the Boston/Cambridge area and San Francisco Bay Area. Is the innovation focus shifting away from New Jersey?

Rather than a shift in focus, large pharma companies are extending their capabilities across the country. It is a global industry, which has morphed to focus on collaboration between large and small companies to a much greater extent – it makes sense that companies would pursue these opportunities. There is plenty of innovation, collaboration and partnering in New Jersey and its surrounding areas as well. The region, extending also to New York and Pennsylvania, is very robust.

What do you see as the main areas of focus for improvement within the industry?

We must maximize our relationships in Trenton and Washington, and ensure that the government is making moves to help and not hurt the industry. There are policy challenges ahead. We need to make sure that BioNJ is fulfilling its role in educating people on what goes into bringing a drug to market; estimates sit at a timeframe of 10 to 15 years and a US$2-billion investment. We will continue supporting this work as well as supporting those companies that are here or interested in locating here. ■

Building a successful hub

Both Boston/Cambridge and the San Francisco Bay Area have unique features that have enabled the biotech industry to thrive. Large academic institutions, hospitals and proximity to international airports provide needed resources for research, business and for budding new talent, encouraging constant collaboration. Both of these cities place a high value on innovation and entrepreneurship

- Kevin Gillis, CFO/Partner, Third Rock Ventures

[Massachusetts] is so critical for the world of biotech for so many reasons. Nowhere else is it as easy to strike up a collaboration simply due to the high concentration of companies and resources. It really does help innovation to have more people, more ideas, more money – everything on a larger scale. It is great to have a big candidate pool for hiring, but it can be hard to compete with some of the larger companies. However, we are able to offer the chance to work on something truly meaningful and life-changing for our potential patients.

- Todd Brady, CEO, Aldeyra Therapeutics

Cambridge today is unquestionably the Silicon Valley of 30 years ago when technology started exploding. Hence, there is a very high level of traffic through the area, including academicians, medical experts and companies. This is a big advantage. There is also an abundance of talent, because anyone that is a specialist or aspiring specialist in the field does tend to gravitate towards Cambridge. We have seen an explosion of our ranks in terms of expertise and innovation in the last four years. We have also been able to attract some of the world's leading advisers.

- Garo Armen, CEO, Agenus

There are so many tremendous technological advances and there has never been a better time to be in the industry. What really makes the Bay Area tick is this energy for entrepreneurship and breakthrough science. The entrepreneurial ecosystem and support infrastructure here are critical. California has a history of innovation and risk-taking that can be seen from the gold rush all the way through to the first high-tech revolution. The vast majority of breakthrough innovations that have happened in this industry have come from the Bay Area - from the first biotech company, recombinant DNA, consumer genomics, antibodies, all the way up to CRISPR; so many innovations have originated on the West Coast. There is an expansiveness of thinking and new ideas and absence of constraint by convention on the West Coast that is second to none in the world.

- Gail Maderis, CEO, Antiva Biosciences

Image courtesy of T2 Biosystems

Fostering an Innovative Ecosystem

"Rather than a shift in focus, large pharma companies are extending their capabilities across the country. It is a global industry, which has morphed to focus on collaboration between large and small companies to a much greater extent – it makes sense that companies would pursue these opportunities."

- Debbie Hart,
President & CEO,
BioNJ

Image courtesy of UPS

From small beginnings: the shifting innovation focus

For a long period of time, the U.S. biopharmaceutical industry has been dominated by large companies with mixed portfolios of commercialized products and candidates coming through the development pipeline. Whilst there are a number of funding options available to smaller companies through grants, venture capital and so on, it is the increasing attention and financial support from large pharma that is really allowing small biotechs and early-stage research to flourish.

As innovation increasingly finds its roots in academic institutions and small biotech startups, the epicenter of medical progress has shifted away from large pharma. The tables have in fact turned – it is now the big pharma companies that gravitate towards the fledgling innovative startups and academic institutions with spin-off potential. PhRMA estimates that 70% of clinical trials are conducted by small biotech companies, many of which have no commercialized products yet, relying instead on private investment to fund R&D.

Beyond funding, large pharma companies bring a number of other resources to the table, including access to infrastructure and expertise in commercialization. Research and development at universities and biotech start-ups is often driven by teams of scientists and engineers that have no experience

32 >>

"Both Boston/Cambridge and the San Francisco Bay area have unique features that have enabled the biotech industry to thrive. Large academic institutions, hospitals and proximity to international airports provide needed resources for research, business and for budding new talent, encouraging constant collaboration. Both of these cities place a high value on innovation and entrepreneurship."

- Kevin Gillis, CFO, Third Rock Ventures

William Hait

Global Head
JOHNSON & JOHNSON GLOBAL EXTERNAL INNOVATION

Founded in 1886 in New Jersey, Johnson & Johnson is a multinational medical devices, pharmaceutical and consumer packaged goods manufacturing company.

Companies across a range of therapeutic areas are taking a precision medicine approach to their drug discovery and development strategies. How does Johnson & Johnson tie these principles into its own pipeline?

We are becoming much more sophisticated about the root causes of disease, having greatly advanced our understanding of human biology and the alterations that occur in many diseases. With precision medicine, we can take into account an individual's genetics, lifestyle and environment to achieve more targeted disease treatment and prevention. This aligns with J&J's commitment to investing in platforms that are focused on disease prevention, interception and cure. In contrast to infectious diseases where we have seen major advancements in prevention and cures, diseases like lung cancer and Alzheimer's are very complex and there is an urgent need to develop a clearer ability to identify the individuals at greatest risk, identify strategies aimed at intercepting the disease causing process and treating the diseases at the earliest possible stage. Our investment in GRAIL is a great example of a novel approach to diagnose malignancies such as lung cancer while it is still curable.

Over the last few years, we have seen an increasing concentration of innovation coming from universities, spin-outs and small biotech start-ups. How integral are collaborations with these enterprises to Johnson & Johnson?

They are critically important. Our ability to grow our business is based on a balance of internal scientific strength and external innovation. We know that a great idea can come from anywhere – inside or outside our company – and we are committed to helping those ideas become healthcare solutions for patients. As an example of that commitment, we formed Johnson & Johnson Innovation to specifically accelerate early-stage innovation worldwide, and through this channel we provide scientists and entrepreneurs with access to our internal experts who can facilitate collaborations across the pharmaceutical, medical device and consumer sectors of Johnson & Johnson. Earlier this year we announced that through our Innovation Centers we executed more than 350 collaborations since their establishment in 2012.

Boston/Cambridge and the San Francisco Bay Area have garnered particular attention for innovation and life sciences activity. Does Johnson & Johnson's strong historical New Jersey presence hold a notable advantage, or is the company's focus shifting towards other hubs?

Johnson & Johnson has a large footprint in New Jersey; we began investing in the region in 1886 and have been an integral part of the community ever since. New Jersey remains a great hub for the pharmaceutical industry and has many advantages including proximity to leading research universities, global transportation hubs as well as access to financial markets. There is also a critical mass of high-quality talent in the region. In addition to our core operational strength in New Jersey, we established our Innovation Centers around the globe in life science hot spots including Boston, San Francisco, Shanghai and London, as well as a global network of JLABS facilities, which are similar to incubators, that enable entrepreneurs to accelerate the delivery of potentially transformative healthcare solutions.

How important is innovation to Johnson & Johnson going forward?

Johnson & Johnson is the world's largest, most broadly based healthcare company with a focus in consumer health, pharmaceuticals and medical devices. As a company, we have made stunning contributions to years of life gained and quality of life since 1886, and we have always been able to evolve to meet the needs of customers. While people are living longer today than ever before, they are likely to spend years or even decades living with chronic health conditions. That is why we believe investing in innovation that is not only focused on treating disease but also preventing it or intercepting it at its earliest stage is paramount. At J&J we are fully committed to delivering disruptive innovation that addresses critical unmet needs in healthcare and makes a difference to future generations. It is also important to ensure the long-term sustainability of our healthcare systems. Increasing our investment in innovation is an important part of Johnson & Johnson's strategy, and in 2017 we achieved record levels of investment with over US$10 billion in research and development. ■

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Last summer, we received MilliporeSigma's Golden Ticket and then Agilent's Golden Ticket this January. These awards support residence at LabCentral, the premier launchpad for biotechnology startups. We very much value the recognition from Agilent and MilliporeSigma; the awards were the result of a highly competitive process, and definitely help to validate Angiex as a promising, high-impact startup. Building relationships with industry leaders like Agilent and MilliporeSigma is extremely important for a start-up, and especially for us. MilliporeSigma is a potential GMP manufacturer of our drugs and Agilent creates high quality equipment for HPLC and mass spectrometry, which we will be using heavily.

- Paul Jaminet, CEO, Angiex

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in bringing a drug to market. "Partnerships are essential for small biopharmaceutical companies, even in the face of abundant capital, because a lot can be learned and leveraged in a way that can help diversify technical, regulatory, financial and scientific risk in exchange for the upside that may follow," highlighted Robert Blum, CEO at Cytokinetics, a Bay Area biotech focused on developing muscle activators. "Partnerships also help infuse a discipline into the company - it is very easy to develop a myopic way of thinking about science and potential therapeutic value, and it is always good to be challenged by a partner that may have a shared interest but may come at things from a different angle. Partnerships provide a forum within which ideas and processes are vetted much more objectively, rigorously and regularly. We too often see companies becoming too enamored with their own science and cannot see the forest for the trees."

Cytokinetics has itself taken advantage of industry partnerships to advance its pipeline, focusing on proteins and pathways implicated in diseases where muscle function is weakened or dysfunction occurs. Cytokinetics is working with both Amgen and Astellas in cardiac muscle and skeletal muscle respectively. So far, Cytokinetics has received US$600 million from its partners in addition to capital raised from institutional investors. In the case of its partnership with Amgen, Cytokinetics had done most of the early research and development and most of the Phase 1 and early Phase 2 studies in developing a candidate to increase cardiac muscle function, addressing morbidity/mortality in high risk heart failure. "As we have now entered into larger and longer clinical trials, those have been done in a co-development format," said Blum. "Now that we are in Phase 3 in our partnership with Amgen, they are sponsoring an 8,000-patient study at their cost, which is being conducted across 35 countries and costing hundreds of millions of dollars. We will be conducting a second Phase 3 trial with most of the expenses reimbursed by our partner. The two trials together will hopefully generate clinical evidence that can form the basis of a registration program for regulatory approval."

Amgen is responsible for the larger-scale manufacturing for clinical trials and for commercialization, whereas Cytokinetics has responsibility for the smaller scale manufacturing. Following commercialization, Cytokinetics would then focus on hospital-based patients in North America while Amgen would focus on the outpatient market, taking care of the larger sales and marketing activity.

Small biotechs will continue to spring up, some finding success through partnerships or independent development, and others quickly exiting the market due to trial failures or inability to adequately finance pipelines. However, as these companies become smarter with their development approaches, targeting better-defined patient populations and implementing more rigorous selection processes for clinical trials, it is likely that a higher number of small biotechs will find success going forward. Smaller investment requirements will make the marketplace more accessible to smaller companies as well as increasing investor appetite due to faster returns. ■

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Too many biopharmaceutical companies being constructed today are choosing to execute programs more autonomously, which is creating more binary risk. Those companies are succeeding or failing fast. This may appeal to certain types of volatility oriented investors looking to build a portfolio of investments, but it does not contribute to the biopharmaceutical ecosystem – we have more fragile companies that are not built to last, which is unfortunate considering how much more scientific knowledge we have that could be harnessed for new medicines.

- Robert Blum, CEO, Cytokinetics

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Morten Sogaard

Vice President and Head,
Genome Sciences & Technologies
PFIZER

Pfizer is a research-based, global biopharmaceutical company.

What are the primary activities of Pfizer's External Science and Innovation (ES&I) team?

We have three legs to the ES&I segment of Pfizer. The first is the original external R&D division, which deals with external investment; the second is Target Science Technologies, which focuses on target generation both through internal capabilities and external networks, also overseeing regionally-based scouts in North America and the United Kingdom, a relatively new component; the third comprises Pfizer's Centers for Therapeutic Innovation (CTI), which involve sourcing projects from academia, with a particular focus on New York, Boston, San Francisco and San Diego. The CTI model involves putting agreements in place with academic institutions and medical centers and working with them to identify drug molecules and take them forward to the clinical stage.

Pfizer's Data and Technology Innovation Strategy Group carries out an annual technology landscape assessment, which helps the company to decide which new areas to enter at which time. We also have subgroups dealing with human genetics and functional genomics, computational target validation and diagnostics. A new vehicle for target generation is the Innovative Target Exploration Network (ITEN) – the idea is that we select a particular area of emerging science and set up a program with two to five academic principal investigators (PI's) and some contribution from Pfizer, which typically lasts about three years. The purpose of these programs is to add novel targets to our pipeline.

Under the umbrella of "precision medicine", how is genomic sequencing changing the shape of the industry?

In rare disease especially, genomic sequencing is already enabling the identification of a number of genes that are good potential targets. Through increasingly high-throughput genome-wide association studies, with "regular genotyping" at a lower cost, we are gaining extremely important insights. For chronic diseases, exome sequencing and genome sequencing are seeing a significant uptick.

Pfizer is currently participating in a consortium alongside Regeneron Pharmaceuticals, AbbVie, Alnylam Pharmaceuticals, AstraZeneca and Biogen to sequence the exomes of all 500,000 participants in the U.K. Biobank. This will give us new insights into potential new drug targets and biomarkers, which would contribute to starting drug programs and lower attrition rates due to better biological concepts and rationale. A number of studies have shown that drug candidates addressing genetically well-validated targets have very high success rates up to the end of Phase 2. We also hope to identify biomarkers that can help us to stratify patients in clinical trials to understand which will likely have the fastest and best responses to the drug.

Many large pharma companies seek to acquire later-stage research that is somewhat de-risked. What is Pfizer's target when it comes to partnering with academic institutions and other companies?

Innovating around novel targets has always been a challenge for pharma companies. They have mostly tended to pursue targets that are better-validated, which will typically mean lower required investment and shorter development timelines. As we move further through development, this is where pharma tends to shine more in terms of identifying compounds and screening. Since most value creation comes later in the pipeline as a candidate approaches commercialization, pharma companies tend not to spend so much time on discovery and earlier-stage research. Nevertheless, we would like to become increasingly more involved in research at its earlier stages. Ventures such as the CTI exhibit an attempt to leverage academic research in a more vibrant way than we have done previously.

For small biotechs, the benefits of partnerships with larger companies are clear, from funding to filling gaps in infrastructure or expertise. What is the importance of these partnerships to Pfizer?

Relationships with smaller biotechs are critical to Pfizer, not just in driving innovation but also in driving our pipeline. One of Pfizer's main considerations is how to put vehicles in place to attract these partnerships. We have started to allocate some seed funding, typically to academic lab research or start-ups in their embryonic stages. We also have Pfizer's R&D Innovate program, which enables new co-creation programs. We are certainly open to doing more Series A and Series B venture investment. ■

Finding Funding: The diversification of the biotech financing landscape

As the number of biotech start-ups has rapidly grown and the drug discovery focus has shifted away from the internal pipelines of large pharma companies, the financing landscape has also adapted in line with market needs. With no revenue from the drug over the development period and high development costs, BIO's claim that more than 90% of U.S. biopharmaceutical companies do not earn a profit is perhaps unsurprising, and highlights a need for external investment.

While early-stage venture capital funds were once large in number and a primary source of funding for the industry, challenging market conditions has necessitated increasing resourcefulness and a diversification of financing sources. "[F]rom 2000 to 2009, life sciences venture capital was a bad place to be; none of those funds really made much money," commented Peter Parker, managing partner at BioInnovation Capital. "Many changed course and moved towards growth equity, and some carved out their life sciences unit and focused on tech. As a result, there are far fewer early-stage life sciences capital firms, with some being Third Rock Ventures and Flagship Pioneering, which create their own ventures, so follow a different model. This leaves about five in the Boston area and four on the West Coast, and then a large vacuum."

Large pharma companies began to fill this void, establishing their own venture capital funds and fostering relationships with biotechs as an extension of their R&D pipelines. "While these partnerships initially generally favored large pharma, as the biotech industry grew and became more confident and the value of the research made them more competitive, they were able to demand better terms from the pharma companies, leading to the creation of more balanced partnerships," noted Janice Bourque, managing director at Hercules Capital, a business development company specializing in providing venture debt. "When the stock market fell and the public market with it, many companies were challenged to stay afloat and many venture capital firms fell by the wayside. Since the re-emergence of the public markets, the trajectory has been interesting."

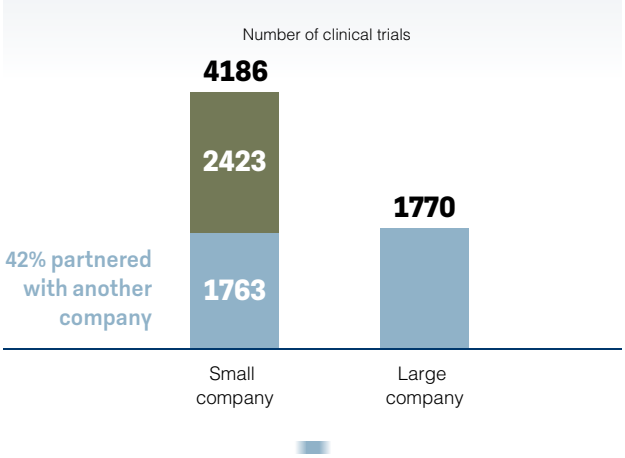
In addition to a range of grants from organizations such as the NIH, there is a large group of angel investors within the Boston and San Francisco communities.

With biotechs seeing increasing support and mutually-beneficial collaboration opportunities from large pharma companies, Massachusetts' companies are particularly well positioned. Highlighting the importance of the significant presence of 18 of the top 20 pharma companies within the state, Travis McCready, president and CEO at the Massachusetts Life Sciences Center, remarked: "An interesting dynamic is taking place: on a per capita basis, we lead the United States in the amount of venture capital being invested into early stage companies… However, unlike in years past, those venture capital dollars are going in larger tranches to a smaller number of companies. The ecosystem has managed to maintain equilibrium because the large pharma and medical device companies have their own investment funds, which amounts to about a billion dollars going into early stage companies. This deployment of investment funds in young companies is not done in any other ecosystem."

70% OF CLINICAL TRIALS ARE CONDUCTED BY SMALL BIOTECHNOLOGY COMPANIES

GLOBAL BIOPHARMA CLINICAL PIPELINE

Source: BIO Industry Analysis, BioMedTracker, 2017



THE TOP 5 BIOTECH VC FIRMS

Source: FierceBiotech

Venture Firm	Dollar Amt. in Millions	Number of deals	Based
New Enterprise Associates, Inc.	$189.78	29	Menlo Park, CA
Versant Ventures, Inc.	$186.87	37	Menlo Park, CA
OrbiMed Advisors LLC	$136.06	21	New York City
New Leaf Venture Partners	$128.33	33	Menlo Park, CA
Third Rock Ventures LLC	$112.76	28	Boston, MA

Another notable source of financial support are the federal and state governments in the form of incentives and investment into infrastructure. The support of the state government has been a great contributor to the rapid growth of Massachusetts' life sciences sector over the last few years, for example, most clearly reflected in the allocation of a US$1 billion fund, distributed by the Massachusetts Life Sciences Center across three major capital categories as a catalyst for the industry's growth. Half a billion dollars was allocated to capital infrastructure, spanning aspects from research facilities to high-end equipment. Within this category, arguably the most widely-acknowledged success has been the LabCentral facility in Cambridge, into which US$10 million was invested. This facility, which provides lab space and resources to its resident companies, contributed to the creation of 402 new jobs and over US$300 million raised in additional financing in 2016 alone, plus the filing of 113 new patents and 27 new licensing agreements.

Of the remaining US$1 billion investment, US$250 million was made available for tax incentives, a huge support in the growth of small and mid-sized companies, and an attractive proposition for companies outside of Massachusetts open to relocating. The final US$250 million was allocated towards an investment fund for pre-seed and seed stage companies, also contributing to internship programs for approximately 500 to 525 high school and college students every year. The Massachusetts Life Sciences Center is now in the process of securing a further half-a-billion dollar investment to be allocated over the next five years.

This strategic allocation of funds, particularly directed towards long-term sustainable growth, puts Massachusetts at a big advantage compared to other life sciences hubs. Other hubs rely more heavily on initiatives and grants directed at particular projects. "One challenge across California is that the industry has had to support its own growth without many incentives provided by the state or federal governments," referenced Joe Panetta, president and CEO at Biocom. "The situation is very different from other hubs such as Massachusetts. State investment in California is generally only through research universities such as UC Berkeley, UC San Francisco, UCLA, UC Irvine, UC Riverside and UC San Diego. 13 years ago, we passed a citizens' initiative, which created our US$3-billion Stem Cell Agency to provide grant funding to academic researchers and small companies within that field."

New Jersey is also particularly committed to creating a favorable framework at a policy level, including a number of financial incentives in support of innovation. For example, the state's recently-formed Biotechnology Task Force is charged with the development of recommended action steps that will inform policy making, with the goal of building a first-class innovation economy. By fostering a supportive ecosystem in which start-ups are able to thrive, the potential for bringing novel drugs to market amplifies.

R&D REINVESTMENT AS A PERCENTAGE OF REVENUE.

Source: Factset, BIO Industry Analysis based on CY 2016 data

RANK	U.S. INDUSTRY	R&D SPEND
1	**Biopharmaceuticals**	**21.3%**
2	Semiconductors	18.4%
3	Electronic Production Equipment	17.6%
4	Internet Software/Services	17.4%
5	Packaged Software	14.3%
6	Computer Communications	13.7%
7	Computer Peripherals	11.7%
8	Internet Retail	10.4%
9	Electronic Equipment/Instruments	9.8%
10	Medical Specialties	7.0%

> "In the Midwest and across different parts of the United States there are incredible discoveries going on, but we are noticing that companies here are really struggling to get the attention they might deserve. There are great research centers in states like Texas, Illinois, Kentucky and Tennessee, among others, but access to capital is much more strained. If the same science was being carried out in San Francisco or Boston, it would be a different story."

- Kevin Elliott, Partner, Procela Partners

By softening the financial burden, small biotechs are better able to progress focused pipelines, bringing new treatments to market and addressing unmet needs more quickly and efficiently. There is therefore some responsibility at the policy-making level to facilitate innovation where possible, which can also be seen in the formation of biotech incubators. These are often hugely competitive, a testament to their value as a stepping stone for companies getting their research off the ground. Cambridge-based LabCentral, which falls within the BioLabs network, is in many ways the forerunner of the biotech incubator model and a key component of the critical mass that has accumulated in the city over the last few years. By venture capital dollars, companies passing through LabCentral's doors have raised over US$2 billion just in the last three years. Today, only 20% of applicants are able to make the final selection.

High demand for this kind of infrastructure has led to the expansion of networks of incubators across the country. Johnson & Johnson's JLABS has locations on the West and East Coast, with the most recent addition being a facility in New York City. In New

> "Every large pharma company now has a venture capital fund, so some companies get big investments from larger firms. However, many companies do not get that chance. Then, there is a large group of angel investors within the Boston and San Francisco communities. The environment has changed a great deal.
>
> **- Peter Parker, Managing General Partner, BioInnovation Capital and Co-Founder and Director, LabCentral**"

Jersey, Princeton University has recently opened its Princeton Innovation Center BioLabs. Another large incubator is soon to follow in New Brunswick.

Following a different financial model but still aimed at progressing companies, accelerators are also playing a key role in bringing start-ups up to speed in the marketplace. SOSV, for example, is a US$250 million venture capital fund focused on accelerating over 150 startups every year through several accelerators around the world. Its flagship and largest program, IndieBio, is in San Francisco. "Before SOSV, most accelerators were software-focused; we pioneered by creating vertical accelerators, particularly in hardware and life sciences," commented Sean O'Sullivan, SOSV's founder and managing partner. "The accelerator itself is very competitive; every year, we receive around 4,000 applicants for our specialized accelerators, of which only 3% succeed. We invest around US$50 million a year into those companies that we select."

Meanwhile, traditional funding channels continue to drive the industry financially, with venture firms citing cutting-edge innovation as the primary consideration when identifying investment opportunities. ■

Janice Bourque

Managing Director
HERCULES CAPITAL

Hercules Capital is the largest business development company focused on venture lending.

Could you briefly outline Hercules Capital's development over the years?
Hercules Capital started as a private investment firm and quickly went public through a listing on the NASDAQ exchange. Hercules is a BDC that focuses on providing capital to some of America's most promising, growth-oriented companies in both the technology and life sciences sectors. Today, Hercules has an investment portfolio that sits at over US$1.5 billion, nearly 50% of which are to life sciences companies, both private and public. We have the capability to provide loans that can range from US$5 million to in excess of US$100 million and our platform allows us to structure our loans in a way that meets that needs of our various borrowers.

What makes a company a good investment prospect for Hercules Capital?
Our approach is broad, but we tend to look for companies that have certain characteristics including strong and experienced management teams, a diversified group of institutional investors, an entrepreneurial focus and that are trying to solve big issues in large attractive markets. On the life sciences side, we are generally focused on companies with diversified clinical pipelines and/or companies that have strong platform technologies.
In life sciences, there are so many variables that cannot be measured, so mitigating risk in multiple ways is an absolute necessity. Having a knowledgeable investor is both good for the company and for us as it allows for a partnership approach to anticipating and dealing with risk. Accelerated approval pathways, strategic partnerships, company goals and factors that can reduce cost are good signs. However, we also realize the value in focusing on the management team and how well they execute on a plan and changes to that plan. Understanding the company's exit or growth strategy helps us better understand our role as a partner.

How have the dynamics of the financing climate shifted over time?
In the early days, there were a larger number of venture capital funds and companies were able to grow with a smaller amount of capital. Institutional investors began to develop very specific relationships with researchers who saw the value to patients in bringing their discoveries to the next level. Thus emerged the valuable research alliances we see today between industry and academia. At one phase in the evolution of the life science industry funding became extremely difficult – venture capital firms were investing less and there still was a lack of IPO's and public investors. Concurrently, the pharmaceutical industry began to recognize the biological innovation being performed in the small companies while noting their own R&D pipelines needed newer sources of innovation and technology. This simultaneous awareness created the environment that allowed for the establishment of relationships between the biotechnology and the pharmaceutical industry. Big Pharma had financial resources that helped fill the financial void for many companies. These partnerships initially generally favored large pharma, but as the biotech industry grew the value of the research increased and became more competitive, companies were able to demand better terms from the pharma companies, leading to the creation of more balanced partnerships. Eventually we saw the emergence of a public investor market with IPO's and follow on investments. This provided further opportunity to the industry as now private companies had the option to provide an exist either by an IPO or an M&A deal as an exit to their investors. When the stock market fell several years ago and the public investor market with it, many life science companies with good research and pipelines were challenged to raise capital and venture debt increasingly became an additional source of capital. We saw the exit of many venture capital firms and the growth of others. We also saw the emergence of the sophisticated high net worth investor and the rise of philanthropic organizations that are focused on a particular disease. We are now witnessing a much more global investor group coming forward, with new investors from countries such as China, Saudi Arabia, and other Sovereign Nations. Since the re-emergence of the public markets, the trajectory for the industry has been exciting. ■

Kevin Gillis

CFO
THIRD ROCK VENTURES

How has Third Rock Ventures developed in line with the life sciences industry over the years?

At Third Rock, we discover, launch and build great companies based on bold ideas that meet at the intersection of science, strategy, business and medicine - where transformational science meets operational reality - providing the best opportunity to make a dramatic difference in patients' lives.

Our investment philosophy has always been guided by the ongoing tremendous innovation in science and medicine. We focus on creating product engine companies, which offer unique opportunities for growth and value in that they are built on technologies with the potential to generate multiple therapeutics.

What factors does Third Rock consider when identifying an attractive investment opportunity?

We create companies with teams that share a common goal: a fearless approach to addressing medical needs through bold ideas and transformative science. We are actively involved in the early stages of our companies' development, typically serving as members of the founding management teams, to build a strong foundation, put in place the right people and culture, and set the companies on a path to scientific and operational excellence.

Could you elaborate on Third Rock's investment model and strategy in building companies?

We take a long-term approach to company building, creating a portfolio of companies with the potential to make a dramatic difference in patients' lives. Our unique Discover, Launch, Build process brings together the best inside and outside experts, allocates capital and resources based on where an idea or company is in its development and provides our companies with the support necessary to advance novel therapies.

What are the objectives for Third Rock Ventures going forward?

Our objectives are the same as they have always been: build great companies that discover and develop products that make a difference for patients. We invest in ideas and are focused on opportunities that could change the future of medicine.

As we celebrate our First Decade, our mission has not wavered: to be the preferred partner for entrepreneurs, investors, employees and industry to build great companies that discover and develop products that make a difference for the patients we serve. ■

Kevin Bitterman

Partner
ATLAS VENTURE

How does Atlas Venture differentiate itself from other venture capital firms in the market?

Our focus today is exclusively on early stage biotechs and seed and series A investments. We are currently investing out of Atlas' 11th fund – a US$350 million fund – which will be allocated to early-stage drug development. We spend a lot of our time looking for exceptional science and transformational technologies and play a very active role in aggregating both science and entrepreneurs around an opportunity. Building infrastructure and resources to support company creation has been an important aspect of what we do. About half of our office space in Cambridge is dedicated incubator space. At any one time, we have 10 or so seed stage companies and about three dozen entrepreneurs cohabitating with us in our offices.

What elements does Atlas look for when identifying a new investment opportunity?

Our approach is very flexible, with the common thread between our investments being groundbreaking science with the potential to address unmet medical needs. We take an incredibly rigorous approach, digging deeply into the weeds of any given area of biology and any potential drug target to assess the approach, the unmet medical need being addressed and, of course, the ability to gather exceptional entrepreneurs around that opportunity.

What are the main objectives for Atlas' growth moving forward?

Atlas is continuing to pursue its strategy of looking at great science across a variety of areas and continuing to build our network of entrepreneurs. There are a few areas in which we will be proactive in looking for opportunities, but a lot of what we do requires us to be reactive in leveraging our network. We plan to start anywhere from 15 to 20 companies from our current fund across a variety of therapeutic areas and different models. While we are committed to maintaining a single office in Boston, we will continue to search for and evaluate science across the globe. ■

Christiana Bardon

Portfolio Manager
BURRAGE CAPITAL
Managing Director,
Oncology Impact Fund
MPM CAPITAL

Burrage Capital and MPM Capital are each focused in the field of oncology. What is your current take on the market?
We are at an unprecedented period of innovation in oncology. There is so much new science surrounding checkpoint inhibition, immuno-oncology, new modalities of treatment such as cell therapy, which together are transforming the care of cancer patients. Previously, with chemotherapeutics, the expectations were really low response rates and a short duration of activity, such that patients would still eventually succumb to the disease. Now, however, we have the opportunity to cure patients. This is therefore one of the most exciting times to be investing in biotech, and more specifically in oncology.

What factors indicate a promising investment prospect?
What is extremely important is the clinical data that these companies go on to generate. Proof of concept and strong pre-clinical data are extremely important to us. We would also prefer an accompanying diagnostic for the identification of patients with the best response rate.

Do the funds invest overseas or primarily in the United States?
Primarily, we pursue cutting-edge science. Nevertheless, our focus is mainly in the United States, of which the key areas of activity are Boston and San Francisco. In fact, Boston is becoming even more predominant because of the infusion of R&D talent into the area. This makes for great recruiting and partnering. We also have several portfolio companies in Europe, and a few interests emerging in Asia, particularly in China.

What are the main objectives for MPM Capital and Burrage Capital?
We want to keep finding great drugs that will help patients. We are not seeking 8% response rates and moderate benefits. We want to cure patients and change the outcome for large percentages of cancer patients. Curing patients of severe diseases is the best way to create value in this marketplace. ■

Kevin Elliott

Partner
PROCELA PARTNERS

Could you briefly introduce the firm and outline how it is differentiated from other organizations?
Procela Partners is a full-service consultancy that helps small and medium-sized biotech companies across the United States and Europe to commercialize internationally. We have three main areas of focus. First is business development and licensing, typically for companies looking for a global or regional partner outside the United States to license their technology to. The second area is facilitating access to funding, which can take two forms. One is non-dilutive research funding in Europe, where there are several funds – we are highly successful in helping our clients access this funding.
The third core area centers around international operations, encompassing anything a biotech company might want to achieve internationally but does not have the resources to do itself. The new market opportunities available to big pharma or even larger specialty pharma companies due to interesting international structuring are often closed off from smaller life sciences companies. Not only do they not have the resources; they often do not even have the support from their investors to make these moves. They will often be laser focused on delivering on commitments made to venture capital firms such as a successful trial or various milestones. We are trying to fill that gap in expertise and capabilities and we have the reach, the personnel and the experience to do so.

What are the next steps for Procela?
Procela's asset-centric biotech model is really where the bulk of our energy will go in 2018. We see some serious potential here. We already have a number of targets identified, and we are expecting significant funding that will enable us to bring a well-balanced portfolio on board. Going into Phase 1 and looking to commercialize in Phase 2a lends itself well to quick payback – we are looking at about two or three years. ■

Lesley Stolz

Head
JLABS BAY AREA

JLABS is a biotech incubator run by Johnson & Johnson, with locations across the globe.

JLABS was established in 2012 in San Diego and is now present in several locations across the country and overseas. How has the strategy developed?
Most of our strategy has been purposeful, although some of it has been opportunistic. Following the launch of our flagship facility in San Diego, we established a collaboration in San Francisco, at the time called QB3@953, reflective of the innovation taking place in the Bay area. We then had the opportunity to expand to a number of other locations with meaningful innovation hubs, beginning with our own site in South San Francisco and expanding to Houston and then Toronto, each of the last two through partnerships. We collaborate with academic institutions or with the government to create a space for start-ups so that they do not have to spend all their hard-earned capital on infrastructure.

What are the differentiators and characteristics of Houston as a biotech hub?
There is a lot of potential for activity in Houston, with a number of excellent medical schools and institutions. In collaboration with the Texas Medical Centre, we are hoping to spark more activity and turn Houston into a hub of innovation for start-ups.

While most investors cite exceptional science as the primary tenet of attractiveness, what does JLABS look for in its applicants?
Our primary mission is to support great science that is meeting an unmet need and that we believe will be attractive to investors. We also look at the team and place emphasis on building a supportive community inside each space, with a combination of serial entrepreneurs and first-time entrepreneurs.
Of course, we also consider companies in areas of strategic interest to Johnson & Johnson. The company's interests are broad and, whilst it is not a requirement that start-ups fall within our strategic areas of interest, it does count as a plus. Our business model centers very much around moving science forward and, if Johnson & Johnson can enter into a mutually-beneficial relationship with a JLABS company, we are certainly open to pursuing partnerships options.

Other than infrastructure, in what other ways can JLABS support companies in developing and commercializing their products?
We do a lot of programming, which also helps companies to build their networks as well as educate themselves on timely topics. We have a very broad database of people that subscribe to learn about our programs and pertinent industry topics, and many that attend our public programs are not part of JLABS. This provides an opportunity for people to mingle and get to know each other. It is a great way to connect a company with the best service provider or foster relationships between individuals.

With time, has there been greater recognition of the value that biotechs bring to big pharma?
Big pharma companies have realized that they are not the only ones that can successfully develop and commercialize drugs, and there is great appreciation for well-run programs within small companies.

There is currently a more pronounced effort to build New York as a biotech hub. Considering its position as a financial hub, what have the impeding factors been so far?
We have been very excited about New York as a hub for a long time. The cost and availability of space are a primary challenge, and the state and city have only recently recognized that a lot of the scientists coming out of academic institutions want to stay there. It takes a concerted effort to create a cluster. Very few have emerged naturally. With the new incubators that are opening up around NYC, including a new JLABS facility, we are very optimistic that we will see an uptick in activity.

With an already-established presence in major U.S. hubs plus further afield in Europe and China, what is the focus for further supporting innovation?
We are constantly looking at how we can support other hubs that do not have the critical mass of the major locations, but do not currently have expansion plans on the near horizon. We try to bring our programming to other locations like North Carolina and Philadelphia, for example, and are continuously extending our educational programming at our current locations. ■

Sean O'Sullivan

Founder and Managing Partner
SOSV

Could you elaborate on the differentiators and advantages of this model over other types of investment or the incubator model?

An accelerator gives small amounts of money to a company for a very small portion of equity, allocating sufficient finance for the company to survive for anywhere from three months to a year. This financial support allows them to move geographically to the location of the accelerator and to progress their projects commercially and scientifically. Within a short space of time, accelerators allow a core group of companies to make a lot of commercial progress and they achieve the validation of being accepted by an extremely competitive accelerator, in turn making them more attractive to other investors.

Before SOSV, most accelerators were software-focused; we pioneered by creating vertical accelerators, particularly in hardware and life sciences. In addition to our initial seed capital, the companies that come through our accelerators can subsequently attract millions of dollars in follow-on and, as they gain traction, we continue to invest more SOSV capital into these increasingly successful companies.

As well as great science being a top priority, what else does SOSV look for in a great prospective applicant?

The accelerator itself is very competitive; every year, we receive around 4,000 applicants for our specialized accelerators, of which only 3% succeed. We invest around US$50 million a year into those companies that we select. We look for companies targeting a marketplace of at least a billion people or whose prospective revenue falls in the realm of billions of dollars. Another selection criteria is that the team has complete mastery of the subject matter and the marketplace. We are looking for companies to arrive with working system prototypes – we aim to have these systems engineered with us rather than companies undertaking basic science research that should already have been conducted before coming to us. We also look for platforms with multiple shots on goal to mitigate risk. ■

Peter Parker

Managing General Partner,
BIOINNOVATION CAPITAL
Co-Founder and Director
LABCENTRAL

For how long are companies generally accommodated at LabCentral before pursuing independent facilities?

Mostly, companies leave because they have acquired the appropriate funding. According to our policy, companies will move out after two years unless they re-apply. We would generally grant an additional year so that they are able to make progress in the lab whilst transitioning to their new location, which can take some time. This way, they are not just waiting and are still able to carry out productive work in the interim. Three years is the maximum, and some companies even leave after as few as six months.

What makes for a successful application?

Each company applies online. The process involves a four-question form to ascertain the area of scientific focus, business plan, founding members and current funding. Companies must have some financial backing to move here. Based on those questions, there will be an interview, either in person or over the phone, and if both sides wish to go forward, we bring them to a four-person selection committee. Through the process, we weed out about half of the companies, sometimes because they are not suited for a co-working environment, as we operate in a very open space. In total, about 20% of companies make it to the final selection. We are a heavily biology-based facility, but we do not discriminate based on scientific area.

What are the key objectives for BioInnovation Capital and LabCentral going forward?

Although we have our own fund, which invests in a few companies around the world every year, the lab activity is the primary focus and their operation is a business in itself. We have also selectively decided to help build facilities at a few other locations, such as Princeton, NYU and near Drexel. Depending on staff and infrastructure availability, we will probably take on other projects. We are also in discussions over building facilities in Australia, London and Paris. ■

Image courtesy of Northeastern

Accelerating pipelines: Drug Discovery and Development

"We are seeing unprecedented amounts of innovation. Because of the amount of innovation and the impact on patients, we are seeing very attractive clinical trial pathways and regulatory pathways. Once a patient population is properly defined that will benefit from a drug, approval can be sought with that impressive response rate. European and US regulatory authorities try to be very supportive because they want to get effective drugs to patients as quickly as possible."

- Christiana Bardon,
Portfolio Manager, Burrage Capital
and Managing Director, Oncology Impact Fund, MPM Capital

From Volume to Value: A shift in innovation focus

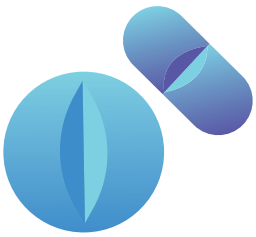
Through a deeper understanding of disease, coupled with novel technologies and approaches, the industry is moving towards more specialized treatments, stepping away from the blockbuster model that has long been the standard, and further towards the discovery of cures. The great overarching theme driving current approaches to drug discovery and development is precision medicine, which incorporates the understanding that every patient is different, both in terms of experiencing a disease, and reacting to a particular course of treatment. Biomarkers, for example, have become widely used to monitor and predict the effects of drugs in the human body. "We are becoming much more sophisticated about the root causes of disease, having greatly advanced our understanding of human biology and the alterations that occur in many diseases," voiced William Hait, Johnson & Johnson's global head of external innovation. "With precision medicine, we can take into account an individual's genetics, lifestyle and environment to achieve more targeted disease treatment and prevention. This aligns with J&J's commitment to investing in platforms that are focused on disease prevention, interception and cure. In contrast to infectious diseases where we have seen major advancements in prevention and cures, diseases like lung cancer and Alzheimer's are very complex and there is an urgent need to develop a clearer ability to identify the individuals at greatest risk, identify strategies aimed at intercepting the disease causing process and treating the diseases at the earliest possible stage. Our investment in GRAIL is a great example of a novel approach to diagnose malignancies such as lung cancer while it is still curable."

Mainly due to the large number of intervention points, oncology has become the poster child for precision medicine and, as the therapeutic area of highest investment, is experiencing a great deal of traction.

According to Clarivate Analytics, the top three areas of therapeutic focus combined represented 56% of investment into the industry in 2017, with cancer accounting for

47 >>

7) Abbvie
Total Revenue: 28,216 Billion USD
Total R&D Expenses:
4,982 Billion USD
Headquarters:
North Chicago, Illinois



TOP 10 USA COMPANIES BASED ON R&D SPEND AND REVENUE

2) Roche

Total Revenue: 44,368 Billion USD
Total R&D Expenses: 10,392 Billion USD
Global Headquarters: Basel, Switzerland
USA Headquarters: Indianapolis, Indiana

1) Pfizer

Total Revenue: 52,540 Billion USD
Total R&D Expenses: 7657 Billion USD
Headquarters: New York City, New York

3) Sanofi

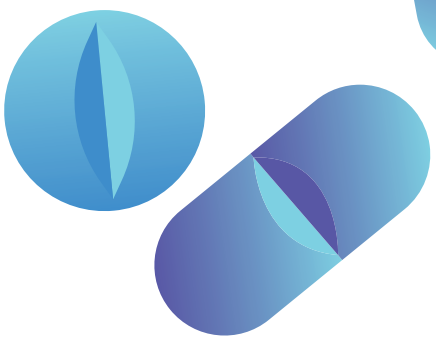
Total Revenue: 36,663 Billion USD
Total R&D Expenses: 6697 Billion USD
Global Headquarters: Paris, France
USA Headquarters:
Bridgewater, New Jersey

4) Johnson and Johnson

Total Revenue: 36,256 Billion USD
Total R&D Expenses: 10,554 Billion USD
Headquarters: New Brunswick, NJ

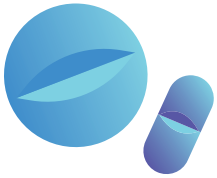
5) Merck

Total Revenue: 35,390 Billion USD
Total R&D Expenses: 10,000 Billion USD
Headquarters: Kenilworth, New Jersey



6) Novartis

Total Revenue:
33,000 Billion USD
Total R&D Expenses:
8972 Billion USD
Global Headquarters:
Basel, Switzerland
USA Headquarters:
East Hanover, New Jersey

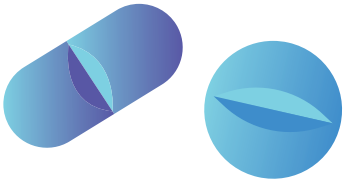


8) Gilead

Total Revenue:
25,662 Billion USD
Total R&D Expenses:
3,374 Billion USD
Headquarters:
Foster City, California

9) GlaxoSmithKline

Total Revenue: 24,038 Billion USD
Total R&D Expenses: 6,235 Billion USD
Global Headquarters: UK
USA Headquarters: Warren, New Jersey



10) Amgen

Total Revenue:
22,849 Billion USD
Total R&D Expenses:
3,562 Billion USD
Headquarters:
Thousand Oaks, California

David Cory

CEO
EIGER BIOPHARMACEUTICALS

Founded in 2008, Eiger BioPharmaceuticals is a late-stage biopharmaceutical company focused on developing and commercializing targeted therapies for rare diseases.

How has Eiger BioPharmaceuticals developed its pipeline around its rare disease focus?

Our work began with the hepatitis delta virus, which causes the most severe form of viral hepatitis infection, and currently has no approved therapy. We identified a specific host target called prenylation, upon which HDV relies to reproduce, which stemmed from technology licensed out of the laboratory of Prof. Jeffrey Glenn, a virologist by training and faculty member at Stanford University. With the target identified, we licensed a drug from Schering-Plough (now Merck) – a well characterized, small molecule, oral drug called Lonafarnib. We took this drug directly into Phase 2 studies, demonstrating proof-of-concept in patients infected with HDV, followed by a full Phase 2 program where dosing regimens for a registration study were identified. Eiger plans to move into Phase 3 with a single, pivotal clinical trial by the end of year. Hepatitis delta is a disease that impacts 15 million to 20 million people around the world, mostly throughout the Middle East and South East Asia, and with heavy populations in China and Mongolia. Although HDV is designated as an orphan disease in the US and EU, globalization and heavy migration from regions of high endemnicity have led to an estimated prevalence of 100,000 and 200,000 in the US and EU, respectively.

This process of developing well-characterized drugs acting on newly identified or novel targets in rare diseases significantly reduces the time and cost of drug development. Following the same process, we built a portfolio of novel Phase 2 clinical programs targeting rare diseases with multiple programs positioned for success by identifying a novel target in a rare disease and finding an existing drug that we were able to license and bring rapidly into the clinic. We have now done this three times over multiple diverse rare diseases, including hepatitis delta, post-bariatric hypoglycemia, and lymphedema.

How great is the unmet need across Eiger's areas of focus?

We are targeting rare diseases with relative large market potentials. Hepatitis delta impacts an estimated 100,000 patients in the United States and almost 200,000 patients in Western Europe. Post-bariatric hypoglycemia has a current estimated prevalence of around 70,000 in the United States and Europe and is growing. With obesity and type 2 diabetes growing worldwide, so has the need for bariatric surgery and the prevalence of associated postprandial hypoglycemia which occurs in 5 to 10% of gastric bypass surgeries. Lymphedema comprises two very different patient types. Primary lymphedema impacts ~35,000 patients worldwide and is idiopathic. Secondary lymphedema can occur in patients post-surgery or post-radiation if they have had lymphatic manipulation due to cancer, which afflicts tens of millions of people around the world. There are no currently approved pharmacological therapies to any of our pipeline programs.

What are the next milestones for the candidates in the pipeline?

We just had a face-to-face meeting with the FDA on our lead program in hepatitis delta which was very positive. The agency indicated that our next study can be a single pivotal trial for registration. We plan to be in Phase 3 by the end of 2018, stepping from mid-stage into late-stage clinical development. We also have three Phase 2 studies ongoing in HDV (LIMT), post-bariatric hypoglycemia (PREVENT) and lymphedema (ULTRA) – we will have top-line results from each in the third quarter of 2018. We have several near-term catalysts for value creation.

With inherently small addressable patient populations, are there sufficient incentives to develop orphan drugs?

There are great incentives to develop orphan drugs, including increased regulatory guidance and reduced total patient population requirements in most cases. The pricing that companies are able to obtain, especially in the United States and even in Western Europe, can be attractive. Eiger is somewhat unique in that the patient populations in our targeted pipeline programs are rather large for orphan diseases.

Going forward, how will Eiger continue to broaden its orphan disease focus?

Proof of success in our existing pipeline programs will allow us to bring life changing medicines to patients and become commercially successful, creating confidence in the investment community and facilitating ongoing efforts to expand the pipeline in the future by allowing us to repeat this efficient venture model. ■

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US$80.7 billion, mostly through grants and deals. Neurology/psychiatric treatment was second at US$17.2 billion, followed by immune therapies at US$15 billion. Infection accounted for US$14.3 billion in investment.

Concerns were voiced following a drop in drug approval rates in 2016 due to higher hurdles for approval and evidence of safety and efficacy. 2017, however, saw more than 50 novel drugs approved – more than any other year in the past two decades. Improving trial success rates also greatly reduces the average drug development timelines and cost as a result, which should enable reduced drug pricing in the longer run due to lower reimbursement costs.

Demonstrating clear clinical benefit in areas of high unmet need sits favorably with the FDA, which has shown greater flexibility in many instances as a result. New Jersey-based Rafael Pharmaceuticals (previously Cornerstone Pharmaceuticals), for example, is focused on areas of high unmet need in oncology and is allegedly the only oncology company with five orphan designations, held for its lead candidate, CPI-613, in the treatment of pancreatic cancer, AML and myelodysplastic syndromes (MDS) and more recently Burkitt lymphoma and T-cell lymphoma. "In Burkitt lymphoma, there are around 10,000 patients in the United States, of which 30% have relapsed," highlighted Sanjeev Luther, Rafael's CEO, by way of example. "There is no standard of care for these patients, and the median OS is only 90 days. Our drug has shown great activity; since the unmet need is so large, we managed to attain orphan designation within six weeks rather than the usual six months."

The program will be initiated soon at three sites as a small, single-agent trial. Its success will be measured according to an increase in patient life span by 25%, from 90 days to 120 days. The company's strategy is to bring a new indication to the market every year, and is currently developing another drug, CPI-618, as well as having recently acquired two further molecules within the realm of cancer metabolics.

On par with more effective and even curative treatments, a wider range of options and deeper understanding of the patient are paving the way towards greatly improved outcomes. "The likelihood of success with a known genetic target, a good molecule and the right patient population is very high," noted Barbara Weber, CEO at Tango Therapeutics, which is focused on identifying novel genetic drug targets for specific cancer subtypes. "I do not know of a situation in which a drug failed with this combination in place. In addition, we can get a good sense of the strength of the clinical signal to expect with pre-clinical models that closely match patient tumors. This approach also makes sense financially because by knowing which patients to address with drugs that have a large therapeutic index, we can expect clinical proof-of-concept in our in Phase 1 studies."

Tango is currently pursuing three areas of drug targets: tumor suppressor gene loss and classic synthetic lethal pairings to drug those tumors; context-dependant on-

cogenes; identifying drug targets following the development of in vivo systems to define which tumor suppressor genes are mediating immune evasion, leading to the ability to enhance activity of immune checkpoint inhibitors.

By targeting more specific patient populations and focusing on areas of greatest need rather than greatest volume, companies are finding more success through streamlined development timelines and faster market entry. While the financial reward following market entry may seem less attractive for a smaller patient population without adding a much higher price tag, saving time and cost over the development period means a significantly lower reimbursement burden and much faster returns for the company and its investors.

Enhancing outcomes

In addition to innovation in drug discovery, renewed focus on improving patient outcomes and favorable regulatory pathways have increased the attractiveness of drug redevelopment. Specialty pharmaceutical companies are taking advantage of the FDA's 505(b)(2) mechanism, focusing on aspects such as bioavailability and delivery methods to improve and enhance drugs that have previously entered the market.

As new molecules in development increase in complexity, many suffer from solubility and bioavailability challenges. However, upping the dose is not always possible due to associated side effect profiles and toxicity. "The dose burden in oncology in particular can be extremely high," noted Jim Huang, CEO at Ascendia Pharmaceuticals, a recent graduate from New Jersey's CCIT incubator

> "The abbreviated 505(b)(2) pathway has become much more popular, primarily because it is difficult to identify new drug targets. The 505(b)(2) pathway enables companies to find new indications without starting from scratch with a new molecular entity, but still address unmet medical needs. The existing pharmacology and toxicology information can be used, thus it is easier to get to market with a much lower R&D investment. This is very attractive for many companies. Many generics companies are also venturing into the branded space. Pursuing NCEs will likely be too great a jump for them; they are more likely to pursue abbreviated pathways."
>
> **- Jim Huang, CEO, Ascendia Pharmaceuticals**

and focused on advancing a pipeline of enhanced formulations of existing drug products. "Bioavailability is often very low, meaning a large dose is often required, and some PK variation may also be caused – this can translate into efficacy issues and toxicity issues. If we can boost bioavailability by a multiple of four, we can significantly reduce the dose burden and enhance the PK property."

Ascendia also offers contract services for pre-clinical and clinical stage drug candidates, and is exploring ways to facilitate controlled drug release as well as applications of its technology for oral delivery of large molecules.

Although oral solid dosage remains the prevalent form of delivery in the market, increasing focus on patient centricity is leading companies to consider the most optimal form of drug administration. In paediatric and geriatric patients, for example, there is a growing preference in topical and transdermal delivery, particularly in pain relief. One company pursuing this route is Grace Therapeutics, which is advancing its GTX-101 candidate for Postherpetic Neuralgia – shingles pain – for which the current treatment is the lidocaine patch. "Patients are generally treated by gabapentin and its analogs, a whole collection of antidepressants, plus the patch concurrently," outlined George Kottayil, Grace Therapeutics' co-founder and CEO. "Opioids are frequently used. There is a need for a better delivery system for relieving pain as a result of neuropathic pain."

Highlighting the shortcomings of the lidocaine patch in taking about two weeks to give adequate pain relief, Kottayil continued: "Grace Therapeutics came up with a first-in-class solution – a method dose spray delivery system, in essence a 'thin film in a can'. There are two phases to delivery of this product. The spray particle size is between

10 and 100 microns, so the smaller particles penetrate the skin and go to work right away. Once the spray has settled on the skin's surface, it forms a thin drug-imbedded film and the solvent evaporates. The drug is then delivered continuously over the next 24 hours. This gives both an immediate and sustained effect. Nothing like this has been created or approved before. It is packaged in a 30ml bottle that fits in a pocket or purse and can be self-administered easily. Due to increased concentration of permeation in the skin, there are no side effects, even if more than 20 sprays are applied."

Grace Therapeutics' pipeline is focused on orphan and rare diseases, with other candidates addressing ataxia-telangiectasia, aortic aneurysm, subarachnoid haemorrhage and trigeminal neuralgia. The company expects its first approval in 2018 and to generate revenue in 2019/2020.

Just as companies are driving medical progress through novel molecules, they are also paying increasing attention to the patient's experience with that drug. This translates to a greater focus on delivery of the drug, plus a more targeted approach.

Enabling technologies

As well as a change in attitude towards drug discovery and development approaches, this shift towards higher-value, more targeted medicines is facilitated through the increasing availability and accessibility of a number of technologies. For example, diagnostic methods are being incorporated throughout the drug development process rather than just to determine the best course of treatment for a patient in the hospital or physician setting.

Equally, advances in technology are facilitating more efficient and targeted drug discovery methods. Progress in genomic sequencing and greater affordability of the technology is enabling scientists to sequence ever-greater pools of people more quickly, for example. "Next-generation sequencing is getting less expensive and it is becoming easier to define large pools for barcoding and individually label cells for screening purposes," noted Paul Diehl, chief operating officer and director of business development at Cellecta.

Morten Sogaard, vice president and head of genome sciences and technologies at Pfizer, echoed: "In rare disease especially, genomic sequencing is already enabling the identification of a number of genes that are good potential targets. Through increasingly high-throughput genome-wide association studies, with "regular genotyping" at a lower cost, we are gaining extremely important

> "Immunotherapy was one of the first types of cancer therapy used over 100 years ago. And it is an extension of the cancer vaccines and immune modulators first developed in the 1990s. Drug targeting is part of the "magic bullet" approach which began in the 1970s. Furthermore, newer therapies are typically used in combination with, or sequentially following, existing ones, rather than supplanting them. So, we see a very large market for Tosk's technologies and products far into the future."
>
> **- Brian Frenzel, President and CEO, Tosk, Inc.**

insights. For chronic diseases, exome sequencing and genome sequencing are seeing a significant uptick."

Cellecta develops advanced high-throughput RNAi and CRISPR technologies for the discovery and functional characterization of novel therapeutic targets and drugs. The company's core expertise is in cell biology and molecular biology.

Since the rate of innovation across these technology areas is high, many highly-focused start-ups are coming to the fore with solutions. ReviveMed, for example, is a recent addition to the LabCentral incubator in Cambridge, Massachusetts. The company utilizes technology leveraging metabolomics data to monitor diseases within the human body through analysis of metabolites and proteins. "The majority of precision medicine platforms focus on gene data, DNA and RNA," commented Leila Pirhaji, CEO and founder of ReviveMed. "This is because the data is widely available. By comparison, metabolite data has been severely under-utilized because it is not so widely available and is very hard to measure. It is comparable to the uptake of genome sequencing 20 years ago."

> "We penetrate the virus with the supercritical fluid and then rapidly expand the system through depressurization... We then thought to reverse engineer the technology to make nanoparticles out of phospholipids, of which cells are made. We now had particles that could encapsulate material to improve their delivery. For example, in cancer there are many poorly-soluble products which must be nanoencapsulated to improve their bioavailability. We can do this without damaging proteins or molecules and without residual toxins. We have a much safer, sustainable drug delivery platform.
>
> 
>
> **- Trevor P. Castor, CEO, Aphios Corporation**

By applying machine learning and data integration, Pirhaji has developed a precision-medicine platform that focuses on developing the right therapeutics for the right patients. "AI companies often arrive with a new tool to look at the data differently," highlighted Pirhaji. "What we are bringing to the table, however, is entirely new data that people have not looked at before. Our focus will be on the discovery process and bringing the drug to the clinic."

ReviveMed's current place at LabCentral is funded through a Novartis and LabCentral Golden Ticket Award, which provides funding for one lab bench space for a year. The company is continuing to develop its technology and pursuing nonalcoholic steatohepatitis (NASH) as its first indication.

As technology continues to progress, drug discovery and development processes become more efficient and streamlined, enabling faster patient access. Being able to define patient populations better also enables companies to create more targeted treatments with more streamlined pathways to market, since they are more likely to demonstrate positive results in trials when being administered to patients with the highest likely response rates. ■

Across the valley of death: bringing academic research into the market

Cited by many as the primary contributing factor in the success of a technology- and research-driven industry, academic institutions cannot be overlooked as a vital driving force of the life sciences sector. Moreover, the role of universities in supporting the life sciences industry has evolved. While educating students and preparing them to enter the workforce remains the core focus for any academic institution, an increasing emphasis is being placed on translating research into real-world applications.

Universities across the country are increasingly recognized as important and advantageous partners to industry in driving innovative progress. "Massachusetts did not become the top life sciences hub in the world by chance," stated Robert K. Coughlin, president and CEO at the Massachusetts Biotechnology Council (MassBio). "There would be no biotechnology or life sciences industry in Massachusetts were it not for the world-class academic institutions and academic medical centers. We have the best and brightest scientists in the world working to develop new, breakthrough cures and treatments. Together with a thriving life sciences industry, there is no unmet medical need known to humankind that somebody in this market is not trying to solve."

Equally, California's public university system under the University of California umbrella comprises several schools and more than 238,000 students and 190,000 faculty and staff. Although encouraging pursuits in a range of academic areas, the UC schools are focused on driving innovation in biotechnology. The University of California, San Francisco, is California's top recipient of NIH funding, followed by Stanford University, the University of California, San Diego and the University of California, Los Angeles.

Universities have long welcomed and pursued collaborations with the broader industry – not only are there benefits in terms of funding, but students are able to gain more practical experience and better position themselves for opportunities following their graduation. "Many of our graduate students and post doctorate fellows will go on to start their own companies or be taken up into the companies that they have previously collaborated with," commented Ruben Flores, head of the office of innovation and commercialization at the University of California, San Diego. "We try to prepare our students for the job of the future. The industry is changing very rapidly, and we provide the tools and explore and address different areas, so they may choose their own direction once they have finished their studies. We provide a framework in which students can innovate and fail in a safe environment, encouraging them to try new things without the fear of serious repercussions. Our students are encouraged to look at things with a different lens and consider

> "Innovation often comes through unusual, unorthodox approaches, which may lead to unexpected outcomes. Academic laboratories filled with students ready to explore new ground serve as an 'innovation engine' that provides those new discoveries that can then serve as product development drivers for biotech and big pharma. One of the traditional bottlenecks has been a less than optimal transfer of new discoveries and innovation from academia to industry. As more academic translational entities come online the amount of technology transfer to biotech and pharma should increase."
>
> **- Peter Reinhart, Director and Clinical Professor, Institute for Applied Life Sciences, UMass Amherst**

> Within the life sciences space, we have world-renowned programs in drug discovery, development and delivery. We have a very strong presence in bioanalytical chemistry, which concerns mostly large-molecule protein-based science. Our focus is on real-world problem solving. Rather than developing hammers for the sake of having hammers, we place an emphasis on developing hammers to actually hit a particular nail. This is not the typical academic approach.
>
> **- Ken Henderson, Dean, College of Science, Northeastern University**

existing challenges in a different light."

Northeastern's relationship with industry is particularly proactive, in line with its "Discover, Partner, Innovate" tagline. 97% of its students partake in six-month placements at companies as part of the co-op model. "The university has historically been very integrated with the outside world," says Ken Henderson, dean of the college of sciences, Northeastern. "Our main differentiator is the experiential education we offer, which involves an integrated learning model, combining classroom and professional experience. Northeastern places heavy emphases on the co-op model."

The university then integrates this into students' overall education, ever changing their curriculum based on the needs of the current workforce. Identifying a potential gap in the workforce, the university has also begun to push forward its experiential PhD programs, working with companies to jointly develop research programs. "A new area of focus for us is how to educate continual learners," highlighted Ken Henderson. "As technology rapidly evolves, there is a need for the workforce to be retrained and educated in different ways. We are currently looking at how to fill the educational gaps for leading companies and build lasting relationships. We have actually been working with the state legislature to lobby for inclusion of a talent development component within the new life sciences bill. This concerns how to train those people for the highest-level positions and filling in the missing skills gaps."

A recently-launched experiential program with GSK exemplifies the enterprise-to-enterprise model. The program is specifically aimed at GSK's current employees that want to get a PhD, and the company considers it as a talent development program. GSK is also seeing it as an opportunity to strengthen ties with a strong research institution. Participants are co-mentored between senior researchers at the company and Northeastern faculty, and may conduct all their research on site at the company. This is an innovative model which so far is not widely used in the United States.

Playing a more active role

Recognition of the value of early-stage research carried out at universities has grown. Since they do not function as commercial entities, students and faculty members have more freedom to explore ideas and theories without financial risk and pressure to commercialize.

However, a dichotomy exists in the formula for university partnerships with companies in the surrounding ecosystem: whilst companies would prefer not to take on the risk of acquiring very early-stage research projects, universities also lack the expertise to develop products to their later stages. In the case of therapies, there is a significant

gap between identifying a target or area of interest and actually developing a drug to address it. "It is rare that a company would approach a university and develop an idea from the very early stages of research – most companies and investors view the risk as too high," noted Anne-Marie Maman, executive director of the Princeton entrepreneurship council at Princeton University. "Universities therefore have to bridge the gap between science and a point at which the idea can be successfully licensed to outside entities. Many universities are struggling with this."

More and more universities are building out internal expertise to advise students and faculty members on constructing business models, and some are even establishing internal funds and programs aimed at advancing technologies. New Jersey-based Rutgers University, for example, has built a TechAdvance fund up to about US$3 million. Following an iterative review and critique process, the majority of submissions are ultimately approved for one of two different types of funding: the TechAdvance grant of up to US$100,000, renewable up to two years, or a one-time TechXpress grant of up to US$10,000. "Access to these smaller tranches of funding is critical in the biopharmaceutical world because companies often will not have key data, scale up material for testing, prototype devices and so on, that are needed to file for IP," commented David Kimball, vice president for innovation and research commercialization at Rutgers. "The TechAdvance fund has only been established for eight months, but we have granted almost US$1.2 million to over a dozen projects to date."

Some universities are going a step further in the facilitation of spin-out companies, supporting students and faculty in actualizing their research. "A lot of current UCSC faculty and students are initiating start-ups", commented Andrea Pesce, industry alliances officer at the University of California, Santa Cruz. "The new commercialization services involve financial and business support for start-up programs, both on and off campus. Sandbox, for example, is a wet-lab incubator located off campus."

A need for translational tools for cutting edge science has driven universities to provide formalized structures in which spin-outs can grow and progress. "Universities are recognized as a valuable source of innovative discoveries," commented Ofra Weinberger, director of licensing and associate VP for technology transfer and intellectual property at Columbia Technology Ventures (CTV), the technology venture arm of Columbia University in New York. "Nonetheless, many discoveries with commercial potential from university labs require further validation before qualifying as investable opportunities. CTV has extensive experience founding and supporting technology initiatives to enable promising technologies to accelerate across the "valley of death" and reach a point of value inflection, and ultimately reach the market as quickly and successfully as possible. We have developed a lab-to-market accelerator network to incubate and further advance technologies that have commercial potential by providing access to resources that include education (boot camps), mentorship (product/drug development team), and funding (pilot awards)."

Programs such as the Venture Catalyst's suite of innovation resources at the University of California Davis and undergraduate incubators such as the Basement at University of California San Diego are also aimed at supporting the growth of research and facilitate the actualization of ideas so they may contribute to the rich biotechnology ecosystem in a meaningful and impactful way. Over on the East Coast, Princeton University also recently announced the opening of the Princeton Innovation Center BioLabs.

Universities are increasingly prioritizing getting start-ups to a place where they are better resourced, supported and able to effectively raise a solid first round of institutional venture capital. Through incubators, universities are working to bridge the "valley of death" and ensure that great science does not sit on the shelf collecting dust.

Academic institutions continue to form the backbone of a great deal of innovation in the life sciences industry. The presence of top universities across the life sciences hubs such as California, Massachusetts and New Jersey present an excellent opportunity for collaboration and, as such, will continue to be a key factor in attracting companies, as well as acting as an ever-growing source of new companies. ■

Dushyant Pathak

Associate Vice Chancellor for Technology Management and Corporate Relations & Executive Director of Venture Catalyst
UC DAVIS

One of the 10 campuses of the public and land-grant University of California system, UC Davis is a comprehensive research university.

As a life sciences campus, how broad is the scope of research at UC Davis?

UC Davis is one of only a few truly comprehensive research universities in the nation, with exceptional strengths in the life sciences complimented by nearly all other disciplines. We are unique in our ability to conduct translational research all the way from fundamental biological research to its applications in terms of healthcare delivery and therapeutics. With that full gamut of fundamental life sciences research, we graduate more PhDs in the biological sciences than any other university in the United States each year. We have one of the most rapidly growing biomedical engineering departments, a designated Comprehensive Cancer Center and our school of medicine is expanding and growing in Sacramento.

The majority of inventions disclosed to the university each year are in the life sciences and human biomedical and health spaces. Start-ups launched out of the university follow a similar profile.

How does UC Davis leverage synergies in its expertise across different disciplines?

One of our strengths is taking an approach that harnesses the One Health concept and synergizes it with engineering technologies to take a holistic approach to human health. Since the One Health concept encompasses inputs into human health, we are well positioned in our emphasis on agriculture, the environment, animal health, food safety and security. All of these aspects are in fact critically important for health, wellness and prevention of disease. Addressing the ever-rising cost of healthcare will not stem from drugs and devices, which paradoxically increase the cost of healthcare. It is the health, wellness and prevention aspects that can be expected to have an impact on reducing ever-rising healthcare costs.

Bringing this together with our strengths across areas such as diagnostics, devices, pharmaceuticals and biotherapeutics, we really have the ability to deal not just with prevention, but also health interventions. With our strong computer science and engineering focus, we also get into digital health and other technology-enabled products that will become critically important as we are more successful with extending the lifespan of the population.

What are the primary sources of funding for UC Davis?

Funding received over each of the last five years is between US$700 million and US$800 million and comes from a combination of industry collaborations, foundation support and government grants. Approximately US$60 million of that came from industry-sponsored research last fiscal-year. A recent NSF report ranks UC Davis in the top 20 public universities for industry-sponsored research and engagement.

How does the Office of Research endeavor to support translational research at UC Davis?

The Technology Management & Corporate Relations division of the UC Davis Office of Research stewards and protects university intellectual property through its InnovationAccess unit, facilitates cross-disciplinary and transformative research collaborations with industry through its Office of Corporate Relations and supports the formation and growth of research and technology enabled startups in the region through Venture Catalyst's suite of innovator resources.

While tracking the number of patents filed and number of inventions disclosed is not necessarily the most meaningful measure of excellence in translational outcomes, one of the things that we have been tracking is how many licenses have been executed, normalized against the amount of research funding brought in to the university. On this measure, we have consistently been significantly above the UC system average.

What are the primary areas of focus for UC Davis' Venture Catalyst going forward?

Through its Venture Catalyst program UC Davis has so far been focusing on the large end of the funnel – early support for university technologies and the start-ups they foundationally enable. We look at how to get these startups to a place where they are better resourced, supported and able to effectively raise a solid first round of institutional venture capital. We have been effective in connecting some of our start-ups to our network of investors, and we are now looking to fill the gap between the support we have been providing and the more robust Series A and B round investments that lies further downstream. One way in which we can do this is by raising our own university-affiliated and regionally focused seed-stage venture fund. We believe that now that the fundamentals are solid, we are in a strong position to extend our platform further towards the market. ■

David Kimball

Vice President for Innovation and Research Commercialization
RUTGERS UNIVERSITY

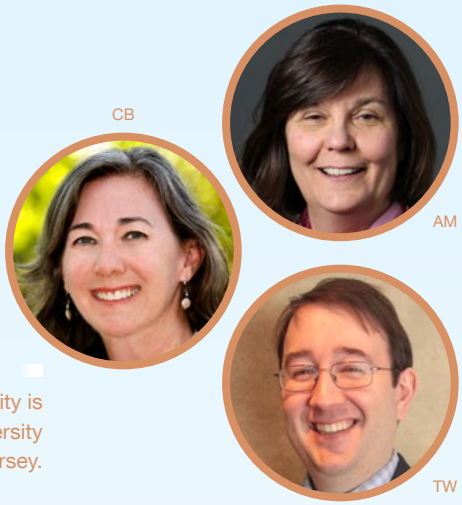
Rutgers, the State University of New Jersey, was established in 1766.

How critical are the life sciences within the university's portfolio of research?
Rutgers merged with the University of Medicine and Dentistry of New Jersey in 2013, and it is the only large academic institution with a medical center and school in the state. Rutgers medical school has two locations: New Jersey Medical School is in Newark and the Robert Wood Johnson campus is located in New Brunswick. Life sciences, which had already been a large component of Rutgers' research activity before the merger with the medical schools, has become an even greater area of focus at Rutgers. As an example, Rutgers University Cell and DNA Repository (RUCDR Infinite Biologics) is the world's largest university-based cell and DNA repository. Additionally, a number of spin outs have come out of Rutgers University and the medical schools. In 2017 alone, six new start-ups were created at Rutgers, and we currently have 75 active start-ups formed around Rutgers technologies.
A number of inventions have come out of Rutgers University through collaboration between basic scientists and the scientist clinicians at the medical school. One recent high profile invention is a BioMarin drug that was approved last April called Brineura. This is an enzyme replacement therapy for CLN2 Batten disease, a progressive, deadly genetic disease that affects children. It is quite rare, with some 500 to 1000 cases in the United States, but replacement of the genetically nonfunctional enzyme with Brineura solves the problem. Although it is not a cure in the sense that patients must continue receiving injections of Brineura to replace the faulty protein, it does allow these children to grow and thrive, whereas before they would suffer a debilitating downward course. Since the IP belongs to Rutgers, this creates a useful revenue stream back to the university. We have used these revenues for strategic initiatives such as our TechAdvance fund.

Could you elaborate on the support offered through Rutgers' Tech Advance Fund?
We have been able to build our TechAdvance fund up to about US$3 million. The TechAdvance application starts with a notice of invention from the faculty; it is required that a submission has been made to our office that there is an invention at hand. Three outside experts independently review and critique the submission; we then distill down the critiques and send them back to the faculty member. It is an iterative process, and we may go back and forth between submitters and reviewers a few times, in order to fine tune the proposal. This enables us to get submissions to a point where the majority of them –thus far – have been ultimately approved.
The Tech Advance Fund operates on a rolling basis. There are two different types of funding: the TechAdvance grant of up to US$100,000, renewable up to two years, and also a much smaller one-time grant of up to US$10,000 which we call a TechXpress grant. Access to these smaller tranches of funding is critical in the biopharmaceutical world because companies often will not have key data, scale up material for testing, prototype devices, etc. that are needed to file for IP. The TechAdvance fund has only been established for eight months, but we have granted almost US$1.2 million to over a dozen projects to date.

What are the primary areas for continued development and focus?
We are building out a Corporate Engagement Center, which will report to both the Office of Research Commercialization and to the Rutgers University Foundation. This will create synergies between ORC and the Rutgers Foundation in our joint approach to industry. Our mission at ORC is to find creative ways to engage business and to assist the faculty at enabling the highest quality research with appropriate patenting, marketing and licensing.
Another example of a new direction ORC is moving in is the microbiome. Rutgers has a long-term commitment to build world-class faculty and facilities to study the microbiome. An illustration of this is our commitment to build a sterile gnotobiotic facility in Newark, where highly controlled microbiome studies can be performed. This is a research area that has been exploding in the quantity and quality of research, and in potential therapeutic and commercial applications. Our office can make a real difference by doing the market research and trying to understand the market need and commercial opportunity of microbiome technologies and discoveries. ■

Coleen Burrus, Anne-Marie Maman & Tony Williams



CB: Corporate Engagement & Foundation Relations
AMM: Executive Director
Princeton Entrepreneurship Council
TW: New Ventures Associate
PRINCETON UNIVERSITY

Founded in 1746, Princeton University is a private Ivy League research university in Princeton, New Jersey.

How integrated is Princeton with the surrounding New Jersey life sciences ecosystem?

CB: We remain strongly focused on life sciences; even more so now that we have a dedicated person working closely with our faculty in Molecular Biology and the surrounding life sciences community in New Jersey. Princeton University recently took stock of New Jersey's ecosystem to identify potential gaps. Since most of the incubators are near capacity, we recently opened the Princeton Innovation Center BioLabs, plus the New Jersey governor just announced that a large incubator will be opening in New Brunswick. We have also initiated a Biomedical Data Science Day, which brought in 40 representatives from 25 local companies to hear research presentations from our faculty working in this space.

AM: We all find ourselves collaborating frequently with other academic centers and ecosystem partners in central New Jersey. The Princeton Innovation Center BioLabs is a wet lab/dry lab co-working space, which differs somewhat from other BioLabs spaces, since we support chemistry, material science and engineering research as well as biology. Since the incubator is available to our faculty, the focus is broader than just life sciences. It is also not limited just to Princeton University start-ups. We have just accepted two more companies, giving us a total of eight.

Is there a lot of scope for cross-fertilization between different research areas at Princeton?

CB: We are seeing a great deal of cross-over from the technology side in particular – we have a strong interest in computational biology and bioengineering, for example, and have an ongoing collaboration between Intel and the Princeton Neuroscience Institute. Tools for data analysis and data collection, coming out from areas such as computer science and electrical engineering, are now being repurposed and focused on solving life sciences problems.

How does New Jersey's innovation ecosystem compare to that of other hubs?

TW: Boston, for example, has an extremely vibrant ecosystem of investors, entrepreneurs and scientists – it is the melting pot for life sciences activity. New Jersey is not quite there yet, but this is the ambition. The Princeton Innovation Center BioLabs is a step towards creating a critical mass of exciting, young companies that in turn will attract entrepreneurs.

CB: Another notable project, to which the New Jersey Economic Development Authority has contributed US$1.5 million, is the New Jersey Research Asset Database. Information on faculty members involved in STEM fields at five universities in New Jersey – Rutgers, Princeton, Rowan, NJIT and Stevens Institute of Technology – is added to this database so that the industry can easily find researchers to connect with. We see it as a very valuable tool, not just for industry but also for university researchers to identify fellow researchers at other institutions and establish partnerships.

AM: The New Jersey Big Data Alliance (NJBDA) is another exciting initiative, which coordinates all the big universities in New Jersey to advance computing innovation and education.

In 2017, 5% to 6% of Princeton's research funding came from industry. How much emphasis is placed on the commercial aspect of these relationships?

TW: Fundamentally, we are an educational establishment. When the university is given a choice between achieving a commercial goal versus pursuing cutting-edge science, the research will always come first. This will never change at Princeton. Even when a research sponsor comes on board, there is an emphasis on following an academically-appropriate path to generate interesting results rather than handing over full intellectual property rights.

Could you explain the growing tendency of universities to bring research further along the development pipeline themselves?

TW: It is rare that a company would approach a university and develop an idea from the very early stages of research – most companies and investors view the risk as too high. Universities therefore have to bridge the gap between science and a point at which the idea can be successfully licensed to outside entities.

What are the next focus areas for further development of Princeton's life sciences research?

CB: The goal is to broaden and deepen our relationships with key companies in New Jersey and really expand our activity with them. We are, however, a global university, and maintain our interest in partnering with companies around the world. Our primary role is to drive research, not just through partnerships, but also through making the right introductions and facilitating conversations. ■

Krystyn Van Vliet

Professor
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

How does MIT leverage its strong industry connections to bring its research into the market?

Research in the biopharmaceutical industry is expensive, and MIT competes for the available funding like everyone else. Where we try and differentiate ourselves is by creating opportunities for private investment. One way in which we do this is by housing spin-offs in incubators. LabCentral, for example, is adjacent to MIT's campus and provides lab facilities to small companies to support their growth. Another example is The Engine, a special incubator accelerator focused on tough technologies – for example, a new manufacturing technology that would require five to ten years of investment and capital. MIT's participation in these protected environments helps us to adapt to limited available funding, in order to bridge the valley of death from idea to market.

What are MIT's further objectives when it comes to industry cross-collaboration?

At MIT, we focus on discoveries that will help create a better world. Strategic industry partnerships are instrumental in realizing those goals to create positive real-world impact. We will continue to forge partnerships from early-stage research to commercialization with companies located in Cambridge and those headquartered elsewhere. Spinning our work off into smaller companies can derisk the technology, and we will remain commited to converting research into real-world applications and solutions. ■

Sadhana Chitale

Director,
Life Sciences Technology Transfer,
Technology Ventures and Partnerships
NEW YORK UNIVERSITY

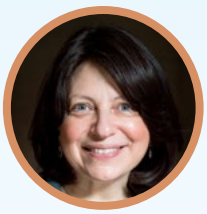
Many companies view very early-stage research as too high risk for investment. In what ways does NYU support its faculty and students in advancing and de-risking technology?

We run various internal proof of concept funding programs such as the Applied Research Support Fund (ARSF) at NYU Langone Health Campus and Technology Acceleration and Commercialization (TAC) award programs at our Washington Square Campus. Our Therapeutic Alliance program offers a virtual incubator program which assists in conducting validations of early stage observations and helps engage with investors and biotech and pharma partners. Based on input from an advisory board consisting of experienced professionals, some of these programs are then advanced further along in partnership with specialised CROs to further conduct drug screening and other pre-clinical work to further de-risk the technology.

What are the next objectives for the office in supporting the actualization of research and assisting students and faculty in getting their research into the market?

For the past ten years, NYU has been consistently ranked number one in terms of licensing revenues. This is a tough record to keep up with and we want to continue with our efforts in partnering, in making sure early stage technologies move further along the value chain and in our educational outreach with regards to technology commercialization. ■

Ofra Weinberger



Director of Licencing and Associate VP for Technology Transfer and Intellectual Property
COLUMBIA TECHNOLOGY VENTURES

How is the role of universities evolving in the life sciences innovation ecosystem?

The trend of technologies being successfully licensed speaks volumes about the changes that we are undergoing as an industry. Columbia Technology Ventures (CTV) enters into approximately 100 exclusive license agreements per year. In the past, we were spinning out four or five start-ups per year around technologies developed in the university's laboratories. However the number has now increased to between 20 - 27 start-ups per year. CTV has been involved with launching well over 200 companies based on Columbia's intellectual property, many of which have ended up receiving professional VC funding, getting acquired, or holding an IPO.

CTV has a particular focus on start-up companies. We use a standardized licensing approach for all Columbia university startups, very low upfront fees, fixed equity percentages, low or no early-year milestones, and deferred past patent expenses. This approach has been very well received by both entrepreneurs and the venture community, and has contributed to an increase from about5 IP-backed startups per year in 2008 to 20 to 27 startups per year recently. With the increasing complexity of technology comes a requirement for more complex collaborations to generate solutions. We have seen a dramatic increase in interdisciplinary collaborations at Columbia, for example between engineers, clinicians, chemists, biologists, and data scientists, which is reflective of recent trends in both academia and industry. ■

Patient selection: the right drug for the right patient

Healthcare cost reduction is an on-going conversation and challenge within the life sciences industry. While a great deal of attention has been focused on lowering drug prices, relatively little has been placed on reducing avoidable treatments through a better understanding of treatment pathways and more effective diagnosis. According to PhRMA, better use of medicines could eliminate US$213 billion in U.S. health care costs annually, amounting to 8% of the nation's health care costs. Furthermore, the Health Industry Distributors Association estimates that lab tests represent only 2% of healthcare spending while influencing 70% of medical decisions.

Beyond the cost benefit, more effective diagnostic tools also tie in to an increasing emphasis on patient-centricity. Nowhere is this more pertinent than in the infectious disease space. "The current paradigm centers on the hypothesis-based testing of the clinician," commented Mickey Keresz, founder and CEO at Karius, a diagnostics company that has developed a test enabling clinicians to rapidly diagnose infectious diseases by detecting the DNA of over 1,250 pathogens from a standard blood draw. "This is a long and tedious investigation process, which results in empirical treatment with broad-spectrum antimicrobials, a lot of lost time and money, and confusion and suffering. The introduction of genomics into infectious disease diagnostics allows us to capture all microbes within a single test. The way this is done is by looking at the genetic material that these microbes shed into the bloodstream as they infect the patient. Every bacteria, fungus and virus has a genetic code, and that genetic material is shed into the bloodstream as it replicates, which is what we pick up. With sequencing, digitizing and applying machine learning and analytics, we can produce a report that tells the clinician what that patient was infected with."

Treating patients with drugs empirically leads to a lot of unnecessary care and, in the case of antibacterial drugs, can also lead to resistance. "In the absence of strong diagnostic information, clinicians will use sophisticated formulas and start on one drug and then move on to the next if it has not taken effect in a 12 hour period," highlighted John McDonough, CEO at T2 Biosystems, a diagnostics company focused on sepsis. "80% of the time, this guesswork has led to the right drug by the time blood culture results comes back which is often days later. Well over 50% of the patients treated will not have needed the drug and the use of drugs when not needed can lead to drug resistance and a costly overuse of medication. The drug resistance can mean that if that patient needs the drug in the future, it might not work for them."

In other disease areas, current diagnosis options can be extremely invasive and often unnecessary, highlighting a need for alternative options. In cancer, for example, surgical pathology has always served as the gold standard for diagnosis. "In the United States alone, over half-a-million people undergo a work up on a nodule to determine if they have thyroid cancer," noted Bonnie H. Anderson, CEO and chairman of the Board at Veracyte, a genomic diagnostics company

> We determined that there was a high rate of inconclusive results from current diagnostic methods, leading to patients undergoing extensive testing and often surgery, because surgical pathology has always served as the gold standard for diagnostic truth. Because of this, many patients who do not have the disease in question would have been able to avoid the risk and cost of an unnecessary procedure if a better test existed.
>
> **- Bonnie H. Anderson, CEO and Chairman of the Board, Veracyte**

based in San Francisco. "Roughly 100,000 patients every year do not get a diagnosis from the first test when that nodule is worked up using methods we have available today. This ambiguous point is where we developed our first genomic test, Afirma, to fit into the clinical pathway of care. All of our classifiers have been built using machine learning, which we started using 10 years ago. This has allowed us to create highly accurate, very informative tests. So, when the clinical pathway hits a point of ambiguity, our tests inform the physician on what to do next, helping many patients. To date, we've performed over 100,000 Afirma tests and estimate we've helped more than 40,000 patients avoid unnecessary surgery and removed over US$800 million in surgery costs from the healthcare system. Because we are collecting genomic information, we can also often inform on those cancers that do need to go to surgery and help physicians decide the extent of surgery. We are transforming the way diseases are diagnosed."

Veracyte has two further products: Percepta, a lung cancer test, and Envisia, a first-of-its-kind test in interstitial pulmonary fibrosis diagnosis. Veracyte's Percepta test is based on a signature of genomic changes that occur in the airway when a patient has or is at risk for the development of lung cancer or other diseases, rather than being based on a signature of the tissue from the actual nodule. Referring to this area as the "field of injury", Anderson explained: "With lung cancer, everything that is breathed in exposes the airway to toxins and carcinogens that disrupt the genomic pathway. That, combined with the patient's immune status, could determine whether the patient gets lung cancer or whether they are able to fight it off. There has also been published evidence suggesting that field of injury can be used to predict COPD or other lung conditions. With Percepta, we have been able to measure the level of change in the airway and develop a signature that highly correlates with cancer."

Percepta enables diagnosis through the use of a brushing of the main lung airway, rather than an invasive procedure. "Also, early detection of disease generally implies that the patient already has the cancer," continued Anderson. "There is a very exciting movement now around the idea of intercepting patients before they actually develop the disease. Cancer is a big element of that. When considering what technologies could be used to get early detection of a patient at risk of lung cancer, the field of injury seems to be the perfect tool. We therefore have early work underway and collaborations with Boston University to examine if we can use a nasal swab test to detect early changes and predict a patient's risk of developing cancer, even before they get it."

Pending a coverage decision for Envisia, Veracyte hopes to have all three tests commercialized and covered by Medicare by the end of 2018.

Maximizing success in clinical trials

In conjunction with rising drug development costs, regulatory burdens have also increased, resulting in more complex clinical trials. According to PhRMA, after an average development process of 10 to 15 years, only 12% of investigative medicines entering clinical trials are ultimately approved by the FDA.

As well as determining optimal treatment pathways for patients, diagnostic companies are supporting more targeted patient selection for clinical trials. Alongside the clear benefit of finding the right drug for the right patient, finding the right patient for the trial – in other words, the patients likely to have the highest response rates – could vastly improve the trial success rates, leading to a higher number of approvals.

By better defining addressable patient populations and more precisely predicting likely individual responses, companies are able to reduce a great deal of risk in their clinical trials. ■

> Diagnostics companies can greatly benefit drug development because more effective diagnostics identify sick patients more quickly who can benefit from a drug. This helps patients and also drug companies running clinical trials, as it can accelerate the time it takes to run the clinical trial.
>
> **- John McDonough, CEO, T2 Biosystems**

Paul Harkin
Kevin Ellison

PH

KE

PH: President
KE: Business Development Manager
ALMAC DIAGNOSTICS

Almac Diagnostics is a stratified medicine company specializing in biomarker-driven clinical trials, leading to CDx approval and commercialization.

What have been the primary focus areas for Almac Diagnostics' U.S. activity?

KE: Almac Group consists of multiple business units providing services to the pharmaceutical industry; every segment works together to accelerate and improve the drug development process. Almac Diagnostics comes in on the front-end of that equation, offering more of the biomarker, assay development and validation and delivery service so that we can work with pharma to run diagnostic tests to identify patients that they can enroll in their trials. We also fit in at the end of the process. Should any of these biomarkers further develop into companion diagnostics, Almac Diagnostics would be able to work with that pharma partner to submit the companion diagnostic for regulatory approval and ultimately play a part in the commercialization of the test.

PH: A year and a half ago, about 70% of our business was in the United States, with the remainder in Europe. However, it is probably closer to 50:50 now. For some time, U.S. companies took a more aggressive approach to precision medicine, and there were a higher number of oncology-focused businesses in the United States. This activity seems to be much more balanced now. We are also seeing a greater focus on precision medicine in other therapeutic areas, which is also reflected in our client makeup, particularly in inflammation and neurodegenerative diseases. Our partner lab in China also enables us to run clinical trials in China since taking patient samples out of the country is often not an option.

In which therapeutic areas does Almac Diagnostics specialize?

KE: We are really agnostic in terms of disease area. We focus primarily in oncology but our diagnostic experience also spans CNS, infective diseases and immunology.

What are the primary applications of Almac's DNA Damage Response Deficiency (DDRD) assay?

PH: The DDRD assay is a proprietary Almac assay originally developed for use in early stage breast cancer but is currently being validated in other disease areas such as ovarian, esophageal and colorectal cancers. It is a gene expression assay that detects DNA damage response deficient tumors associated with loss of the FA/BRCA pathway. The assay was initially intended to be a predictor of responses to any agent that damages DNA. As an extension, we presumed it would also predict response to agents like PARP inhibitors. With that intention in mind, we have done quite a few validation studies over the years.

However, an even more interesting utility that has emerged is as a predictor to immune checkpoint inhibitors. We now have our first clinical data proving that the assay does predict response to these agents. Moving forward with this assay, we want to take it down an FDA approval pathway and have decided to take it forward on a large gene expression panel, the Illumina TruSeq RNA Exome panel. When we engage with our pharma partners, we see a real reluctance to part with their clinical samples, particularly if they believe they will only get one assay result back. In a manner analogous to the DNA panels, by making this assay available on a full transcriptome panel like RNA Exome, not only can we give the results for our assay back, but we can give the results for any gene expression assay back off that panel. This de-risks the use of those samples, presenting a more attractive proposition to the pharmaceutical company.

Could you give an update on the Illumina Trusight Tumor 170 cancer mutation panel?

KE: This is an oncology-focused panel developed by Illumina, which demonstrates a move towards panel-based testing where multiple biomarkers can be tested on one panel. It allows a much more detailed treatment plan to be formed by the oncologist for their patient.

What are the objectives for Almac Diagnostics going forward?

PH: So far, most of our growth has been organic. We will continue to grow our business to support biomarker development in clinical trials. A lot of the assets in development are coming closer to commercialization and in some cases we will be expected to support the product launch – over the next couple of years we will build out those capabilities to support our partners. We will also be building out our capabilities to manufacture and distribute in the diagnostics space as some of our ongoing studies move closer to commercialization. ■

Mickey Kertesz

Founder & CEO
KARIUS

The Karius test harnesses next-generation sequencing to detect fragments of cell-free DNA from bacteria, viruses, fungi and protozoa that may be circulating in a patient's bloodstream.

How did Karius first come into being?
Through research at Stanford in 2014 looking at cell-free DNA, we realized that there was a faint but informative signal coming from microbes. Digging deeper into that signal, we realized it could be applied to infectious disease diagnostics.

What are the differentiators of Karius' platform from others available?
The Karius test gives physicians a single blood test that can deliver a potentially life-saving diagnosis, often more quickly than traditional testing methods such as blood culture, when time is critical. With cell-free DNA, there are three main benefits: everything, everywhere, in real-time. Firstly, cfDNA allows us to see nearly every class of microbes with a single test. Secondly, an infection can also be picked up anywhere in the body, meaning that the patient may not need to undergo an invasive biopsy. Lastly, cfDNA closely tracks the level of infection in real-time – if a patient has an infection and it clears, the cell-free DNA signal disappears.
Compared to other diagnostic companies, our main differentiator is that we are a comprehensive test, and most others are narrow panels or tests for single pathogens. While blood cultures are fairly broad and can grow a variety of microbes, they are prone to becoming sterile once the patient is put on antibiotics. Once this happens, the patient is even harder to diagnose, but our test can still detect the pathogen DNA for some time after treatment is intiated. The genomics approach therefore carries many advantages to all alternative options.

How rapid has the uptake been for the test?
After proving the test's clinical utility, we launched our early access program last year. This enabled a set of high-profile institutions such as Rady Children's Hospital to use the test and provide feedback to us. This year, we are launching the test nationwide. The uptake has been exciting, especially in immunocompromised patients, pediatrics and sepsis.

Could you elaborate on the advantages of the test in immunocompromised patients, pediatrics and sepsis?
Immunocompromised patients include every oncology patient that has gone through chemotherapy. These patients are susceptible to a wide range of infections, making our broad approach especially helpful. We have seen a lot of success here in identifying pathogens that in some instances were not even on the radar of the clinician. There have been some jaw-dropping results, honing in on the specific infections these cancer patients have and allowing clinicians in some cases to narrow the incredibly strong, toxic, broad-spectrum antifungals to a single targeted anti-fungal, for example.
In pediatrics, time is often crucial. There is also inadequate blood volume to test many things in parallel. The ability to diagnose from a single blood draw is therefore extremely powerful in pediatrics. And for sepsis, we ran a study last year enrolling 350 patients that presented with sepsis. We followed their diagnostic odyssey and found that using all available traditional diagnostic tools, only 40% of patients were diagnosed after 8 days. On day 2, only 18% were diagnosed. Results for many standard tests are relatively slow. Running the samples through the Karius system, we were able to identify 60% of the infections on day 2.

What work is being conducted internally to further develop the technology?
Internally, we have extensive R&D to create the next version of the technology. We also work with the pharmaceutical industry to empower them in their clinical studies. One benefit to the pharmaceutical vertical involves facilitating enrollment in clinical trials. Enrollment of the wrong patients is one of the most potentially damaging aspects in a clinical trial. Equally, it is important to know that they do not have any other background infection that could cause them to fail on the therapy. We recently announced one partnership with Nohla Therapeutics, which has a cell-therapy for oncology patients to reduce the rate of infection after chemotherapy. They are using our test for a range of measurements within that study.

What are the next steps for the company in terms of new developments?
The first priority for 2018 is to touch as many patients as possible, first in the United States and then beyond. As we do that, it is important that we keep listening to our customers and implement their feedback. However, taking a novel approach to the market requires us to be not only reactive but also proactive. A blend of these two factors is what carves out the road map for the future. Looking a little bit further, I am confident that in five or six years, genomics will be the standard way to diagnose infectious diseases. It makes little sense to wait for microbes to grow in a culture when the DNA signal is there in the blood at the time of the draw. It makes just as little sense to require an invasive biopsy from the patient in the case of a deep-seated infection when the signal is available in the blood. Our team is proud and humbled to be leading this paradigm shift. ■

Advancing oncology: a more individualized approach to cancer

As the poster child of precision medicine, mainly due to the large number of intervention points, oncology research has seen an increasingly narrowed focus in conjunction with the recognition that all cancers are different. "As we develop a greater understanding of the science behind cancer, acceptance increases that not all cancers are the same," stated Richard Peters, president and CEO at Merrimack Pharmaceuticals, a Massachusetts biotechnology company targeting biomarker-defined cancers through 10 wholly-owned programs. "While the primary concern previously centered around the anatomical definition of cancer and this remains important, understanding the molecular signature of the cancer has also increased in importance. The source of the cancer in terms of the organ does not really matter; what really matters is what is making it grow."

Immuno-oncology has been a particular area of focus in recent years, with the industry experiencing an unprecedented pace of clinical studies in cancer immunotherapy. The 2017 approval for Merck's KEYTRUDA is a significant milestone – KEYTRUDA (pembrolizumab) is the first PD1 inhibitor in combination to show overall survival in nonsquamous non-small cell lung cancer (NSCLC).

As with any new therapy, cost will initially be a challenge until the technology develops. The manufacturing process for CAR-T therapies, for example, is very complicated. A CAR-T must also be built not only for every individual patient, but also for every target within that single patient. "Just like with antibacterial resistance, the cancer can become resistant to CAR-Ts as they lose their surface target, which the CAR-T is made to recognize during the suppression process," emphasized David Martin, chairman at Xyphos. "Every CAR-T therapy that is now approved or in the pipeline is a single-target agent. So, a child with leukaemia on a CAR-19 therapy is very unlikely to have a durable complete response. Less than half will be durable for more than five years. What happens is that they lose the target and another CAR has to be built."

Xyphos is addressing challenges in CAR-T therapy, such as lack of control of activation and perseverance of CAR-T's in the patient, plus single-target issues. "[S]ince these are 'living' therapies, there is essentially no control over them once the patient has been injected," said James Knighton, Xyphos' CEO. "Addressing lack of control of activation and perseverance of those CAR-T's in the patient and single target issues, there are some second-generation therapies coming along the pipeline that have different engineering mechanisms that will be able to kill them or even tune them down. However, this does not ensure survival over a long period of time. In cases of a refractory recurrence relapse with the same target, that cell still needs to be around. This is not controlled at the moment."

Xyphos' CAR-T cell, referred to as a convertibleCAR, can be converted to different targets, activated, killed, and its perseverance can be controlled. While the technology is still in the R&D phase, the idea is to present a single CAR-T that has been properly engineered so it does not induce an attack on the host and will not be rejected as the immune system recovers. The central belief is that there will be one off-the-shelf

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There are certain advantages to approaching oncology treatment with a smaller molecule. Our goal is to eventually get cancer patients out of the infusion chair. It can be very difficult for patients to make the time to come in every two weeks to receive infusions of the antibody. Our alternative would be to carry a bottle of pills to take throughout the day. That is one of the biggest advantages we see for oral drugs. Another difference is how the two molecules linger in the human body. Antibodies will usually stay in the system for a longer period of time, so side effects that are usually the case with typical infusion must be suffered for several days before the drug leaves the system. Small molecules leave the body in about a day, meaning that unwanted side effects should dissipate much faster than the typical antibody.

- Ali Fattaey,
CEO,
Curis

"

CAR-T that will suffice for all patients and all targets.

An emphasis on getting these new treatments to market has also translated into more favorable pathways. "Because of the much higher efficacy and in some cases curative effect of I-O treatments, we have seen development timelines shrink from the typical eight to 10 years to as little as four years or less," highlighted Garo Armen, CEO at Agenus, a clinical-stage biotechnology company focused on progressing its pipeline of checkpoint antibodies, vaccines, and adjuvants, utilizing a number of technology platforms in an integrated approach.

Whilst faster market entry seems very much conducive to medical progress, companies may be challenged to realize ROI targets as efficiently as before due to higher levels of competition within a shorter timeframe. "As development timelines decrease, we will see obsolescence rates go up significantly," continued Armen. "Whereas in the past companies have had a 10 to 20-year market monopoly, with the potential for many more new market entrants in a shorter time frame, that era has now come to an end… True innovation is rare. We are seeing the same trends in biotechnology that were previously seen in technology. When technology became popular, the market became very crowded because it presented a significant opportunity and therefore attracted a lot of capital. However, only a few companies persisted and prospered long term. The same is starting to happen in biotechnology and particularly in immuno-oncology. Financing is always available. The question is not whether there is enough financing available, but rather is the capital being allocated properly."

Agenus holds an extensive portfolio of checkpoint antibodies, cancer vaccines and cancer microenvironment modifiers. Among the checkpoint antibodies, anti-CTLA-4 and anti-PD-1 antibodies are the key building blocks of the company's combination strategy; it is in multiple clinical trials with combinations. Two additional antibodies – GITR and OX40 – are in clinical trials, in partnership with Incyte.

Despite exciting advances in immuno-oncology, it has become apparent that the treatable patient population size is perhaps smaller

than at first projected. "In line with the discovery of the role that the cancer cell plays in protecting itself, the discovery of checkpoint inhibitors is perhaps most significant," emphasized Adelene Perkins, president and CEO at Infinity Pharmaceuticals, an immuno-oncology company developing IPI-549, an oral, once-daily product candidate that selectively inhibits PI3K-gamma. "These inhibitors have shown some stunning results, with almost curative effects. The question then became why we were seeing these profound effects in such a small proportion of patients and why, even in the tumor types in which they work, such as melanoma and head and neck cancer, only between 20% to 40% of patients benefit. Those patients then also often ultimately relapse."

Following research to understand the limitations of checkpoint inhibitors, Infinity discovered the importance of macrophages in supporting the tumor, either playing a pro-tumor or an anti-tumor function. "These macrophages can be specifically reprogrammed, so instead of supporting the tumor they fight it," continued Perkins. "This is mediated by a target. Our team developed a specific inhibitor that can enable the reprogramming of the macrophages from this M-2 function, which is pro-tumor to an anti-tumor M-1 function. Our extensive pre-clinical work showed how reprogramming these macrophages will enable them to fight the tumor and overcome resistance to checkpoint inhibitors. Right now, we are replicating that pre-clinical work in the clinic to show the ability to overcome resistance to checkpoint blockades."

Cancer continues to hold the greatest proportion of the life sciences industry's attention. New therapies coming through pipelines place greater emphasis on improving quality of life as a measure of positive outcome as well as ultimate survival. ■

"The ongoing concept of a molecular definition of cancers will continue. Once we start to understand the genetic underpinnings of these various cancers and how they behave differently, we will better understand how they respond to different treatments. Just because they have the same tissue of origin, does not mean two cancers are the same. The ability to better define these cancers will improve treatment options."

- Christiana Bardon, Portfolio Manager, Burrage Capital and Managing Director, Oncology Impact Fund, MPM Capital

Mitchell H. Finer, PhD

Co-founder and CEO
ONCORUS

Oncorus is a biotechnology company developing a portfolio of next-generation immunotherapy products leveraging its proprietary oncolytic Herpes viruses platform.

What was the motivation behind starting the company at this point in time?
Oncorus was founded in late 2015 following the FDA approval of Amgen's oncolytic herpes viral therapy, IMLYGIC® (talimogene laherparepvec), which was armed with GM-CSF. This established a clear regulatory path for the development of oncolytic virus immunotherapy. I had joined MPM Capital around the same time and oncolytic viruses had already been on the firm's radar; we all thought we could improve both virus and payload.
Due to the instability of the genome of cancer cells, a number of mutant proteins are generated. When the virus enters the tumor cell and kills it, those proteins are released. Viruses also create danger signals when they infect cells – an immune response is created if there is DNA in the cell cytoplasm or double-stranded RNA present. The infected cells produce cytokines, but this is not enough to elicit a long lasting immune response to the tumor antigen. Amgen armed the virus with the GM-CSF cDNA so the virus could both kill tumor cells and boost the recruitment of antigen-presenting cells to stimulate an immune response. IMLYGIC was approved in the United States in fall 2015, and we began raising funding only a few months later with JP Morgan.

How does Oncorus' approach differ from Amgen's and others in the market?
We wanted to improve potency whilst also ensuring safety. To make these viruses safe, viral genes must be deleted. However, any time genes are deleted, the virus is crippled. We have a different way of making this virus safe. We retained a gene (Gamma 34.5), which enables the virus to replicate very efficiently but we engineer the virus so that when it gets into cells it senses the cellular environment - whether the cell is a normal cell or a malignant cell. There are small non-coding RNAs called microRNAs that are expressed by many normal differentiated cells. MicroRNAs control genes that impact cell division – they shut them off and promote differentiation. That is the antithesis of a tumor. It is well known that these cellular microRNAs are gone in tumor cells. In essence, we trained the virus. When it enters a normal cell, it can determine if there are microRNAs characteristic of normal cells. If there are, then the virus aborts replication. If entering a tumor cell, which lacks microRNAs, the virus would be free to replicate. What makes Oncorus unique is also our capacity to add arming genes that engineer the virus to be powerful and bring together many cell types of the immune system, which is far beyond the ability of any of the other oncolytic viruses. This strategy is expected to strongly enhance anti-tumor immune response.

From this approach and from Oncorus' OV platform, there are now three preclinical programs. Could you talk us through these?
We have two different products that are injected directly into tumors – ONCR-1 for injection into brain tumors such as glioblastoma and ONCR-2 for other solid tumors. Both for ONCR-1 and ONCR-2 product candidate, we have a unique payload combination to promote antitumor immunity and reduce immune suppression.
Our third program is a very innovative platform for systemic and repeat delivery, which follows the idea of injecting the virus intravenously rather than intra-tumorally. One challenge is that we have immunity to certain viruses. We are working on stealthing approaches to prevent immune detection before the virus reaches the tumor target. This is an early-stage program, but it is showing promise.

How do you expect the company to progress in the coming years?
Oncorus' next milestone is getting into the clinic, which will happen in 2019. We anticipate filing our second IND toward the end of 2019 and will hopefully demonstrate therapeutic benefit for cancer patients in 2020. ■

Ali Fattaey

CEO
CURIS

Curis is an oncology-focused drug development company.

How has Curis developed since it went public in 2000?

Our current pipeline programs are the result of efforts that extend over the last five years, the period in which our current strategy of carrying out development with an eye to commercializing drugs ourselves has been in place. Prior to this, Curis' strategy was to develop technology internally and then out-license programs to other firms for commercialization.

Two of our drug candidates are in the clinic now and we just recently brought a third drug into the clinic. Our programs fall into two categories: immuno-oncology drug candidates and precision medicine candidates, primarily in hematologic malignancies.

Could you elaborate on Curis' relationship with Aurigene and Genentech?

Our Genentech relationship was formed in 2003 and illustrates the older Curis model. This included an out-licensing of all development and commercial rights for the partnered drug and involved Curis retaining royalties. We continue to receive royalties from that particular drug.

The Aurigene collaboration is a "Curis 2.0" relationship, where we in-licensed the drug candidates and their commercial rights globally, with the exception of rights in Russia and India, which Aurigene retained. We control development and we have taken charge of commercialization. Aurigene then receives royalties. Our strategy to gain rights for drugs to control development and commercial rights led to us pursuing a partner with the front-end of discovery up to Phase 1. Aurigene was a good fit for us as a partner because its history is in chemistry and non-clinical work, and they were without clinical ambitions. Aurigene would therefore fund development up to Phase 1, and Curis would then cover further development and costs. The model was innovative in terms of covering each other's responsibilities and sharing those risks. We also provided Aurigene with some of Curis' equity instead of exchanging dollars, so Aurigene became fully aligned with Curis' interest. It is one of the first relationships formed in that way.

Looking at the CUDC-907, which is in Phase 2, could you just speak to the specific unmet need that this is addressing?

CUDC-907 fits in with Curis' focus in precision medicine in hematologic malignancies. All of these malignancies are driven by particular genetic alterations. Some genetic alterations are observed across multiple diseases. We look at these diseases to see if they are genetically altered in specific genes and then address that particular target. CUDC-907 specifically addresses B-cell malignancies, or lymphomas particularly, that have MYC alterations. Our Phase 2 trail tested the hypothesis, based on what we had seen in early clinical development, that CUDC-907 could provide clinical benefit for B-cells with lymphomas with MYC alterations. We have shown that treatment can result in durable complete responses in MYC-altered B-cell lymphoma, and this is a clinical result we are going to take to the FDA.

What are the differentiators of CA-170, for which Aurigene is a collaborator?

CA-170 falls in the group of checkpoint inhibitors, meaning it influences inhibitory immune checkpoints in order to allow immune activation against the tumor itself. The key differentiator between CA-170 and the several immune checkpoint drugs that are currently approved is that CA-170 is the first small molecule, orally-available drug to address the same area as these antibody immune checkpoint drugs.

There are certain advantages to approaching oncology treatment with a smaller molecule. Our goal is to eventually get cancer patients out of the infusion chair. It can be very difficult for patients to make the time to come in every two weeks to receive infusions of the antibody. Our alternative would be to carry a bottle of pills to take throughout the day. That is one of the biggest advantages we see for oral drugs. Another difference is how the two molecules linger in the human body. Small molecules leave the body in about a day, meaning that unwanted side effects should dissipate much faster than the typical antibody.

What are the near-term and longer-term objectives for the company going forward?

We expect to file the NDA for CUDC-907 with regulators in late 2019. With that in mind, we would begin to build our organization around addressing the feedback we receive from the FDA. One of the most important things for us is to understand what our launch will look like, in terms of who the prescribers are and ensuring our product, marketing plan and packaging are all set up. This all starts now. We are also continuing to consider whether Curis will put together its own sales force. ■

Brian Frenzel

President and CEO
TOSK, INC.

Tosk, Inc. is a small molecule, oncology drug discovery and development company.

Could you briefly introduce Tosk and the company's pipeline?

Tosk has four cancer drugs in development. Three selectively block the adverse effects of widely-used cancer therapies, and the fourth targets the kRAS oncogene. We call this approach Proven Solutions Improved℠ and our products Companion™ drugs, since they are administered alongside existing, widely-used cancer treatments to improve outcomes for patients.

What are Tosk's most advanced products?

Our most advanced product is TK-90, which is in "proof-of-concept" clinical studies for mucositis side effect reduction. A second drug candidate, TK-39, selectively blocks cardiotoxicity, a life-threatening and permanent side effect of the anthracyclines, such as doxorubicin and Doxil®, and other cancer drugs. We expect TK-39 to enter clinical studies in 2019. The side effects we address not only impact the quality of patients' lives but can be dose-limiting. Furthermore, side effects can be costly to treat, debilitating, and even life-threatening.

How does Tosk discover Companion™ drugs?

Tosk has two discovery platforms, both using Drosophila melanogaster, the common fruit fly. Tosk believes that screening in a living animal is more effective than the cell-based, biochemical, and molecular modeling methods typically used by others.

We have used our "side effect fly" model to discover drugs that selectively block toxic side effects found in cancer therapies. Drugs currently available typically treat side effect symptoms, not their underlying causes. Tosk's Companion™ drugs are intended to reduce or eliminate the need for these palliative relief therapies. Since our goal is to reduce drug toxicity, it is also important that our Companion™ drugs do not have any significant side effects of their own.

Tosk has also developed a "genetically modified fly" technology to discover drugs that block the effects of cancer genes. This involves implanting human cancer genes into flies, then screening for compounds that block their activity. We harness this technology to address targets for which traditional drug discovery methods have failed, and that are often referred to as "undruggable", such as mutant kRAS.

We have recently received a US$2 million grant from the US National Cancer Institute to fund our kRAS discovery program. The initial goal is to make certain cancer drugs effective in patients who currently do not benefit from treatment. These include Erbitux® and other EGFR-inhibiting drugs, which are currently not effective in 40% of patients. Such a kRAS drug would also have the potential to be a direct cancer monotherapy in patients with mutated kRAS tumors, such as in many pancreatic, colon, and lung cancers.

Will demand for Tosk's products be affected by new products for cancer currently in development?

The market for effective cancer therapies in industrialized countries is growing due to aging populations. And, since our drugs are low-cost, small molecules, they will be affordable in less wealthy countries as well.

Our approach is very much in line with the pattern of incremental improvement in outcomes for cancer patients that historically has come from better use of existing therapies and combining them with new therapies. The press has been full of articles recently on "breakthroughs" in cancer, such as precision medicine, immunotherapies, and drug targeting. We applaud these efforts, but observers should keep in mind that these initiatives are really part of a long history of continuous, incremental improvements in cancer care.

Drug targeting is part of the "magic bullet" approach which began in the 1970's. Furthermore, newer therapies are typically used in combination with, or sequentially following, existing ones, rather than supplanting them. So, we see a very large market for Tosk's technologies and products far into the future.

What are the next steps for Tosk's four products in the pipeline?

We expect to establish clinical proof of concept for TK-90 for mucositis side effect reduction this year in a study of 60 head and neck cancer patients. TK-39 for cardiotoxicity side effect reduction is in the last stage of preclinical development, and we plan to initiate clinical studies for it next year. We have two other drugs in the pipeline, one for nephrotoxicity side effect reduction and, as previously discussed, one to block the effects of the kRAS oncogene, both of which are undergoing lead selection and optimization. We are very optimistic about the future benefits that each of these programs can deliver to cancer patients worldwide. ■

Infectious Diseases: Addressing growing resistance

According to Clarivate Analytics, infection was the third-highest area of investment in 2017, at US$14.3 billion versus US$80.7 billion into cancer and US$15 billion into immune therapies. As in other disease areas, the infectious disease space is one of high unmet need. Furthermore, this particular market segment carries an additional challenge: drug resistance. "Two factors drive resistance: overutilization and long links of usage for prolonged periods of time," noted Ankit Mahadevia, CEO at Spero Therapeutics, a Cambridge-based biotech focused on treatments for multi-drug resistant (MDR) bacterial infections. "While all drugs will eventually build a resistance, choosing the appropriate populations and using them in the right way helps to delay the onset of resistance."

The importance of developing antibiotics to stay ahead of the bacteria has been manifested through some recent steps to support the progress of research in this area. CARB-X, part of Boston University, was awarded US$250 million in 2016 following a call under the U.S. presidential CARB process for a biopharmaceutical accelerator to support companies in collecting clinical data and attracting outside funding. The organization then recruited the Welcome Trust and NIAID, a NIH division, as part of the process – these each contributed US$155 million and US$50 million respectively. "Groups of academics have been researching antimicrobial resistance for decades, but there have been problems on the business side, including the failure of the normal tools of intellectual property and capital formation to solve the need for new antibiotics," commented Kevin Outterson, CARB-X's executive director. "As soon as an antibiotic leaves the lab, resistance starts to develop. Furthermore, the more we use the antibiotic, whether in livestock or humans, the further the effectiveness degrades. So, it is a maintenance problem. All other drugs may be viewed as an innovation issue, but in the case of antibiotics, a long-term infrastructure and maintenance stance is required."

CARB-X has 24 companies in its portfolio representing eight new classes, with five or six more in addition from companies that are not yet publicly-announced.

Backed by CARB-X, Spero Therapeutics is addressing several unmet needs in this space. Its SPR994 candidate, the most advanced product in the company's portfolio and currently in Phase 1 trials, is poised to potentially be the first oral carbapenem approved in the United States and European Union. Commenting on resistance to oral Gram-negative antibiotics used to prevent hospitalization and/or help transition the patient home after hospitalization, Mahadevia commented: "Drugs that once filled this void are now seeing resistance at anywhere from 10% to 15% in the community setting and 30% to 35% in the hospital setting. It is a scary proposition to expose these patients to a hospital setting or prolonged hospital visits where even worse bugs exist. This is a multi-billion dollar market and offers a real opportunity to advance in a space that hasn't seen a new oral Gram-negative agent in more than two decades."

Spero's second group of portfolio products, its Potentiator Platform including SPR741 and SPR206, addresses the growing, deadly group of Gram-negative bacteria in the hospital setting needing an IV therapy. Through progressing its pipeline, Spero expects to transition from a Phase 1 company to a Phase 3 company in the next 12 months.

Since current treatment pathways center on the hypothesis-based testing of the clinician, leading to empirical treatment with broad-spectrum antimicrobials and a lot of lost time and money plus potential resistance, it is clear that better diagnostic methods are also required. There has been an extreme rise in the number of rapid diagnostic tests, which have seen increasing adoption in the hospital setting. This also paves the way for the uptake of more targeted treatments into the marketplace. "Knowledge of the precise pathogen that is infecting the patient will result in physicians being confronted with a choice of whether to give the patient a broad-spectrum antibiotic or a more targeted therapy," commented Vu Truong, founder and CEO at Aridis, a San Jose- based biopharmaceutical company focused on infectious diseases. "The physician will most likely choose the targeted therapy. Hence, we believe that the industry will shift from conventional, empirical broad spectrum therapies to evidence-based, diagnostic-driven targeted anti-infectives."

One of the main hurdles in adequately addressing the challenges in infectious diseases has been the reimbursement model. For in-patients in the United States, antibiotics fall under a hospital's Diagnosis-Related Group (DRG) bill, a bundle payment within Medicare, which also includes the bed, operating room, nursing and other consumables. Hospitals are therefore incentivized to economize on these costs. In the outpatient market, a primary challenge is that consumers have come to view antibiotics as inexpensive. "One statistic illustrates the comparison between oncology and antibacterials perfectly," highlighted David Martin, chairman at Xyphos. "CAR-T treatment will cost about US$300,000 to US$500,000 per course of treatment – this would be impossible for antibacterials, although both will save lives. In fact, until a few years ago, antibiotics had a higher efficacy and durable

response rate than any of the anti-cancer drugs. However, as a society, we have become so used to getting a life-saving drug for pennies. The high price tag for anti-cancer drugs is causing some discussion, but we see much less attention on topics like raising the price of an antibiotic."

With origins in Avid Biotics, which has now been divided into two companies – Xyphos and Pylum – Xyphos is focused on CAR-T cell therapy, whilst Pylum remains focused on bacterial diseases. Speaking of challenges in finding major investors, James Knighton, now Xyphos' CEO and co-founder, added: "There are companies in this space with Phase 3 products with a market cap of US$150 million to US$200 million. It would be difficult to find a company in the CAR-T space with a Phase 3 product with a market cap of less than US$5 billion."

While the United States is widely considered a high-value market, finding reimbursement in overseas markets can be even more challenging. Commenting on the reliance of many countries on those with a higher-value market to pay for the development cost, Nima Farzan, CEO at PaxVax, commented: "For example, in Hepatitis A, there are two existing vaccines but there are constant supply shortages. When there are shortages, companies tend to focus their supply on the U.S. market, where prices are higher, meaning more pronounced shortages in lower-cost countries. As some countries in Europe set vaccine pricing or prevent even inflation based price increases, we see vaccine pricing that can be aligned with some developing markets. This can be sustainable when higher pricing is an option in the U.S. but can make it very economically challenging to develop a vaccine like Hepatitis A for just the EU market. When patients pay US$10 per dose in a country like Spain, R&D costs can be recouped if this is offset by a patient paying US$100 per dose in the United States, if all doses are being sold for only US$10, the price does not help support the development cost."

PaxVax is a leading independent vaccine company developing and commercializing specialty vaccines that protect against existing and emerging infectious diseases. The company has two commercialized vaccines – Vivotif, a typhoid vaccine acquired from Johnson & Johnson in 2014, and Vaxchora, a cholera vaccine approved by the U.S. FDA in 2016. PaxVax also has three novel candidates – for chikungunya, Zika and HIV – and two redevelopment programs in the pipeline – for adenovirus, funded by the U.S. military, and Hepatitis A, previously marketed by Johnson & Johnson in Europe under the name Epaxal.

Referencing the challenges regarding reimbursement, Farzan continued: "There are a few ways to address such challenges. On the "push" side, there is the possibility for various organizations to fund development. On the "pull" side, we have possibilities, such as forward-purchase agreements or award mechanisms. For a while, Priority Review Vouchers (PRVs) were a very successful mechanism. However, what has happened is that the programs have been expanded, there are many more vouchers out there, and they are selling for a lot less, barely offsetting the development costs. With a success probability of one in five, the reward has to be relatively substantial."

Other proposals include a substantial market entry award to companies bringing novel antibiotics to market, easing pressure on companies to sell in huge volumes.

As an area of extremely high unmet need that is only growing over time, attention on infectious diseases remains high. However, the area is lacking in financial incentives compare to other disease areas and therefore risks a dearth of new drugs – given the length of drug development timelines, this is a challenge that must be addressed to anticipate new products entering the market in about a decade's time. For candidates in current development, institutional investment options alone may not be enough to drive companies' pipelines to commercialization, particularly as the opportunity is not considered to be as highly opportunistic as other therapeutic areas due to lower payouts. Given the length of drug development timelines, bringing these drugs to market in a timely manner will in large part pivot on support from organizations such as CARB-X and other programs. ■

> **"The vaccine industry has consolidated into a handful of large pharma players pursuing bigger opportunities, which are typically routine vaccines. We decided to focus on overlooked disease areas – while market opportunity might be smaller, there is also less competition and more unmet need as well as a commercialization pathway that is more amendable to small companies."**
>
> **- Nima Farzan, CEO, PaxVax**

Current Challenges in the World of Infectious Diseases

David K. Hong, MD
Karius Medical Director

Dr. Hong joined Karius after 14 years at Stanford University, where he was Clinical Assistant Professor of Pediatric Infectious Diseases. He also served as chief of pediatric infectious diseases at the Stanford-affiliated Santa Clara Valley Medical Center. His prior studies in respiratory virus infections in children focused on host–pathogen interactions and novel adjuvants for respiratory virus vaccines. Dr. Hong obtained his MD from Northwestern University Medical School and trained in Pediatrics and Pediatric Infectious Diseases at the Stanford University School of Medicine. He is board certified in both pediatrics and pediatric infectious diseases.

One of our greatest challenges is the continuing global impact of infectious diseases. Infections cause roughly 20% of all human deaths each year.

Pandemics and epidemics have changed the course of history and society, from ancient plagues to HIV/AIDS to cutting-edge biological warfare. The enormous impact of infectious diseases on our world cannot be overstated — and should not be underestimated.

Approximately 1,400 known species of human pathogens exist to wreak this staggering havoc on us, but to put it into perspective, these pathogens account for less than 1% of the total microbial species sharing this planet.

PATHOGEN CHALLENGES

Here are a few of the current global trends that make our relationship with infectious diseases so challenging:

Climate change and vector-borne disease
Warmer weather brings more mosquitoes, and mosquitoes spread pathogens like Zika and Dengue from infected hosts to healthy bystanders. Also, the greater diversity of plants and animals that flourish in a region, the richer variety of pathogens is present there.

Antimicrobial resistance
Bacteria can rapidly evolve and adapt in response to changes in their environment, especially when external influences like antibiotics are overused or inappropriately used. The World Health Organization recently released a priority list of 20 antibiotic-resistant "superbug" pathogens with a plea for scientists to research new treatments for these global threats.

Too much data
Overwhelming amounts of data can accumulate for each patient from multiple sources: biomedical, genomic, clinical, and laboratory/diagnostic. It can be hard to filter the signal from the noise and get a clear picture of the real problem.

Increasing numbers of immuno-compromised patients
More patients than ever before are receiving bone marrow transplants, solid organ transplants, chemotherapy, and immuno-suppressive treatments. Caring for these patients can be difficult because the list of potential infections is much longer when immune systems are weakened. Existing tests are not always designed to look for less common pathogens.

Emerging threats
Some of the high-impact infectious diseases facing the world today include Zika, Ebola, West Nile, Influenza, food-borne illness, and global pandemics like HIV, TB, and Malaria. There are also ongoing threats from neglected tropical diseases and parasites, healthcare-associated infections, and invasive fungal infections, not to mention the continued discovery of new and emerging pathogens.

DIAGNOSTIC OPPORTUNITY

With challenge comes opportunity. Despite high mortality from infectious diseases, rapidly evolving pathogens, and a dwindling arsenal of treatments that seems to grow less effective with each passing year, human ingenuity has succeeded in developing new, better diagnostic tests and targeted care protocols.

It was only in the late 1800's that scientists realized microbes could cause specific diseases. Growing bacteria in culture or staining them under a microscope were once the gold standard for diagnosis, and are still commonly used today.

While these methods are still important, newer technologies like PCR and high-throughput genome sequencing enable faster, highly accurate identification. Multiple pathogens can be detected in a single patient, new microbes and genetic variants of known microbes may be discovered, and bioinformatics techniques like phylogenetic comparisons and genome assembly analysis allow for deeper understanding of pathogens to inform potential treatment options.

Next-generation sequencing of DNA fragments circulating in human blood (called cell-free DNA) is another scientific methodology that has been used successfully in other medical fields like prenatal diagnostics, transplant rejection monitoring, and non-invasive diagnosis of cancer. Karius is using specialized and proprietary cell-free DNA sequencing technology for pathogen detection, with the goal of transforming how infectious diseases are diagnosed and monitored. The promise of such genomic technology is that it may promote survival in diseases like cancer or significantly alter the course of a global outbreak.

So how do we tackle the grand challenge of infectious disease diagnosis? We believe the answer is all in the details. Just like an infectious disease specialist would run multiple diagnostic tests while also inquiring in depth about a patient's symptoms, job, diet, travel, chemical or environmental exposures, and social habits – the more we accurately know, the more we can specifically help. And the faster we find out, the sooner we can have an impact.

Let's face this opportunity to save human lives together and embrace the precision medicine approach to infectious disease. ■

REFERENCES
1. Fauci, A. & Morens, D. The Perpetual Challenge of Infectious Diseases. New England Journal of Medicine (2012) 366: 454-461.
2. Tacconelli et. al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. The Lancet Infectious Diseases (2017). http://dx.doi.org/10.1016/S1473-3099(17)30753-3
3. Editorial. Microbiology by numbers. Nature Reviews Microbiology (2011) 9: 628.
4. Fournier et. al. Clinical detection and characterization of bacterial pathogens in the genomics era. Genome Medicine (2014) 6: 114.
5. Caliendo et. al. Better Tests, Better Care: Improved Diagnostics for Infectious Diseases. Clinical Infectious Diseases (2013) 57: S139–S170.

Kevin Outterson

Executive Director
CARB-X

The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) was created to help address the threat of antibiotic resistance.

How did this public-private partnership come into being?

CARB-X, part of Boston University, is a non-profit product development partnership, entirely funded by charitable or taxpayer dollars from the U.S. government via the Biomedical Advanced Research and Development Authority and the Welcome Trust, an English charity. In the first year, we had 18 publicly-announced contracts, and today we have 24, with a further 16 that have been approved. By the end of our second year we should have 40 contracts signed. We have US$455 million to spend over the five years. Our objective is to identify innovation in the anti-bacterial space, focusing on the highest-priority threat bacteria in the top two tiers of the CDC and WHO lists.

What are some of the specific challenges of the in-patient and out-patient markets, particularly regarding reimbursement?

The biggest problem with in-patients in the United States is the cost to reimburse inside the Diagnosis-Related Group (DRG), a bundle payment within Medicare that U.S. private patients pay hospitals, although this has changed a little bit with the new care in the last two years, with accountable care organizations or value-based payment structures for payers. Historically, however, when a patient comes in for a procedure, the hospital is billed with a DRG, which includes everything from the bed and the operating room to the nursing, the consumables and the drugs, which includes the antibiotics. Other elements, such as physician services and any services following the patient's discharge is billed separately. This gives the hospital's finance department and formulaic committee an incentive to economize on all of these costs. However, this is challenging with an antibiotic like Avycaz, which is the most expensive antibiotic in history, despite being dirt cheap by oncology standards, because it is paid for within the DRG. The majority if not all of the successful oncology orphan drugs are paid for outside of the DRG – they are Medicare Part B drugs, not Part A. That distinction makes a world of difference. Companies have proposed legislation for the past five years to move antibiotics from reimbursement inside the DRG under Part A to an out-patient basis under Part B, as with oncology drugs.

The primary challenge in the out-patient market is that antibiotics are treated as inexpensive, throwaway products. They are not being treated as the most valuable drug class in human history. This is an exhaustive global resource, but comparable to selling solar power or wind power if fossil fuels are incredibly cheap. We are burning through the last stocks of generic antibiotics, which is suppressing the ability of companies to get a proper return on investment for new products brought to market.

What, in your opinion, would be a better way for the system to handle these kinds of problems?

Within the Drive-AB process in Europe, we have proposed several incentives, two on the "pull" side and two on the push side. On the "pull" side, we have proposed a substantial market entry award, which would include a billion-dollar payment to a drug company for bringing a novel, powerful antibiotic to market. This eases the pressure on the company to sell in huge volumes for reimbursement. The link between price and volume to ensure reimbursement makes a world of sense in every other drug category. Because of resistance, it makes less sense in antibiotics. The entirety of the Drive-AB team and all involved in this policy agree with this notion, which is really quite radical.

What are the next steps for CARB-X in driving the industry?

We are pre-clinical, so will continue to pick up projects to lead and support up until the end of their Phase I trials. Our goal is for companies to have a sufficient data package so they are ready to go out to investors and raise money for their Phase II. We are therefore, by definition, a decade away from a solution. We are continuing to stoke the pipeline. It has been 55 years since we have had a discovery of a new class of antibiotics against gram negative bacteria, the most dangerous type of bacteria, that has resulted in an approval. Out of our 24 companies, we have eight new classes represented. Of those companies that are not yet publicly-announced, we have another five or six new classes. If any one of those makes it through, this will be the most important innovative development in the space of gram negative antibacterials in 55 years. That is our target. ■

Vu Truong

Founder & CEO
ARIDIS

Aridis is a biopharmaceutical company focused on infectious diseases.

Could you briefly introduce Aridis and the factors surrounding the company's establishment?

Aridis is a privately held company focused on discovery and product development of targeted immunotherapy for infectious diseases. We also have a technology platform to discover potent monoclonal antibodies (mAbs) generated by some patients. We see a number of drivers for the development of anti-infective drugs and predict a movement to narrow spectrum, targeted anti-infectives from the traditional broad-spectrum antibiotic, which is the current standard of care in medical practice today. There are several drivers for this paradigm shift, including a substantial need for new anti-infectives to combat the global antimicrobial resistance problem and the increased desire to minimize perturbation of the human microbiome that is a hallmark of broad spectrum antibiotic treatments.

Another driver for the movement to targeted anti-infectives is the proliferation of rapid diagnostic tests, which can provide up-to-the-hour information on what is infecting a patient, and are increasingly being adopted as part of standard medical practice. Knowledge of the precise pathogen that is infecting the patient will results in physicians being confronted with a choice of whether to give the patient a broad-spectrum antibiotic or a more targeted therapy. The physician will most likely choose the targeted therapy. Hence, we believe that the industry will shift from conventional, empirical broad spectrum therapies to evidence-based, diagnostic-driven targeted anti-infectives. Our monoclonal antibodies are a good fit for that trend. It is our belief that in future we will see more of a precision medicine approach applied to infectious diseases.

In what ways is Aridis' pipeline differentiated from the current standard of care?

One differentiator of our drugs from the current standard of care is mechanism of action. Our mechanism is immune-based – the drugs use components of the patient's immune system to fight infection. The immune system can be hugely and surprisingly effective – not only can we discover rare B cells that make great antibodies to protect the patient, but we can also further engineer that B cell to make antibodies that have properties that are even more effective than they would naturally be. Since the antibodies have a different mechanism of action from existing drugs, when bound to the bacteria they are able to tackle any antibiotic-resistant strains that have occurred from overuse.

The use of diagnostic tests to pinpoint exactly which pathogens are infecting the patient also minimizes overuse of antibiotics. Using the evidence-based approach is key.

As new technologies come into play, how will the role of diagnostics develop with regard to drug discovery and development?

Several different disciplines are emerging that will really start to impact drug development in infectious diseases. The advancement of rapid drug diagnostic tests is one example. On the front-end in terms of target discovery, we are now starting to leverage the massive databases that have been built on all pathogens. Machine learning and data analysis are enabling us to intelligently probe in the sequencing space and figure out where the commonalities are among pathogens. This gives us the ability to use large data to try and look for new targets.

How does Aridis' proprietary platform overcome existing challenges?

Our technology platform allows us to screen the entire B cell repertoire massively in parallel and convert the selected B-cell that is highest in potency into an immortalized cell factory that produces large quantities of mAbs. Once a patient is infected with a pathogen, it takes a few weeks for the immune system to really learn the different features of that pathogen and start to make antibodies to neutralize it. By the time the immune system is in a fairly mature state, it could potentially be making millions of unique B cells – screening all of these is like looking for a needle in a haystack. However, we are able to screen these B cells in parallel at a massive scale. Within about a week, we can identify which one of those B cells has the highest pathogen neutralizing activity or the highest potential. When we find out which B cell produces that unique protective antibody, we can immortalize that B cell right away and turn it into a factory to make antibodies.

What the timeline for Aridis' pipeline?

Several of Aridis' current clinical candidates should be first-to-market based on the current trajectory of clinical development progress. Our global pivotal trial has been launched in about 15 countries around the world and our next project will be launching later in 2018 in around 23 countries. ■

Ankit Mahadevia & Cristina Larkin

AM: CEO
CL: Chief Commercial Officer
SPERO THERAPEUTICS

AM

CL

How has Spero Therapeutics' pipeline developed according to market needs?
There are currently three main areas of greatest unmet need in infection. The first unmet need is the resistance to oral Gram-negative antibiotics that we use to prevent hospitalization and/or help transition the patient home after hospitalization. Drugs that once filled this void are now seeing resistance at anywhere from 10% to 15% in the community setting and 30% to 35% in the hospital setting. It is a scary proposition to expose these patients to a hospital setting or prolonged hospital visits where even worse bugs exist. SPR994, which is the most advanced product in our portfolio, addresses this unmet need and could be the first oral carbapenem approved in the United States and European Union.
The second unmet need is the growing and deadly group of Gram-negative bacteria in the hospital setting where an IV therapy is needed. The market lacks a pipeline to address these highly resistant bugs – our second group of portfolio products, which we call the Potentiator Platform (SPR741 & SPR206), are positioned to fill this void within the hospital setting. The last unmet need is the somewhat overlooked rare infectious disease space. This includes conditions such as Non-tuberculous Mycobacterium (NTM) – an orphan disease with fewer than 100,000 people in the United States affected.

What is the timeline like in terms of bringing these products to market?
SPR994, our lead asset, is currently in a Phase 1 trial. The active pharmaceutical ingredient of SPR994 has been approved in Japan for the last eight years; it is currently approved in pediatric patients for respiratory tract infections and ear infections. We expect to report the Phase 1 results in mid-2018. The FDA has also enable a pathway whereby we may bypass Phase 2 and conduct a single Phase 3 in complicated urinary tract infections following a pre-Phase 3 meeting for approval in the U.S., and we hope to obtain similar guidance from EU authorities. An important point to highlight is that Spero is positioned to transition from a Phase 1 company to a Phase 3 company in the next 12 months. ■

Michael Bigham & Evan Loh

MB: CEO and Chairman of the Board
EL: President, Chief Operating Officer and Chief Medical Officer
PARATEK PHARMACEUTICALS

MB

EL

Could you give us a brief introduction to Paratek Pharmaceuticals?
MB: The company was founded in 1996 in Boston by Dr. Walter Gilbert, a Nobel prize winner in chemistry, and Dr. Stuart Levy from Tufts University. The company was formed to address the challenge of growing bacterial resistance against established antibiotics, a reality further aggravated by the rapid decline of investment in new antibiotics within the broader pharmaceutical industry at that time.
EL: They decided to mainly focus on tetracycline, which had a proven safety profile but was declining in efficacy as the resistance of the bacteria steadily grew. They created a class of modern tetracyclines that preserved the modern safety profile but re-established their efficacy against stronger bacteria strains. A second compound was also developed, for which we have retained worldwide rights – it is a broad-spectrum modern tetracycline which is available in IV form and a once-daily oral form. That in itself is a very significant achievement. Paratek advanced that drug and, over the past two years, we completed three Phase 3 studies, one in pneumonia and two in skin. All three of those trials proved to be successful with really significant efficacy. We are in the process of getting FDA approval of that drug, which is called Omadacycline.

What is Paratek's product launch strategy and plan for the pipeline?
EL: We are undertaking a tremendous amount of work to get ready for the launch within the first quarter of 2019.

What is the longer-term vision for Paratek?
MB: We are making a significant investment in our commercialization infrastructure. Over the course of time, our goal is to add other drugs to our pipeline to leverage our expertise in the antibiotics space as well as to leverage our commercial and clinical development infrastructure. We are currently developing omadacycline to treat urinary tract infections ("UTI"). ■

Improving function: growing focus on neurodegenerative disease

Research in neurodegenerative disease has seen an uptick, although recent setbacks may have unsettled current players. In Alzheimer's disease specifically, there have been three significant candidate failures and, in January 2018, Pfizer exited the disease area entirely along with Parkinson's. Despite challenges, the Alzheimer's market remains one of the highest unmet need areas in medicine today as the sixth leading cause of death in the United States and, nonetheless, the only cause in the top 10 without prevention or treatment.

In line with the growing needs of an aging population, increasing quality of life into old age has become more of a focal point within the life sciences industry. "150 years ago, the average life span in the United States was 40 years old," commented Karoly Nikolich, founder & CEO at Alkahest, which is focused on deriving therapies from blood and its components to improve vitality and function into old age. "There has never before been evolutionary pressure on longevity. Longevity is a new biological phenomenon and therefore has not yet been properly adapted to. There is an associated growth industry surrounding exercising, diet, mineral and vitamin intake and antioxidants. The anti-aging industry today is somewhere around US$150 billion per year, which is quite sizable."

The market has been dry since Namenda's entry in 2004, and there is still some way to go before candidates currently under development might reach commercialization. Alzheimer's drugs in late-stage studies include anti-amyloid antibodies such as Eli Lilly's solanezumab and Biogen/Eisai's aducanumba, and beta secretase inhibitors such as Johnson & Johnson's JNJ-54861911, Novartis/Amgen's AMG-520, Merck's verubecestat and AstraZeneca/Eli Lilly's lanabecestat.

Waltham, MA-based Aphios Corporation is pursuing a differentiated approach to companies such as Eli Lilly and Merck. "There are really three enzymes that effect memory: alpha secretase, beta secretase and gamma secretase," commented Trevor Castor, Aphios' CEO. "These enzymes act on amyloid precursor proteins and form amyloid, which is a neurotoxin that prevents the formation of short-term memories. Inhibiting the beta secretase and gamma secretase enzymes has driven the majority of research thus far. We have gone after alpha secretase, which forms a soluble APP rather than an insoluble amyloid when it acts on amyloid precursor proteins. It works in the opposite mechanism, so our APH compounds up-regulate the alpha secretase to clear out the plaque. We will now have to conduct a Phase 1 and Phase 2 study, which should both be completed in the near future."

Current healthcare dynamics necessitate a continued focus on neurodegenerative diseases. Since this is such a high area of unmet need, companies are likely to benefit from fewer hurdles in approval pathways where clear clinical benefit is shown. ■

> **We are seeing increasing numbers of companies formed and funded in disease areas like Parkinson's and Alzheimer's. One of the key drivers is the Baby Boomer generation, which has a lot of disposable income. The baby boomers control about 60% of available investment capital. Many have seen their parents go through old age and its associated challenges. Every other person above the age of 85 will develop Alzheimer's disease – the statistics are terrible.**
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> **- Karoly Nikolich, Founder & CEO, Alkahest**

Paul Bolno

President and CEO
WAVE LIFE SCIENCES

Wave Life Sciences is utilizing its proprietary synthetic chemistry drug development platform to design, develop and commercialize stereopure nucleic acid therapeutics that precisely target the underlying cause of rare genetic diseases.

Could you give us a brief introduction to Wave Life Sciences?

Wave is a biotechnology company with an innovative synthetic chemistry drug development platform that we are using to rationally design, develop and, hopefully, commercialize a pipeline of oligonucleotides for genetically defined diseases. Oligonucleotides, are comprised of a sequence of nucleotides that are linked together by a backbone of chemical bonds. We realized that the modification of oligonucleotides on the phosphate backbone to form a phosphorothioate makes a "left hand" and a "right hand." Instead of following trends towards mixtures of drugs with a different pharmacology and different toxicology profiles, we decided to focus on single-molecule biology. At our core, we believe that rationally designed oligonucleotides are the key to potentially delivering safer, more effective medicines.

What are the specifics of Wave's proprietary approach?

One aspect is proprietary manufacturing – considering oligonucleotides as molecular bricks. We have built the intellectual property around how those bricks are put together. We look at where they should be placed and locked in, ultimately assembling different modifications to make individually rationally-designed drugs. The other proprietary focus for Wave is around the principles of where to put that "left hand" and "right hand." For the first time, just like our peers in small molecules, we can apply the principles of rational drug design to genetic methods.

Our approach through rational drug design is to develop a single molecule medicine that can actually distinguish between the healthy and the mutant protein. Being able to target a single transcript is very unique. It is genetic medicine without viruses – we do not use a virus to deliver the therapy.

Could you expand on Wave's current pipeline?

While we are building a core focus on the central nervous system and neuromuscular diseases, the platform we have developed is applicable to any therapeutic space. We have the dilemma that we really could go after any genetic target, so we have had to focus.

Our two Huntington's programs initiated their Phase 1b/2a studies in July 2017 and those are ongoing. We will have the data from that study in 2019. We expect to have the data from the DMD exon 51 program, which began in November 2017, in Q3 of 2018. We are also continuing to advance the portfolio for ALS and frontotemporal dementia. The goal is to continue to deliver new programs, build out more therapeutic areas and continue to demonstrate that we can interrogate different tissues and cell types with this class of drugs.

What has been the key catalyst for Massachusetts' success as a biotechnology hub?

What is really unique to Massachusetts is the density of activity. The diversity of that density is also a particular advantage – identifying partners across all stages of a product life cycle is relatively easy. In addition, Massachusetts has been very successful in recycling and retaining the talent pool. This creates an environment that attracts more people. There are great jobs in New Jersey, for example, but there is an added layer of risk in terms of what comes next if something happens to the company. In Massachusetts, people can be confident of ongoing job availability. The risk is lower and continues to feed the industry, as a higher level of talent also attracts more companies.

The next challenge the industry in Massachusetts faces is educating a new workforce. With this high growth comes rising living costs, and there is a lot of responsibility to continue to train scientists and create a local technical workforce. Now that the cluster has achieved a great level of success, it is important to invest in infrastructure and training to make that success sustainable.

What are the next steps for Wave Life Sciences over the next 12 to 18 months?

We will continue to advance our six programs through clinical development in 2018 and move them to important data readouts beginning in 2019. We will also continue to add new programs into the pipeline. Five years from now, we hope to see some of our programs commercialized, and hope to have reached that self-sustaining point where we have a solid R&D engine that is feeding products into a commercial organization that knows how to sell them. ■

Karoly Nikolich

Founder & CEO
ALKAHEST

Alkahest is focused quite broadly on diseases related to aging. What underlying premise led to the establishment of the company?

The original idea came from Tony Wyss-Coray, my co-founder, a board member and chairman of our scientific advisory board. He is also a prominent professor at Stanford. He discovered that connecting the circulatory systems of an old mouse and a young mouse caused the old mouse to rejuvenate, unfortunately at the expense of the young mouse, which showed accelerated aging. He then identified that it is the circulating proteins in plasma that mediate this activity, rather than being cellular. While this rejuvenating activity works for bone and skeletal muscle, heart muscle, the pancreas and other tissues, Tony specifically showed that this is actually true for the brain. This was totally unexpected because although the circulatory system supplies blood to the brain, there is a blood-brain barrier that filters out immunological proteins and foreign invading pathogens.

With a US$3.5 million seed investment, Alkahest was incorporated as a company in January 2014. As soon as we started, we were approached by all the major plasma companies. They saw this as an opportunity to develop new plasma-based products for new indications and recognized this as a huge potential new growth area. We negotiated with all three major companies and, by March of 2017, we signed a deal with Grifols, involving a US$37.5 million equity investment and a US$12.5 million license agreement. Grifols is also funding our R&D activities related to this plasma science.

How has research progressed at Alkahest since its establishment?

We are currently able to analyze more than 5,000 proteins in plasma, which was impossible until about two years ago or so. In fact, the big plasma-producing companies with FDA and European approvals are reporting on only 16 proteins in plasma. We have found that out of five thousand proteins we are able to analyze, four thousand do not actually change as we age – only about 15% of these proteins change. We call these proteins the chronokines.

There are around 10,000 proteins that circulate in the bloodstream, of which we are currently able to analyze half.

What are the next steps for Alkahest?

We would like to start clinical studies in a variety of neurodegenerative diseases: Huntington's, Parkinson's and ALS. Beyond that, we may consider some non-CNS indications as well. We expect that our deep knowledge of plasma proteomics in age and disease will serve as a powerful and innovative means towards new therapies. ■

Robert Gould

President & CEO
FULCRUM THERAPEUTICS

The Fulcrum Therapeutics product engine integrates multiple scientific disciplines to develop new medicines to unlock gene regulation in disease.

Could you give us a brief introduction to Fulcrum Therapeutics?

Fulcrum was conceived within the walls of Third Rock Ventures to pursue an opportunity in creating a small molecule therapies to correct misregulated genes in monogenic diseases in which specific genes are misregulated. The question was whether we could restore the balance of gene expression and regulation. The advantages of focusing on those monogenic disorders is that they lend themselves quickly and easily to patient identification strategies.

Could you discuss the FSHD candidate in Fulcrum's pipeline and the progress being made?

We identified this particular drug candidate through our novel approach to target identification as well as drug screening. We use muscle cells derived from patients with the muscular dystrophy that we are interested in. In the case of the FSHD program, the FSHD patients are making the muscle protein called DUX4, which is toxic to the skeletal muscle cell. It should be turned off, but in their case it cannot be and results in muscle wasting.

We decided to try to identify a biochemical target that would turn off DUX4 production. We succeeded in identifying such a molecular target along with a chemical lead that has advanced very rapidly. We are anticipating filing our IND in early 2019.

What are the advantages of having a much more narrowly selected patient population?

As a monogenic disorder, FSHD is a little bit unique in a few aspects, the first being that there is no effective therapy and it is under-appreciated for what a devastating disease it is. The lack of therapies also translates into low public awareness, which often comes in tandem with an effective therapy that makes people more conscious of the disease. The genetic underpinning of this disease is quite well understood. If a person has more than 10 repeats of a DNA strand that is about 10,000 base pairs long, then DUX4 is shut off. If a person has eight or fewer strands, then the cell continues to make that gene. This is our interest – those with muscular dystrophy that also have eight or fewer strands of this particular DNA. ■

Disruptive technologies

As innovative technologies are developed at unprecedented rates and computational power continues to increase by huge increments, there are many interesting applications across the life cycle of a drug, from discovery through to commercialization and use.

While pharma companies might be receptive to new technologies, the timing of when to implement them is key. For the major players, disruptive technologies such as Artificial Intelligence (AI) and machine learning will first have the greatest impact on processing mature, real-world data on the commercial and regulatory side of the business. Potential outcomes will include the ability to assess which doctors are more likely to prescribe a company's drugs. The incorporation of real-world and clinical trial data will assist physicians in making more informed decisions to help eliminate human error. When fully implemented and sufficiently mature, AI systems will deliver cheaper, more efficient and more comprehensive healthcare to the masses.

The Italian company Antares Vision, a provider of serialization-based track and trace solutions and state of the art vision control systems, has seen serialization requirements drive a revolution in the global pharmaceutical market. "Due to regulatory requirements, companies will have to implement an infrastructure to connect the digital world with the physical world," noted Emidio Zorzella, CEO & co-founder at Antares Vision. "Generated information will be applied to give greater visibility to the supply chain, following distribution up to the pharmacy and the consumer."

In drug discovery and development, the emphasis on targeted treatments and identification of patients with the highest response rates has led to an increasingly prominent role for diagnostic and data analytics companies. "With the technology to divide people into those very small and specific groups, we can really start to pinpoint which patients to target for the trial, inform the drug discovery strategy and then gain dedicated patients for life because of this specific selection," outlined Loralyn Mears, VP sales & marketing at RowAnalytics, a complex data analytics company specializing in digital health, precision medicine, genomics and semantic search.

The phenomenal progress in genomic sequencing has enabled scientists to sequence ever-greater pools of people and do so more quickly and more affordably. "We are at an important inflexion in the market in the field of genomic analysis and genomic technology, particularly next generation sequencing, to support drug discovery, precision medicine and research," commented Tim Wesselman, founder & CEO at Onramp BioInformatics. "A couple of years ago, Nature Magazine estimated that there will be 40 Exabytes of data generated by genomic sequencers by 2025. For institutions to try to manage genomics data is incredibly complex."

OnRamp Bioinformatics provides researchers, biologists and scientists with genomic answers and DNA insights through custom analysis and IT solutions and is particularly focused on its Rosalind™ platform. Rosalind™ uses trusted tools used by biologists within a framework and experience that al-

> "Now that we are past the chasm of mass market adoption of genomic analyses, we will see new individuals, new users coming into our space that understand that deeper insights can be discovered into the mysteries of disease and treatment. J.P. Morgan estimates that genomics will be a US$15 billion market within the next three years. Yet, the healthcare industry sits at US$2.3 trillion. The industry cannot keep up with the current rate of adoption of new technology. In order for the masses to find the answers that will lead to transformative therapies, we need to empower them to get the answers immediately and get the answers themselves. As a result, we will see that the rate of discovery, the rate of innovation, the rate of application of these technologies, will accelerate. That is part of our mission - to enable this industry to overcome pressures, blocks and challenges in order to accomplish more than anyone thought possible."
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> **- Tim Wesselman, CEO and Founder, OnRamp BioInformatics**

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Data science is playing an increasing role in innovation moving forward, explaining why areas such as San Francisco and Singapore are starting to attract more life sciences organizations, offering that blend of wet lab research and technology to drive their innovation.

- Richard Neale, Global Head, Clarivate Analytics

lows them to explore their own data. The platform went live in October 2017, initially with epigenetics and more recently with transcriptomics.

"One of the key enablers of the genomics revolution is the role of Applied Biosystems in making an extremely wide range of genomic assays available on a catalogue basis," noted Rodney Turner, CEO at Ayoxxa Biosystems, a German biotech company focused on the development of its proprietary beads-on-a-chip technology for advanced protein analysis.

Referencing a project with clinicians in Boston working with patients that had undergone double umbilical cord blood transplants in the context of leukaemia as an example, Turner highlighted: "Using our technology, which enabled them to look at a dozen cytokines as markers of inflammation, they identified a preliminary clinical signature for the early onset of graft-versus-host disease. We enable them to study these inflammation-related signs as a marker of the reconstitution of the immune system – the so-called cytokine burst that is often associated with immunotherapy can actually be quantified by the panel that they have explored with our technology. We are then able to earlier define that the patient is on a path to rejection or a path to early acute onset of graft-versus-host disease. It gives physicians earlier insight."

AI and machine learning are playing a more prominent role in recording, processing and distilling information. Another application is the processing of adverse events; every drug has associated adverse events and side effects that need to be assessed and acted upon. By applying artificial intelligence, modern analytics and machine learning, this process can be automated.

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Enhancing human ability

In another realm of application, virtual reality is being used to reduce costs and improve efficiency across the drug life cycle and supply chain. The Bay Area, with its proximity to the major tech players and a thriving biotech hub in its own right, is home to companies such as EndeavorVR, which are using game engines to develop ground-breaking disruptive technologies for the healthcare market. "VR can be used at many stages," underscored Amy Peck, founder and CEO at EndeavorVR. "In the R&D phase, 3D cellular and even Nano cell data can be injected and brought into a virtual environment, enabling collaborators to work together even if they are not in the same environment. This enables the use and re-use of cellular data after it has been digitized, which is incredibly valuable."

For the detection of Parkinson's disease, EndeavorVR is developing Leap Motion technology that can identify the level of shaking of the patient at an early stage of the disease when treatment can offer a better outcome.

Rather than replacing a human workforce, companies dealing in these technologies seek to augment human ability through disruptive technology. Apprentice.io, for example, is an augmented reality platform that has developed software for hands-free devices that enhance the ability of operators, scientists and engineers working in laboratories, lines and suites. When working on life-saving product development, having the assurance to execute complicated tasks with greater control, safety, productivity, stability and reliability is vital. "We are shifting the industry away from text, augmenting complicated written procedures with photo, audio and video content, allowing us to display instructions in a simple way that walks the user through the process and presents the content, whilst capturing data and providing real time feedback," commented Angelo Stracquatanio, CEO & co-founder of Apprentice.io. "This all concerns shifting the industry from process to workflow."

Instead of having to fly sales teams across the globe to train them in one place, VR can be utilized to significantly reduce the costs and time constraints involved in such logistics.

After winning the prestigious award for best new pharma manufacturing product at Interphex in 2016, Apprentice.io's groundbreaking technologies have seen a surge in uptake from pharmaceutical, biotech and manufacturing companies worldwide, with the Asian market being particularly responsive.

As an industry that is already high in risk, implementation of new technologies within the pharmaceutical space has traditionally been slow. "Pharma is a very networked industry, so if one company does something then others take a lot of confidence from that and want to follow suit," noted Manu Goel, SVP and client partner of Genpact, the global professional services firm using big data analysis to deliver digital transformation.

However, the sharp uptake for disruptive technologies in 2018 suggests that the waves of change have already arrived, and will continue to grow exponentially and transform the healthcare landscape. ■

Steve Gardner & Loralyn Mears

SG: CEO
LM: VP Sales and Marketing
ROWANALYTICS

SG

LM

Could you elaborate on how RowAnalytics supports other companies in their discovery and development processes?

SG: When looking at disease populations, many companies experience challenges in trying to find those signals that will enable them to find a new biomarker or to find a new R&D direction to pursue because the range of tools out there is fairly limited. Most tools work by looking for single mutations with an elevated risk of disease or a particular therapy response. We wanted to be able to segregate the population much more specifically. For example, we are working with a research group in breast cancer, and have integrated our data analytics capabilities. The issue here is that the data had previously been looked at about 40 different times already, by others, with mixed results. What our algorithms allow us to do is to analyze the data in a brand new way. We found about 17 mutations working in combination to exert a protective effect, versus the previous record of three. For an R&D project, this has to work in context, and that information needs to be interpreted collectively to be meaningful. We dig deeper into those clusters to find what clinical outcomes are linked and provide these insights to people for use in the R&D setting or clinic.

LM: With patient stratification, all companies tend to look at one factor. However, with our technology, we can look at combinations of effects. This means we can really pinpoint which patients should be in the study, taking into account factors like lifestyle choices, where the patient was raised, what they were exposed to, and so on. We can look at that information holistically and make choices accordingly. It is no longer just about genetics – it may be that a particular pattern of gene variants will lead to disease when combined with obesity or smoking, but otherwise might not, for example, and we can spot those differences. ■

Manu Goel

SVP and Client Partner
GENPACT

As an industry that is already high in risk, implementation of new technologies can be slow. How rapid has the uptake in new technologies and big data applications been?

We have seen a sharp uptake for these new disruptive technologies. For the last five or six years, we have pivoted very heavily on digital transmission. We now have a curated set of 12 different technologies, packaged in an interoperable manner on a platform called CORA. This helps drive better user experience, data flow and automation. While companies have generally used point solutions and deployment in the past, running these platforms in a sustainable manner requires management of both the human and machine element in a cockpit of sorts. That is where our command and control center comes into play, to assess what is happening on a real-time basis.

Over the last two years, we have been working to develop an AI-enabled digitized product solution for pharma companies. Our product deciphers all available structured and unstructured data to determine whether a case is valid. In deployment so far, we have found that almost 40% of the process can be made touchless. It is able to extract a lot of information and put it for human review with high degrees of confidence, and the information can be tracked to its specific source. Since it improves accuracy, compliance is also improved. Cycle time is also reduced and the system can run offline or perform tasks in a fraction of the time they were taking before with human effort. The product will undergo its first release in 2018 and we plan to make it into an end-to-end solution with an in-built technology repository by 2019. It will be a validated solution and a complete industry changer.

How can technology be applied to compliance processes to encourage greater harmonization across different geographies?

Today, all pharma companies create and submit static dossiers to health authorities, which are modified if any changes occur on how the drug is manufactured and sold. We are looking at ways in which this information can be virtually managed, which would forego the need for electronic or physical dossier submissions. Instead, the data would be circulated in a virtual environment which can be accessed by the health authority. Everything would be managed in a transparent, virtual manner, and always remain live. The main challenge here is finding the right health authority to move in this direction that is willing to develop a new way of working with a pharma company. This system also has potential to drive greater harmonization globally, with one common global living dossier and separate dossiers for other countries to address specific market needs. Because this data could be mined much more effectively, the ability to drive insights is much greater. ■

Image courtesy of Corden Pharma

Manufacturing: Upholding Quality

"Despite the changing generic landscape, strategy depends on each product and market. Each manufacturer has its own strategy around which products it wants to pursue. Despite the smaller market size, the expectation is that there will be generic competition to help drive prices down which is both an exciting and challenging endeavor. "

- Paul Krauthauser,
SVP Commercial Operations,
Aurobindo

Competing in a Globalized Market: Quality over Cost

Home to many of the world's leading pharmaceutical companies, the United States is the forerunner in the global market. IQVIA, formerly QuintilesIMS, reported 5.8% sales growth in 2016, up to US$450 billion. The United States' closest rival, China, posted sales of US$108 billion in 2015; about four times less. Alongside the vast number of U.S. companies that continue to expand their reach both throughout the United States and overseas, many international companies have also set up shop for greater proximity to U.S. customers and to take advantage various opportunities.

When it comes to manufacturing, whether for the brand or generic market, cost is a primary consideration. For brand drugs, high development costs and challenging reimbursement models cause companies to strive for efficiency and cost effectiveness throughout their processes. In generics, as competition in the U.S. market increases and the industry becomes increasingly concerned with quality, cost alone is no longer enough of a differentiator for success.

Enhancing performance and reducing human error

Equally, increasingly stringent FDA guidelines ensure that companies operate within a certain set of parameters and companies are eager to follow best practice to support patient safety and highest standards. New technologies coming into play are in large part driven by this emphasis on quality, whether in the form of track and trace solutions to monitor products in the supply chain or robotics and AI solutions to reduce human error and improve efficiency in quality management.

Increasing efficiency also helps to close the cost gap with traditionally lower-cost countries, following the initial investment, which may be prohibitive to some smaller companies. "Over the next three to five years, there will be a big shift in the way technology is incorporated into the workplace," commented Angelo Stracquatanio, CEO & co-founder at Apprentice.io, which has commercialized an augmented reality platform designed to increase productivity, reliability, audit readiness and safety in labs, lines and suites. "Tasks are becoming more complex and have more sophisticated requirements, yet the workforce remains the same in large part."

Apprentice has developed software that runs on a number of headset devices, which then has the capability to display and capture content and transmit it back to the user. Since the technology is headset-based, the user has their hands free to work. The company's second module, Tandem, is a telepresence tool – through a set of glasses, an expert is able to remotely view what the user is seeing, enabling them to troubleshoot any problem and foregoing the need to fly in a vendor at a delay and cost. The remote party is even able to draw on the user's field of view through augmented

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Within the developed markets, the health systems are well defined and somewhat reasonably funded, but in some cases bureaucratic. On the other hand, in the emerging markets, healthcare systems are still developing and the price of the product is still meaningful to the choice made by a physician or patient.

- Alok Sonig,
Chief Executive Officer,
Developed Markets
(North America, Europe, Japan)
Dr. Reddy's Laboratories

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reality. "The technology is intended to serve as a digital apprentice that empowers employees towards a higher output with lower error rates, higher traceability and higher audit capability," explained Stracquatanio. "The industry is moving quickly – as new technologies surrounding precision medicine and single-use processes come into play, the demand placed on the workforce in getting to grips with these innovations is only increasing. Solutions like those put forward by Apprentice allow companies to help their employees bridge that knowledge gap."

Sourcing overseas: upholding quality

Many companies look to lower-cost countries for APIs - India and China, for example, have particularly prominent positions as suppliers of APIs and other pharmaceutical building blocks - but sometimes face challenges in reliability if compliance requirements are not met. The ever-increasing emphasis on quality rightly adds pressure and, indeed, several organizations have fallen at the quality hurdle having been unable to meet price requirements without cutting corners. In 2015, the FDA launched the CDER Office of Pharmaceutical Quality (OPQ) to address gaps in drug quality, with the motto "One Quality Voice". As well as enhancing quality assessments through integrating review and inspection and es-

tablishing consistent quality standards, OPQ has also continued to work with international regulators on ICH Q12. Some efforts are being made to harmonize regulations and compliance requirements internationally. For example, FDA and EMA agreed in March 2017 to recognize each other's audit reports through a reciprocal agreement.

The increasing emphasis on quality and compliance, coupled with rising labor costs, has narrowed the cost advantage of Asian manufacturers and suppliers. In China especially, the market landscape has changed as the government has clamped down on environmental regulations with longer registration periods and a more stringent process. When it comes to sourcing, many companies are seeking to mitigate supply risk through sourcing from multiple companies. "Many companies are moving away from single-sourcing, but this is difficult to do when very niche APIs are required," noted Matt Thiel, president at Rochem, a global leader in developing, sourcing and supplying pharmaceutical, food, nutritional and animal health ingredients of Chinese origin. "The cost to deal with alternate sources is very high. However, in many other commodity areas requiring mainstay APIs, such as nutritional products, we see the multi-sourcing trend continue. While the Chinese government has now started to give more warning about shutdowns so companies are able to plan better, not producing or producing at extremely limited capacity for three to four months makes it very difficult to operate a business. We have had to work with our customer base to find alternatives and ensure a continuous supply."

While U.S. companies will continue to source from overseas, some prefer their suppliers to be locally-based, feeling that close-to-home translates to better quality. Many are reassured by reduced risk surrounding supply chain security. Factors such as launch location will of course be a consideration, and repatriation of manufacturing into the United States and Europe continues to be a trend. Emphasis on quality over cost means that cost alone is no longer enough of a differentiator to be successful in the market. For this reason, many companies are pursuing niche areas and implementing cutting-edge or proprietary technologies. "The challenge in the United States

> **Companies are always looking for ways to be more efficient. A number of these relatively new technologies have been implemented now, so the level of perceived risk has reduced. Pharma is a very networked industry, so if one company does something then others take a lot of confidence from that and want to follow suit.**
>
> **- Manu Goel, SVP and Client Partner, Genpact**

has been a consolidation among the distributors," commented Jay Shukla, CEO at Nivagen, a Bay Area company specializing in the development, acquisition and sales of generic prescription drugs and over-the-counter products for the North American market. "McKesson, Cardinal, AmerisourceBergen and Walgreens are all merging, resulting in only about four buyers controlling about 98% of the market. At the same time, the influx of foreign manufacturers is deflating prices. However, with many of the large players switching their attention to high-value molecules, we should see the market regaining equilibrium and gaps opening up. For the time being, we see more biosimilars coming into the market and more injectables that have previously been hard to manufacture. The market is getting smaller and much more competitive. To differentiate ourselves, our plan is to develop technically-challenging products that are hard to formulate, develop them early and arrive in the market very quickly."

Vertically-integrated supply chains can also be hugely beneficial for companies, offering not only cost advantages, but supply security and control. Whilst supply chains are becoming more globalized, they are still often very complex, particularly as many companies spread operations over multiple locations. "The majority of our products entering the U.S. market are imported, at about 80%, and can only be managed through a strong supply chain," highlighted Alok Sonig, executive vice president and head – North America at Dr. Reddy's Laboratories. "The key is to be able to deliver the product on time in a way that is reliable. We are responsive and scalable but at the same time flexible to the needs of the customers, as they can be very dynamic in this industry. A surge in demand can be quickly followed by an excess of supply, and a product can lose its exclusivity. Over time, we have built the capability to predict the occurrence of these surges in order to manage volumes. Over the last ten years, we have developed good responsiveness and flexibility of the supply chain as a core capability."

Image courtesy of Aragen Bioscience Inc.

Image courtesy of Corden Pharma

Capability over cost

Whilst cost competitiveness remains important, the increasing complexity of many new molecules in development calls for higher levels of technical capability amongst suppliers, paving the way for more technologically-advanced companies to come to the fore. Many multinational API manufacturers are extending their capabilities in niche areas, which are seen as particularly opportunistic due to the higher barrier to entry, in turn reducing competition from many smaller companies that might otherwise hold an advantage due to more nimble cost structures.

A primary challenge of many new drug products is poor solubility and bioavailability, necessitating enhancement. Companies offering solutions in these areas are therefore in high demand. "Many drugs do not make it to market because their solubility or bioavailability is inadequate – it is a great challenge with many new compounds in development," underlined Yann d'Herve, vice president global sales & services – business line healthcare at Evonik, a world leader in specialty chemicals with a significant offering to the healthcare space. "Our excipients are used in these applications through freeze drying or hot melt extrusion to create a solid dispersion. We develop formulations for clients using these two technologies and looking at what excipient and what formulation would best solve these challenges. One technology being used, which is a little bit different and can be used in combination with creating a solid dispersion or alone, enables an increase in the uptake of drugs via specific formulations. These are patented drug delivery technologies, which are especially important for peptides."

Evonik's offering includes brands such as EUDRAGIT for time-controlled release and RESOMER for controlled release specifically in injectable applications. "Brands such as RESOMER enable controlled release of injectable drugs over a period of time, which can be from one week to six or nine months," noted d'Herve. "As well as advantages for the patient, there are also advantages from a compliance perspective. Certain disease areas can be addressed in this way – opioid addiction and schizophrenia, for example, and also oncology."

As the market continues to shift and requirements continue to change, successful suppliers will need to meet a number of requirements, most importantly quality and reliability, and are moving ever more into the role of long-term partners and solution providers. ■

Alok Sonig

Chief Executive Officer, Developed Markets (North America, Europe, Japan)
DR. REDDY'S LABORATORIES

Dr. Reddy's was established in 1984 in India and is a US$2.3 billion company present in nearly forty countries, and the United States accounts for about 55% of sales.

How do the company's U.S. operations fit into the global picture?
The United States is a key geographical location for us and is home to our proprietary business product, focusing on addressing patients' needs through innovative NDA's and NCE's, alongside the 505(b)(2)'s in the fields of neurology and dermatology. Whilst our headquarters are in Hyderabad and the bulk of our operations are in India, we have three sites in North America: an oral solid and topical facility in Shreveport, Louisiana, an antibiotic penicillin facility in Bristol, Tennessee and an API plant in upstate New York, which works on prelaunch products and dosage forms. Our U.S. pipeline is rich, and we expect to file 20+ products every year and certainly anticipate growth in our U.S. footprint. Within the generics segment in North America we have three key business: the retail business (Rx), which is the standard generic prescription business in the U.S., the hospital business which is our specialty Rx business, and is mostly injectable oncology products, GPOs and integrated delivery networks, and the third is our US$200 million OTC business, which has Store brand OTCs as a more significant portion, and also recently added the branded OTC business. We recently acquired six OTC brands from Ducere Pharma: Doan's, Bufferin, Nupercainal Ointment, CruexNail Gel, Comtrex and Myoflex.

How does Dr. Reddy's address different demands across different markets?
Our approach is to be as meaningful as possible in both the developed markets and emerging market contexts. In developed markets we focus on complex generics segments which tend to be more value accretive. Within the developed markets, the health systems are well defined and somewhat reasonably funded, but in some cases bureaucratic. On the other hand, in the emerging markets, healthcare systems are still developing and the price of the product is still meaningful to the choice made by a physician or patient. The portfolio also sometimes has to be adapted to the market based on the disease burden. The aim is to deliver products that are relevant to the market that significantly hold more pricing pressure. It puts us in a unique position to be relevant in both contexts.

In what ways is Dr. Reddy's pushing development in the biosimilars space?
Biologics and biosimilars are critical to our growth in the long term, and we will be looking to address the high cost burden in the biologics space. We are focused on emerging markets including India with extensive efforts on the registration process for our biosimilars programs across multiple markets in Latin America, Asia and Africa. For developed markets we are accelerating our clinical trials programs for our flagship assets, Rituximab and Bevacizumab. We feel we can leverage our work on biologics in India more efficiently and effectively and really address their cost burden. The Indian market tripled in size when we launched biosimilars in therapy areas.

From a regulatory perspective, should there be further developments to make the environment more conducive to new products entering?
As an industry, there has been a drive for the FDA to really streamline and clear up the backlog of ANDAs, of which there are more than 3,000 still unapproved. It is still critical for us to focus on reducing the cost burden by accelerating competitive generic entries.

What are the core areas of focus within the business for the next few years?
In terms of emerging markets, we want to increase our presence in key therapy areas, and grow our presence in regions such as Russia and India. We are also looking at expanding our footprint in a few additional emerging markets to predominantly leverage our strong oncology and biosimilars pipeline. Within the United States specifically, the objectives are to grow the retail, specialty Rx and OTC business. The acquisition of the Teva portfolio and acceleration of the delivery of complex generics will spur growth in the Rx segment. On the injectable side, specialty Rx has a strong pipeline, so that will organically deliver significant value. We are well poised to deliver growth across all three key business segments. ■

Paul Krauthauser

SVP Commercial Operations
AUROBINDO

Headquartered in India, Aurobindo is a provider of broad line generics.

Since Aurobindo's establishment in 1986, how has the company's U.S. presence and strategy developed?
Aurobindo initially started as an API manufacturing company, and for many years that was the company's focus. Eventually, we decided to expand into finished dose generic pharmaceuticals and started the U.S. business in 2004. From 2010 through 2017, our company has been growing over 30% per year based on TRx's. We are now the 4th largest generic manufacturer in the U.S., based on total scripts dispensed. The company has historically been known for its broad portfolio of generic pharmaceuticals including oral products such as tablets, capsules and oral suspensions to injectables and OTC and nutraceutical products. We have recently expanded into the biosimilar space as well. Our strategy is simple, we utilize our global supply chain for economies of scale, vertical integration of API and a focus on innovation to develop a broad pipeline of products.

What are the primary capabilities across Aurobindo's U.S. facilities?
Aurobindo has a wide array of capabilities including, but not limited to, research and development, manufacturing, automated warehousing and distribution of oral solids, injectables, OTC products and nutraceuticals.

In what ways does Aurobindo leverage its integrated supply chain to the company's advantage?
Having an integrated supply chain, known as AuroControl, allows us to oversee every step of the process. When API production is combined with a growing formulary division, state-of-the-art manufacturing, along with high-tech packaging and distribution methods, the result is a highly efficient, cost-effective and flexible model that enables us to continually produce/distribute medicines that improve and save lives at a fraction of brand prices. Furthermore, AuroControl can provide insight into potential disruptions before they occur, allowing us to drive out inefficiencies proactively.

Could you provide an overview of the current state of the generics industry?
The Generic Pharmaceutical Industry jump-started in 1984 with the passage of the Drug Price Competition and Patent Term Restoration Act (informally known as the Hatch-Waxman Act). This key cost-saving legislation provided a modern system of government generic drug regulation in the US. This legislation provides a regulatory pathway for generic drug companies to obtain approval for their products based on manufacturing quality standards and bioequivalence against their intended branded product. This lower cost approval pathway of 'me too' products provides a mechanism for competition in pharmaceuticals which results in lower costs to patients as well as a way to encourage branded companies to continue to innovate with other products to replace the revenue lost when their older products lose patent protection.

As novel drug development tends towards precision medicine and smaller patient populations, how do you expect the generics landscape to develop?
Despite the changing generic landscape, strategy depends on each product and market. Each manufacturer has its own strategy around which products it wants to pursue. Despite the smaller market size, the expectation is that there will be generic competition to help drive prices down which is both an exciting and challenging endeavor. Unless there are very high barriers, we would always expect strong competition.

What will the focus areas be for the expansion of Aurobindo's portfolio, capabilities and geographic footprint?
Our focus areas will be to continue to support the oral solids and injectables businesses as well as our OTC products and nutraceuticals. We are also looking to expand our portfolio in the near future to include biosimilar, brand and 505(b)(2) products.

What does Aurobindo's prospects look like from a pipeline perspective?
Aurobindo USA received 39 ANDA approvals this past year and launched 27 products in the same timeframe. Overall, we have 242 approved ANDAs, 35 tentatively approved ANDAs, and 72 ANDAs under review. Aurobindo has been a perennial top performer in the generic industry in terms of ANDAs submitted to the FDA each year and ANDAs launched. We do not anticipate a slowdown in our pipeline program. ■

Jagadeesh Rangisetty

CEO
BIOPHORE

Headquartered in Hyderabad, India, Biophore is engaged in the development and manufacture of niche pharmaceutical products for the generics industry.

With the company's first fully-owned facility coming online in 2018, what have been some of the major developments at Biophore over the last 12 months?

In 2017, we filed close to 15 DMFs for the U.S. market, which puts us in the top five companies globally for DMFs filed for this market. Our portfolio is extremely varied, covering peptides, macromolecular complexes, contrast agents and oncology APIs. Our own API facility will be up-and-running in 2018 and is on track to be fully-functional by August. This will greatly add to our API manufacturing capabilities. At the moment, our focus remains very much on the U.S. market where we have upwards of 100 customers, but we plan to push more towards other geographies. We are also planning to work with brand companies, where we would exclusively manufacture APIs for a particular brand. By the end of 2018, we should have three or four APIs exclusively manufactured for brand companies.

Outside of the United States, what geographies is Biophore focused on?

We want to be active in the Latin American market , Turkey and the Asian market, particularly in China, Japan, and Russia. These are our target markets. We also have a presence in Europe currently, which we would like to grow further through newer products. With a lot of tech transfer happening in these regions at the moment, we see a lot of opportunity in niche APIs. We want to forward-integrate with formulation technology, which would enable us to provide customers not only with the API but with the formulation technology to manufacture these products at their sites. Our goal is to share this knowledge with our global partners and give them an exclusive API supply.

Many companies try to leverage the cost advantage in India for the U.S. market. What differentiates Biophore?

It is our high technology capability that sets Biophore apart – we are able to supply APIs that require processes like ultrafiltration, lyophilization, solid-phase synthesis and macromolecular synthesis. In these areas, we take early advantage of the IP – after tracking the molecule quite heavily and creating the IP component of the process or polymer, we take the capability to the U.S. market. This is where we are most successful right now.

Do you see both increasing opportunity and competition in the Chinese market?

China is becoming more regulated and moving closer to the United States. In the past, India has tried to import APIs from China, but the situation has changed a great deal. India now tries to export APIs as much as possible, particularly to the U.S. market. Our plan is to take the niche APIs we have to our Chinese partners, with the accompanying formulation technology, in order to ensure a long-term collaboration.

There are still barriers for formulations to be manufactured in India for the Chinese market, so we prefer to supply the API and formulation technology and for the manufacturing to take place in China.

How great is the advantage of manufacturing in India over the United States?

API manufacturing in the US is quite challenging, especially in terms of meeting development regulations. There is also an issue with scale: API manufacture requires huge infrastructure. Then, there is the cost of the manpower this involves. For all of these challenges, manufacturing in India poses the better prospect. We have very well-defined resources, larger infrastructure capability and better time-efficiency. Provided compliance is properly addressed, India has huge advantages.

Going forward, what are the next milestones for Biophore?

The next foreseeable milestone will be when we start manufacturing injectable products in the next few years. We also want to innovate to improve what we already have: we want to focus on the molecules at an early stage and log the IP on these; and also to focus on biosimilars, which is an area in which we are already working. We just need to scale up our activities in these areas to better serve the global market and plan to initiate R&D in biosimilars in the next 12 months. We are also working on a new platform technology, which will mature into a lab in the next 12 months, at which point we will look at taking it into manufacturing. ■

Jay Shukla

CEO
NIVAGEN PHARMACEUTICALS, INC.

Nivagen is engaged in the development, acquisition and sales of generic prescription drugs and over the counter products for the North American market.

What are Nivagen's core areas of focus?
Nivagen is focused in three areas: developing generic and OTC products, developing 505(b)(2) programs and commercializing prescription and OTC products from foreign manufacturers in the U.S. market. We have launched more than 21 products under the Nivagen label in the last two years. In-house, our development capability is limited. We normally conduct about four to six programs in-house at a given time, and between eight to ten programs through a co-development or partnership model with contract service organizations. We are increasingly focusing on the injectable market as an area of interest because of the saturation in orals.

We have a lab in Davis, right next to UC Davis, that is primarily focused on 505(b)(2) products – converting existing molecules into a newer dosage form. This can include converting a lyophilized powder into a solution, or bringing a "grandfather" drug into compliance via a safety and efficacy study, for example.

How does Nivagen utilize the advantages available in different geographies?
Our geographic scope is broad when it comes to working with companies overseas to commercialize their products in the U.S. market, from countries such as China and India to many across Europe. With instant access to 160 national points of distribution, Nivagen has a presence in chain drug stores, regional wholesalers, mass merchandisers, hospitals, GPOs, mail order pharmacies and other major buying groups. The industry is moving towards India, especially for low-margin, high-volume products. We are now exploring Bangladesh and have a few projects there right now. One reason for the shift we are seeing from India to Bangladesh is the quality of manpower. In Bangladesh, many of the businesses are privately owned by a handful of families, so there is a lot of money available for CAPEX investments. This presents a strong advantage.

How is the U.S. generics landscape developing?
The generics market is deflating right now. However, the market should settle down over the next couple of years. Big players are downscaling activity – for example, the Novartis/Sandoz discontinuation of many generic product, plant closure in Alabama by Par, and Teva's announced closure of non-profitable generics business.

The challenge in the United States has been a consolidation among the distributors. McKesson, Cardinal, AmerisourceBergen and Walgreens are all merging, resulting in only about four buyers controlling about 98% of the market. At the same time, the influx of foreign manufacturers is deflating prices. However, with many of the large players switching their attention to high-value molecules, we should see the market regaining equilibrium and gaps opening up. For the time being, we see more biosimilars coming into the market and more injectables that have previously been hard to manufacture.

What does Nivagen look for in an overseas manufacturing partner?
For companies that we are considering to market in the United States, we of course look at the economics and factors like vertical integration, whether they might have their own API, compliance, financial strength, and their ability to support the required volume. We have auditors everywhere that will assess companies around the world, or we will hire a consultant to audit on our behalf.

Are there any particular challenges in the injectables segment?
The challenge is that CMOs are extremely expensive in the United States in terms of tech transfer. There is also not a great deal of capacity in injectables – there is a need for good quality, affordable CMOs. However, venturing outside the United States for injectables is extremely challenging because of high levels of FDA scrutiny, particularly in injectable sterile products. European companies are often very slow; this is problematic as speed is essential in generics for rapid market entry. China and Taiwan pose challenges because of communication. The U.S. market is therefore clearly the most favorable for high-priced injectables. We are in the process of building our own manufacturing base in Sacramento, which should have commenced by the end of 2019.

What are the next steps for Nivagen going forward?
We have a few good molecules following the 505(b)(2) pathway, which are currently in the clinic. One is currently awaiting a response from the FDA and would be the first prescription therapy in a billion-dollar market. This should increase Nivagen's valuation and enable us to tackle larger programs. We will also continue commercializing products for other companies and continuing to grow our market share. ■

Nick Grasman

Lead Market Manager – Dow Pharma Solutions
THE DOW CHEMICAL COMPANY

Dow Pharma Solutions develops functional excipients and APIs that enable improved pharmaceutical delivery and enhanced solubility.

How has Dow's presence evolved in the life sciences space, and how has the DuPont merger impacted the company's strategy?

Dow has had a strong presence in the pharmaceutical industry through its excipients offering for a long time. Some of the more prominent changes include the acquisition of the other half of Dow Corning, which brought a range of silicon-based products into our portfolio, introducing new applications such as topical development and transdermal films – areas in which Dow has traditionally not had a strong presence. Historically, our main competence has been oral solid dose, an area in which we continue to be very strong.

The merger with DuPont plus DuPont's acquisition of FMC has added another set of excipients to our portfolio, primarily focused on oral solid doses but very complementary to Dow's existing portfolio. We now have a product portfolio that touches almost every aspect of oral solid dose, from tablet binders for compression and granulation binders to tablet coating systems and modified release matrices.

Bioavailability and solubility enhancement are primary considerations for any drug development company. In what ways can Dow support the efforts of these companies?

We have been heavily researching the area of solubility enhancement for some time. Many new APIs coming out of development need significant solubility enhancement to boost their effectiveness. A couple of our polymer products are already in the market as lead candidates. One of these is hydroxypropyl methylcellulose acetate succinate (HPMC-AS), a soluble polymer with PH-dependent solubility, which can be used to get a drug past the stomach and into the intestine, for example, before the coating dissolves and releases the drug. This works particularly well in spray-dry dispersions, a technology by which a poorly-soluble drug can be dissolved in a non-aqueous solution and spray dried – the polymer helps to lock in the active ingredient in a higher-energy but more soluble form.

What we really bring to the table is the ability to modify the polymer within monograph ranges, so it is appropriate for drug solubilization. Not many companies have the scale or scientific expertise for this. We have put together a Formulation-By-Design kit, which enables customers to test different ranges and find the polymer that works best for solubility enhancement.

Whilst oral solid dose remains the leading dose form, are there any trends towards other dose forms?

Topical administration is becoming more popular, as well as transdermal. These are interesting because they include technologies with favorable applications in pediatric and geriatric care, with drivers from both a regulatory perspective and population demographic perspective. Being able to administer medication to geriatric patients in a way that does not require the patient to remember to take a pill in favor of a long-acting patch, for example, is a huge advantage.

Companies are pursuing more challenging therapeutic areas and approaches, which is driving a lot of earlier-stage interest in parenteral-type applications. However, these trends are not yet seen in the mass market. Even in these instances, there is still a preference to move away from injectable formulations to an oral formulation where possible.

What are the advantages of Dow's global presence, and are there any areas of strategic focus within the United States?

We see a great deal of activity in Boston/Cambridge and the Bay Area for emerging technologies – there are a lot of smaller independent companies that are eager to pursue next generation solutions. We try to connect with as many of these teams as possible to show them what we can offer from a polymer science perspective and get feedback on their performance needs and requirements.

What are the next areas of focus in terms of R&D and new additions to the portfolio?

We remain primarily focused on excipients and we are not developing new dosage form technology ourselves. However, we are participating in the development of many of these new doses – we are interested in working with companies in 3D printing, for example, to work out the excipient needs. There is also currently a great deal of research around continuous manufacturing and better flow performance – we want to be part of these conversations from an excipients perspective. For example, Dow's METHOCELTM DC2 polymers have better flow performance to enable direct compression and skip granulation steps, which is more amenable to a continuous manufacturing process. We are constantly in a feedback loop with the industry to understand its excipient needs. ■

Image courtesy of Corden Pharma

The Spokes of the Wheel: Contract Services

"We have to adapt to the New Normal in the market through the presence of orphan drugs and unique high potent medicines. These more specialized and higher-value medicines require greater diligence and care and an appropriate supply chain to maximize yields."

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

The Indispensable Partner: Contract Services

Outsourcing continues to be an attractive proposition for companies of all sizes for a variety of factors. Partnering with contract service companies to fill gaps in capability or technological expertise is an attractive proposition, often favorable to making acquisitions or building out in-house resources, and in some cases necessary.

Years ago, large-scale CMOs began to venture into the development side, resulting in a number of contract development and manufacturing organizations (CDMOs). In addition to offering flexibility and time efficiency, many of these organizations also offer capabilities and innovative processes as an advantage. Large Pharma companies often turn to CMOs and CDMOs for areas of niche or specialized expertise, such as biologics, antibody-drug conjugates (ADCs) and highly potent compounds. According to business-intelligence provider visiongain, the pharmaceutical CMO market is expected to grow at a CAGR of 6.4% over the next three years, and at 5.7% over the following five, with the market reaching an estimated US$88 billion in 2021 and US$124 billion in 2027.

Catalent leads the pack, continuing to grow and add new technology capacity, investing over US$1 billion back into the company, including over US$600 million of CAPEX and more than US$400 million in M&A, in the last five years. Having been purchased from Cardinal Health by Blackstone Private Equity and a few others in 2015, Catalent is now a fully-public company traded on the New York Stock Exchange (NYSE) following Blackstone's sale of its last remaining interests in September 2016. In 2017, Catalent has continued to add capabilities with the acquisition of Accucaps, a Canada-based developer and manufacturer of Over-the-Counter (OTC), high-potency and conventional pharmaceutical softgels. In addition, the CDMO has also completed a US$15 million expansion at its Winchester-Kentucky control-release facility, doubling capacity, and in April 2017 completed an expansion project at its Kansas City, Missouri facility to significantly increase controlled- temperature storage capabilities for its clinical supply business and announced the completion of a two-year US$4.6 million expansion at its Singapore clinical supply facility in February 2018.

Large pharma companies have increasingly looked to outsourcing of core competencies with a view to streamline internal operations and focus on areas of excellence. At the other end of the spectrum, small biotechs often simply lack the in-house capabilities and resources to bring a drug from discovery through to commercialization themselves. "The current worldwide market for outsourcing is about US$5 billion," commented Menzo Havenga, president & CEO at Batavia Biosciences, a company branding itself as a one-stop-shop focused on accelerating the transition of biopharma-

ceutical product candidates from discovery to the clinic. “Only 12% of the outsourcing market is big pharma, meaning 88% of the market is derived from biotech… The six most important drivers for organizations to consider outsourcing are scale-up, cell line development, medium development, improved yield, new tools testing, and clinical manufacturing. We are active in all these areas and have unique offerings for our client’s consideration.”

Building on its five technology platforms – SCOUT, STEP, SIDUS, SCOPE and SATIRN – Batavia’s ambition is to be one of the Top 100 global CDMOs by 2025, reaching US$50 million in revenue by 2025, and doubling its workforce of 120 people. Since offering a full suite of services to clients is highly beneficial, Batavia is likely to pursue an acquisition to expand its clean room facilities and manufacturing capabilities.

Alongside favorable trends towards outsourcing is a preference to work with fewer contract service partners, leading to integration of capabilities within the contract service segment. In addition, higher demand means that contract service companies are eagerly positioning themselves to take on a higher number of clients and larger projects. “Because demand is currently exceeding supply, there is a scramble and we see consolidation of organizations and

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Joseph Colleluori

Senior Vice President
Corporate Development
LONZA GROUP

Headquartered in Switzerland and traded on the Swiss stock exchange, Lonza is a leading supplier to the pharma and biotech industries.

Lonza is a leading global CDMO. How has the company developed to assume its current market position?

From its initial focus on carbon rods at the end of the 19th century, Lonza moved into basic chemicals, building the world's smallest cracker on its main site in Switzerland. From that chemical base, Lonza became the first company to establish contract manufacturing. In the 1980s, we built a fine chemical complex (FCC) and turned our attention to large companies like Merck and BMS that were beginning to move from chemicals into pharmaceuticals. Although many of these companies considered manufacturing to be at the core of their activities, we were able to convince some of them that we could manufacture the APIs and intermediates for them. Rather than covering all bases, this would allow them to stick to core competencies such as research, development, regulatory processes and marketing. The business continued to grow with the establishment of a facility in China, where we were able to do some additional chemical small-molecule manufacturing for big pharma companies. In 1996, Lonza became the first biologics CDMO. With the exception of vaccines, there had previously not been many biologics in the market. We bought a company called Celltech Biologics with an operation in Slough, U.K., which was in the process of finishing a large biologics operation in Portsmouth, New Hampshire. This became our biologics division, which has grown to be a prominent component of Lonza's business.

What have been the major recent advances in technological capability?

In 2017, Lonza made the largest acquisition in its history and acquired Capsugel for US$5.5 billion. From there, we moved even further into a different type of modality, adding particle engineering to our existing modalities of chemicals, biologics, cell therapy, gene therapy and viral therapy. Whilst Capsugel is widely known as the world's largest manufacturer of hard capsules, the company also had capabilities that supported not only encapsulation but also drug formulation.

How can Lonza effectively fill the knowledge and infrastructure gap for smaller companies with limited resources?

Our ability to support companies not only with a core service, but also to handle FDA requirements and make sure that facilities are ready for launch and scale up is a very valuable proposition. The objective for these companies is to get their product to market as soon as possible, especially since cash flow is a big issue for many. They therefore rely on us for our experience, knowledge and reliability to ensure that their products are launched on time.

What is the significance of Lonza's recently-announced partnership with Denali Therapeutics?

The partnership deal with Denali Therapeutics stemmed from the company's focus in the neurodegenerative space. One of the challenges in the neurodegenerative space is that, once a product is approved, high demand will likely cause a huge jump in required quantities overnight. The population size for a disease area like Alzheimer's is huge. In the instance that a company lined up its own manufacturing facility and their drug then failed to get approval, they would be faced with wasted capacity following a significant investment. Lonza's capacity support around the world helps to balance risk that a company would otherwise take on itself and to scale up rapidly in the right territory, when needed. It is also worth noting that Denali's pipeline includes a range of potential therapeutics from small molecules to complex biologics. Our experience across these modalities is a clear advantage.

What are the plans for further addition of capabilities and capacity expansion?

Lonza has a very balanced perspective on organic and inorganic growth. We invest heavily in our operations globally, with CHF 450 million in 2017, plus five acquisitions. With our Capsugel acquisition, we are moving up the value chain and will continue to look for acquisitions and partnerships to extend our technological capabilities and geographic footprint where it makes sense. We have also recently expanded our parenteral drug product services for difficult-to-formulate sterile products at new laboratories we opened up in Switzerland last year.

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Increasing bioavailability is the biggest trend we see. Reducing the dose needed for patients has some valuable advantages. This is what drove us towards wet nanomilling. We are able to reduce particle size down to the 100 to 500 nanometer range, which aides in increasing bioavailability. Another unique advantage to nanomilling is for less soluble APIs. We can effectively mill to nanometers and matrix the API into a suspension for an oral, injectable or topical product. We also see a strong trend towards liquid-filled capsules again in the market, which is an area in which we specialize. We have several projects advancing with this technology.

- Stephen L. Schweibenz, President, Alliance Contract Pharma

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their manufacturing capabilities, especially overseas in developing markets such as China," said Michael Osborne, director of business development at the Boston Institute of Biotechnology, a CRDO specializing in microbial fermentation and mammalian cell culture processes.

Leveraging expertise across both the U.S. and Chinese markets, the Boston Institute of Biotechnology is utilizing accompanying advantages to position itself as a partner of choice to the life sciences industry. "The cost of development and manufacturing is approximately 40% to 50% less than in the United States," continued Osborne. "This alone clearly demonstrates why some U.S. companies might choose to partner with us on some initiatives overseas."

Contract service companies such as Catalent and Patheon are particularly successful in offering integrated solutions. Patheon, for example, utilizes its simplified development path, OneSource, claiming to eliminate eight to 12 weeks of development time for small molecules and 14 to 20 weeks for large. Meanwhile, smaller companies flourish when working in specific technologies in which they excel that the larger companies might not have extensive expertise in.

A notable transition for many contract service companies has been a refocus around core areas of specialization, rather than a previous trend to become all things to all customers. While an integrated service over the life cycle of a project is still preferred, contract service providers have recognized that offering key differentia-

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Dr. Stephan Kutzer

Chief Executive Officer
ALCAMI CORPORATION

Alcami is a CDMO focused on the clinical supply segment of the pharmaceutical industry, primarily in the United States.

What have been some of the major components of Alcami's rapid expansion strategy?

We invested US$25 million in 2017 with the goal of making Alcami the perfect partner to small biotech and pharma companies. We opened over 5,000 square feet of lab space, fine-tuned for analytical capabilities and formulation development as well as biological testing capabilities. By moving our headquarters over to Durham, we also consolidated our presence – Durham's Research Triangle Park (RTP) is a major innovative hub in the United States. We have added about 15 new jobs there this year and it is likely that we will add another 50 per year by increasing our lab space by significant amounts, with a clear focus on biotech development as well as our microbial and mammalian-type process development for biological API development.

We have also built a brand new facility in St Louis with two floors of lab space for compendial testing for both the East and the West Coast, as well as our mid-west customers. In addition, we have made significant investments in small molecule API manufacturing. Furthermore, we opened a second line with sterile filling capabilities at our Charleston facility, which we are starting to validate and qualify.

What is the significance of Alcami's new sales offices in San Diego, California and Cambridge, Massachusetts?

We have identified the early-stage clinical supply segment as an under-served industry, which is very critical for innovation within the pharmaceutical industry. More than 90% of the molecules in new therapies are developed in small and mid-size biotech and pharma companies. Many are developed in universities by brilliant scientists with innovative ideas and science, but those scientists do not necessarily have about the expertise in manufacturing, the regulatory approval process, or how to make a molecule producible at scale, deliverable and sellable into the market. This is where Alcami comes in.

We offer a fully-integrated service, from API development all the way to specialized packaging and drug formulation, following the molecule through the value chain to make the drug a success. Our vision is to become the company with the most successful product launches per year in the U.S. market. We support customers from pre-clinical conception all the way through to a successful commercial launch.

In what ways is Alcami able to reduce drug development costs through greater efficiency and faster timelines?

Speed is the differentiator in the clinical space. By utilizing our fully integrated services and one project manager per project, we are able to cut down the development timelines of these molecules to a third of what could be achieved elsewhere. We now have already 14 fully-integrated programs that we have built from the API into a product and this number is growing. This has only taken us one year to achieve.

With the implementation of serialization requirements around the corner, is Alcami well positioned from a compliance perspective?

We are on the road to introducing a drug tracking mechanism and linking drug supply data. Serialization is being put in place due to misuse issues in manufacturing. The beauty of operating in a regulated market is that these measures are enforced. We are at the forefront of this tracking capability and all drugs manufactured and packaged by Alcami are up to the required serialization standard and can be traced right to the beginning of the manufacturing process. It is wonderful that the industry is putting these measures in place to keep patients safe.

What will we see over the next 12 months in terms of expansion, addition of new capabilities and general strategy?

We are currently actively looking for additional financial sponsors for our very aggressive growth plans. In the near future, we will be placing a strong emphasis on adding biologic capabilities and increasing our sterile capacity. Acquisitions also remain a focus within our strategy. In line with our strategy to attract more overseas customers looking to launch their products in the U.S. market, we are in the process of hiring a substantial sales force.

We also plan to set up a base in Germany. The theme is always the same: we have to have a local hub, local presence, local community and work with innovative companies to help them to launch in the United States. Furthermore, we are thinking about how we can get our hands on molecules earlier, so we will likely be pursuing partnerships with CROs. ■

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We are seeing a lot of investment going into small companies and start-ups which have their basis in deep research and science. Many of these companies want to be virtual and therefore do not want to invest in labs or manufacturing or in general hardware.

- Manni Kantipudi,
CEO,
GVK BIO

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tors in fewer areas is more advantageous. "It can be a challenge to keep up with the rapid rate of change in the industry," commented Michael Quirmbach, vice president, global sales & marketing at CordenPharma, a CDMO supporting pharmaceutical and biotechnology companies, with facilities in the United States and Europe. "We have to be selective in terms of which areas we want to be active in – a company cannot be active in all areas. It is important to decide where our strengths lie and where we can offer value to our customers."

Through specialization, contract service companies are really able to drive efficiencies for their customers. Time is often key in the life sciences industry, particularly when bringing drugs to market, and where small decreases in development timelines can lead to significant reductions in cost. "Speed is the differentiator in the clinical space," emphasized Stephan Kutzer, CEO at Alcami. "If a CDMO can help its clients take even one day off their clinical trial and bring a product to commercialization a day early, the customer saves a significant amount of time and money. Being able to speed up the clinical trial, optimize pathways and make the regulatory pathway clearer, also allowing our customers to focus on the scientific aspects, enables Alcami to save more time and money for its customers. This is making drug devel-

> In the United States and Europe, we are starting to see many continuous manufacturing systems, but primarily for relatively large batch sizes. Japanese companies, however, excel in smaller continuous manufacturing systems of 20kg or less. Oral Dosage (OD) tablets are a new technology for Japanese companies, offering great opportunities for an ageing society. CMIC is actively looking for the right opportunity to manufacture OD tablets in the United States.
>
> **- Makoto Matsukawa, SEO and Corporate Development Head, CMIC Holdings Co. Ltd.**

opment cheaper and more affordable. The focus on drug prices is absolutely critical. A great deal of investment in drug development is wasted on inefficient trials or through misdirection – creating something that does not meet the needs of consumers. By cutting down timelines through an integrated approach, Alcami is on the right path to reduce drug costs and ultimately making drugs more affordable for patients."

Also catering to time-sensitive requirements in the clinical trial space is PCI Pharma Services, which has launched its PCIFastTrack™ offering in response to some customers finding themselves in dire situations and in desperate need of a particularly fast service. Clinical trial success is absolutely pivotal, particularly for smaller companies that may have few or only one product in the pipeline. "These small emerging pharmaceutical companies we see entering the market with maybe only one therapy in the pipeline need a lot of help bringing their product to market," commented Justin Schroeder, PCI Pharma Services' senior executive director – global marketing & design. "The most pressing issue for these companies is funding. They live between capital cycles so finances must be carefully managed. Clinical trial results have a significant effect and can result in dissolution if unfavorable. We are able to service these small companies from first in-human clinical studies all the way through to commercial launch and ongoing supply, providing scalable solutions as they grow. Even if these companies are bought by a larger company, since PCI is the preferred partner for 19 of the top 20 pharmaceutical companies globally, we can provide continuity in instances where the supply chain may otherwise experience disruption."

PCI prides itself on rapid turnarounds for clinical trial materials and, through its PCI-

Image courtesy of Corden Pharma

FastTrack™ offering, has re-evaluated and streamlined its policies and procedures to meet requirements in time-critical cases, offering several tiers of expedition to meet customer needs.

Contract service companies along the stages of development and manufacturing will continue to consolidate, both in order to take on larger contracts and to provide evermore integrated service capabilities to their clients. Worldwide growth in API volumes, increasing use of generics and growing opportunities for penetration in developing markets, coupled with these increased outsourcing requirements by large innovator companies, indicate that the industry will continue to experience strong growth. At the same time, the influx of small companies and biotech startups has also resulted in increasing demand due to a lack of internal manufacturing capacity. ■

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The industry's demand for quality improvements is causing longer time lines for projects due to the tremendous amount of analytical work required. Smaller companies typically have less robust tech packages due to their inability to finance that level of testing as a trade off for speed. At Flamma, we help to provide the necessary and required in-process controls and other tests to optimize their manufacturing route.

- Ken Drew,
Senior Director,
North America Sales & Business Development,
Flamma Group

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Aslam Malik, Patrick Park & Jeff Butler

AM: CEO
PP: Vice President
JB: Executive Director, Project Management
AMPAC FINE CHEMICALS

AMPAC Fine Chemicals manufactures APIs and intermediates primarily for the U.S. market.

AM

PP

JB

Following a 75-history, where is AMPAC Fine Chemicals positioned in the market today?

AM: AMPAC Fine Chemicals originated from a company called Aerojet, which mainly supported the Department of Defence. This required chemists and engineers to make novel materials, leading the company to build capabilities in developing hazardous and toxiccompounds. During the aerospace industry downturn in the 1990s, we began to diversify. One area in which we excelled was in making chemicals for the pharmaceutical industry. Aerojet Fine Chemicals started growing as a small division of Aerojet, and was sold in 2005 to American Pacific Corporation.

At AMPAC Fine Chemicals, we use the technologies developed over many years at Aerojet to our competitive advantage, focusing primarily on energetic chemicals, also known as hazardous chemicals, which require very special techniques. There are very few companies in the world that can manufacture these chemicals safely and reliably at commercial scale. Another core competency is manufacturing highly potent chemicals. As drugs have become more potent, we have applied our technologies to make them safely at commercial scale. Although we work with life sciences companies from pre-clinical to commercial stages, our focus is primarily on projects that are in Phase 2 clinicals through commercial manufacturing.

How extensive is AMPAC's geographic scope, both within the United States and overseas?

AM: We have four facilities in the United States; two in California, one in Virginia and one in Texas. So far, our main focus has been in the United States and Europe, but we are also making major progress in Japan.

What are the primary motivations behind operating out of the United States over lower-cost countries such as India or China?

PP: India and China are great places for production of raw materials and key building blocks but our focus has always been on the regulated GMP steps. In addition, we focus on production of Controlled Substances, Schedule II-V. According to U.S. law, Schedule II compounds must be manufactured in the United States. This means that there is less competition from lower-cost markets.

Could you elaborate on the company's core capabilities?

AM: In terms of technology, while we cover most basic organic chemistry transformations, a notable area of expertise is Simulated Moving Bed chromatography (SMB). SMB is used for purification on an industrial scale. As we see a greater number of products with chiral centers and greater complexity, this technology is perfectly suited for these purifications. We have seen a lot of growth in this area. Another area of particular strength is controlled substances.

In terms of new technology capabilities or processes, is there any internal R&D or planned expansion underway?

JB: A major focus is continuous processing. There is renewed energy and attention on this area from many companies in the industry. We are now looking to reacquaint customers with our continuous processing capabilities which have been practiced over the past 60 years. We are also continually making improvements in our high potency capabilities.

AM: Another area in which we have made a lot of recent investment is in analytical testing, involving some very complex methods. For example, we offer ICP-MS services – a type of mass spectrometry for detecting heavy metals. This is now required by the FDA and EMA, which has resulted in a lot of growth in this area forAMPAC Fine Chemicals.

What are the next stages for AMPAC Fine Chemicals?

AM: Right now, our California and Texas plants are running at high capacity. Our goal is to bring the recently-acquired Petersburg, Virginia plant up to full capacity as well. Having recently signed a long-term deal with a leading controlled substance customer to produce a portfolio of their APIs & intermediates, we are confident that we will be able to accomplish this goal in the near future. This is a major focus for AMPAC Fine Chemicals. ■

Vivek Sharma & Ramesh Subramanian

VS: CEO
RS: Vice President – Strategic Marketing
PIRAMAL PHARMA SOLUTIONS

Piramal Pharma Solutions is a leading global CDMO covering the drug life cycle from discovery through development and all the way to commercial manufacturing

VS

RS

How extensive is the company's offering today?

VS: We have three development and commercial manufacturing facilities in North America: Riverview, Michigan for high potency APIs, Lexington, Kentucky site for injectables, and the complex-high value API site in Aurora, Canada. In addition, we have two facilities in Europe; an oral solid dosage and API manufacturing facility in Morpeth, England and an Antibody Drug Con-jugate (ADC) site in Grangemouth, Scotland. We also have several facilities in India, including API sites in Ennore and Digwal, and two sites in Ahmedabad, one dealing with discovery R&D services and the other for oral solid dosages, and an injectables R&D site in Mumbai. Finally, we have an oral solid dosage manufacturing site in Pithampur, India, for oral solids manufac-turing.

Could you provide an update on Piramal's U.S. strategy?

VS: All of our three sites are undergoing major expansions as we add capacity and capabilities. Having recently acquired our Riverview site in the United States, we are expanding its footprint and increasing our high potency capability up to 10 ng/m^3. We are also tripling our Fill/Finish lines at our facility in Lexington, Kentucky, and increasing lyophilization capabilities by a factor of almost 10.

RS: We are investing US$90 million across our facilities globally. There are a couple of drivers for this: Our current customer pipeline includes ~110 programs in late-stage (Phase II/III) de-velopment, with many of these for strategic clients that we have preferred relationships with. As these programs near commercialization, the additional capacity is required to meet launch needs. The second driver is capability enhancement: for example, 10 ng/m3 OEL allows us to make ADC handles for customers, who can then complete the conjugation and fill/finish within the Piramal Pharma Solutions umbrella. This integrated approach is much appreciated by our customers, as they prefer interacting with one service partner and a single program manager, as long as they can deliver on time at the highest quality.

What is Piramal's strongest focus in terms of therapeutic area?

RS: Oncology remains our strongest area of focus. We continue to augment our capabilities in this space by building out or through acquisitions. Since oncology is a broad area with many different therapies/technologies, we have had to take a more specific focus.

Particularly with smaller companies, are there any shifts in demand for contract service providers?

VS: We see increasing demand for a more integrated service offering- an offering that includes some combinations of drug substance, drug product, and clinical trial supplies. Our customers are trying to consolidate their suppliers and optimize the time to market for their products. A significant portion of our expansion investment is aimed at addressing this 'integrated trend' in the market- we are able to deliver value both in terms of speed and costs. We are proud of our track record: over 60 successful integrated programs executed, with a current set of 30 opportunities.

There is a long-standing relationship between the United States and India when it comes to importing APIs and other pharmaceutical building blocks. Are you starting to see more competition from countries such as China?

VS: China has been manufacturing pharmaceutical products for a long time; our customers come to us because of the high quality of our products. We have strong technical capability, reliability, and their trust. Given these relationships, we do not expect our customers to migrate based on cost alone, especially if we continue to execute and invest in supporting their future needs. Factors such as speed, access to cutting-edge science, and the 'ability to sleep well' through working with a reliable partner are often the drivers we hear from customer. We continue to listen, invest in people and science, and hence have seen significant growth in business and customers.

Going forward what are the steps for Piramal?

VS: We have an aggressive growth strategy and are focused both on organic growth and on acquisitions that bring value. In the near-term, we expect to add more sites to the Piramal Pharma Solutions family, to both increase capabilities and expand our geographical footprint, while continuing to invest in augmenting our current network.

Michael Quirmbach

Vice President, Global Sales & Marketing
CORDENPHARMA

CordenPharma is a CDMO supporting pharmaceutical and biotechnology companies, with facilities in the United States and Europe.

In which parts of its business has CordenPharma experienced most growth over the last year?

One of the key areas of growth has been in high-potency API and drug product manufacturing, primarily to be used in oncology. We recently acquired a facility in Boulder, Colorado, from Pfizer in November 2017, which is now our second facility in Boulder to support these capabilities, since it is an area in which we see increasing demand. We are also completing an investment of > €10 million at our CordenPharma Plankstadt facility in Germany for a state-of-the-art oral solid dosage manufacturing plant. The investment has been supported by one of our key customers.

Another area of strong demand has been the injectables market, for which we continue to invest and expand our capabilities in CordenPharma Caponago (IT). This is a critical area for CordenPharma, and we expect the plant to be operational by the end of the second quarter of 2018. We are installing two high speed manufacturing lines for aseptic fill and finish of vials, prefilled syringes and lyophilized products, which will support our customers from clinical phase to commercial supply

In addition, we also completed an investment into oligonucleotide manufacturing last year at our CordenPharma Colorado facility in Boulder, CO. This is another very hot area in the industry right now, as many major pharmaceutical companies are moving towards their utilization. We expect the first oligonucleotides to be approved around mid-2018 and we are one of only a few companies to have manufacturing capabilities in this area.

How extensive is the support that CordenPharma can offer to smaller companies?

Although we work for all of the top 20 pharmaceutical companies, we also work for many of the leading biotechs, which account for about 60% of our customer portfolio. We are one of the few companies able to offer what we call an 'end-to-end' service; from the initial clinical supply, we not only produce the API but also manufacture the drug product, all the way through the value chain to commercialization.

Does the rapid rate of innovation in the industry pose a challenge?

We have to be selective in terms of which areas we want to be active in. Beyond our current areas of proficiency, there is scope for expansion into biologics. With biologics, the primary challenge is the difficulty in finding a good facility. Our business model centers on acquiring assets from big pharma that are no longer of interest to them and turn them into contract manufacturing facilities. With biologics, it is difficult to find good assets at a reasonable price that also have the potential to become multi-purpose facilities.

The deadline for serialization requirements is just around the corner. With the challenges involved, what does this mean for CordenPharma?

We have three sites that are affected: one site is completely ready, the second is partly ready and the third will be ready by mid-2018. A primary challenge with serialization is that there is no harmonized system readily available, with different countries having different requirements. For us, it has been slightly easier than for other companies as we only have drug product facilities in two countries, but of course we supply to a wide global market – one of our facilities serves over 100 markets. There are no shortcuts with this process: only companies that meet these requirements will succeed in the market.

What are the next steps for CordenPharma?

Geographically speaking, we will remain focused on the United States and Europe. The critical areas going forward for capability expansion are to strengthen our technology platforms such as injectables, highly potent & oncology and peptides, oligonucleotides, lipids & carbohydrates. For our customers, overall total costs, quality and time required are the most important factors we are constantly striving to improve. This is why we will continue to focus our operations in these two markets.

Today, CordenPharma has more than 300 customers globally. All facilities serve all geographies, but our U.S. facilities are about 90% dedicated to U.S. customers, along with a few Japanese companies. In addition, we serve many U.S. customers from Europe as well. As biotechs continue to emerge, we will be on the lookout for new customers in this space. We are also trying to build a steadier customer base by focusing on the top 50 pharma companies. Since we have acquired mostly under-utilized facilities, we still have a lot of capacity available to scale-up our activities. ■

Jeff Schwegman

CEO and Founder

AB BIOTECHNOLOGIES

AB BioTechnologies was founded in 2008. What was the perceived gap in the market at the time of establishment?

Having worked in a number of large contract service companies in the pharmaceutical industry, I recognized that, while they were highly proficient in commercial scale batches, they were not nearly as strong in small-scale clinical batches. My background in lyophilization development and formulation lent itself well to providing solutions to cater to this gap in the market. There was a very strong business model to leverage around serving smaller companies. AB Biotechnologies was initially founded as a teaching and consulting provider, and gradually developed its laboratory services over an eight-year period. Two years ago, we started putting plans together for a small-scale GMP manufacturing facility.

What is the significance of AB BioTechnologies' new 23,000 square foot facility in Indiana in terms of capability and capacity expansion?

The new facility will allow AB BioTechnologies to manufacture product for human clinical trials. The existing lab meets Good Laboratory Practices (GLP) rather than Good Manufacturing Practices (GMP). However, the new facility will meet GMP requirements, allow AB BioTechnologies to supply materials for human administration. When AB BioTechnologies bought the land for the new facility, it purchased enough for a second phase of construction with oversized utilities to accommodate and support another building.

What are the next steps for AB BioTechnologies?

The first step will be to get the GMP facility up and running and to carry out all the accompanying responsibilities associated with such a substantial expansion. AB BioTechnologies is scheduled to finish its media fills by the end of this fall – such a rapid turnaround from beginning construction to completion a is almost unheard of. The facility has been built and equipped with the latest technology, enabling greater efficiency. The filling line is state-of-the-art and requires almost no human intervention. Real progress has been made in the last two years, and AB BioTechnologies intends to continue on this upward trajectory. ■

Makoto Matsukawa

SEO and Corporate Development Head

CMIC HOLDINGS CO. LTD.

Could you provide us with a brief introduction to CMIC and its background in the United States?

In 2007, CMIC acquired a manufacturing plant in New Jersey, which became CMIC CMO USA, a contract service provider for oral solid drug development and GMP manufacturing. CMIC Inc. (formerly JCL Bioassay USA) is a GLP service lab located in Chicago. CMIC's core business is the provision of services to Japanese pharmaceutical companies. CMIC is currently partnering with CRO's in the United States to strengthen ties between the Japanese and American markets. The aim is to eventually establish a CRO facility in the region.

How is the U.S. market viewed by Japanese companies such as CMIC in terms of strategic focus?

The United States has the strongest pharmaceutical market in the world and is therefore an important area of focus for any multinational pharmaceutical companies working in the industry. In December 2000, total sales revenue for Japanese pharmaceutical companies represented 60% of sales in Japan. However, in 2017, global pharmaceutical products held a 60% share of sales, with Japanese products accounting for 40%.

CMIC prides itself on its high technology capability. Could you elaborate on some of the processes and technologies in place?

Japan has many of the best quality management systems worldwide. Quality is paramount for pharmaceutical products, and the manufacturing technology used by Japanese CDMO's is often more advanced than American manufacturing systems, such as automation. CMIC Japan's CDMO facilities are highly automated and we recently invested in two fully-automated injectable production lines, one for high potency products.

In the United States and Europe, we are starting to see many continuous manufacturing systems, but primarily for relatively large batch sizes. Japanese companies, however, excel in smaller continuous manufacturing systems of 20kg or less. Also, orally disintegrating tablets (ODT) technology is very common in the Japanese market but still relatively new in the United States, offering great opportunities for paediatric and geriatric populations.

What are CMIC's main objectives in the United States over the next two years?

We are continuing to invest in our U.S. growth. In 2019, we will double the size of our manufacturing facility in New Jersey. In addition, the potential acquisition of a CMO is an area of future interest, depending on the candidate. CMIC intends to develop its business portfolio, alliances and increase opportunities in North America, which remains a key area of potential growth. ■

Packaging: Keeping up with requirements

Particularly as the sensitivity of novel drugs increases, so does the need for innovative, reliable packaging. Equally, with an increase in value, the components and systems related to the drug come under increasing pressure and scrutiny. If they fail to maintain efficacy, or if delamination occurs causing a product recall, the drug will be prevented or at least postponed from reaching the patient. "The quality and patient safety aspects of the package continue to be the most critical requirements for the packaging container," noted Nadir Lahmeur, VP sales and marketing at SGD Pharma Packaging. "As the drug products become more sophisticated, we have increased our research in understanding drug interactions with our glass containers. A highly innovative drug will not fulfil its full potential if it is stable only for a short time."

As such, SGD is working on internal treatments to further minimize the interaction between the glass and the drug product. "We can already offer the capability to siliconize the internal surface of the glass container to limit the interaction between the glass and the product as well as optimize the reconstitution of the lyo or powderproducts," continued Lahmeur. "Another area identified as a growing trend is pre-sterilized containers that come ready to fill. There is a mounting interest from the market for packaging solutions to allow companies to accelerate their development timelines by having access to sterile components from small quantities for lab studies or early clinical phases to commercial quantities for companies seeking to forego the vial washing and sterilization operations completely. To meet this market requirement, SGD has partnered with the Stevanato Group to offer SGD molded sterile vials using Stevanato's EZ Fill platform."

With an increase in specialized requirements and high technology capability often comes a tendency to outsource to companies that are particularly focused on the service in question. According to the Association for Packaging and Processing Technologies (PMMI), about one third of all processing and packaging in the pharmaceutical and medical device industries is handled by contractors. According to a 2017 paper published by the association, using contractors allows smaller batches to be run that would otherwise slow down production in-house, plus provides access to highly-specialized equipment such as blister packs and pre-filled syringes.

Regulation and compliance expertise is also a benefit brought to the table by contract packagers, particularly for smaller companies that may not have dedicated regulatory experts on their teams. With the U.S. implementation deadline for serialization lined up for November 2018, followed by Europe in February 2019, some contract service companies will likely be knocked out due to failure to implement and comply, particularly as requirements differ according to region. "One of the biggest challenges with serialization is that there are differences between individual markets and a single solution or requirement is lacking," highlighted Justin Schroeder, senior executive director – global marketing & design at PCI Pharma Services. "For example, while most markets use a 2D data matrix barcode, China uses a linear barcode which has to be both acquired and submitted through the Chinese government. PCI has intrinsic knowledge of these markets so can provide expertise to its customers and has the expansive capacity in place to be able to support these requests. We can also offer serialization as a modular service for already-finished goods."

Serialization is being put in place due to misuse issues in manufacturing. The beauty of operating in a regulated market is that these measures are enforced... It is wonderful that the industry is putting these measures in place to keep patients safe. Of course, these additional hurdles for patient safety, drug control, supply control and supply safety could cause some players to be knocked out of the market. Nevertheless, those companies that are not properly capable of keeping patients safe should not be in the marketplace at all.

- Stephan Kutzer, CEO, Alcami

Serialization is the first step towards a more integrated and universal approach to traceability, and those companies looking ahead to the next technologies will be best-placed for success in the long term. As packaging requirements for new drugs coming into the market become more demanding, companies with highly technical capabilities will see greatest demand for their services. ■

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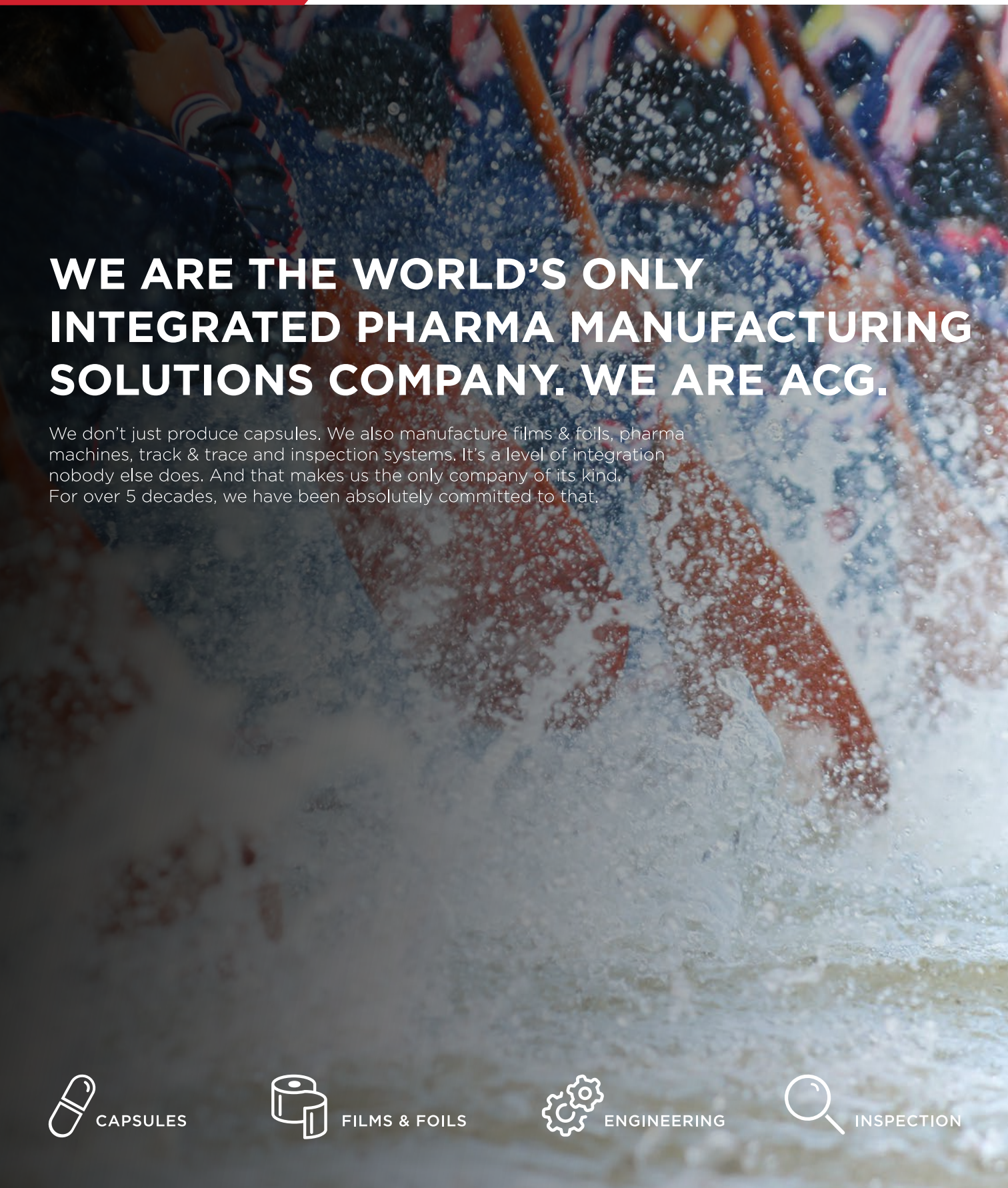

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CAPSULES

FILMS & FOILS

ENGINEERING

INSPECTION

Justin Schroeder

Senior Executive Director – Global Marketing & Design
PCI PHARMA SERVICES

PCI Pharma Services provides integrated pharmaceutical development services to the global healthcare market.

How has PCI Pharma Services expanded its capabilities and geographic presence over the past year?

We have made significant investments in the last 12 months. In October 2017, we acquired Millmount Healthcare, a contract packaging services provider based near Dublin, Ireland. This acquisition enables PCI to expand its footprint and capacity in commercial packing and helps to mitigate some of the uncertainty brought on by Brexit by maintaining a position in the European Union for product release and supply chain continuity. In addition, the acquisition has added a brand-new facility in Dublin for potent compound packaging, which bolsters our thriving potent compound manufacturing business. Adding a point of entry and release in the EU also aids our clinical trial supply business. PCI has also acquired Australian company Pharmaceutical Packaging Professionals (PPP), a provider of clinical trial supplies. PPP provides drug manufacturing, packaging and labelling, as well as storage and distribution of medicines for the Australian market and the wider Asia Pacific, expanding our capabilities in that region.

We have also made significant investments into our manufacturing capability with the expansion of the award-winning center-of-excellence in Tredegar, United Kingdom. We also added a Xcelodose system for both potent and non-potent drug-in-capsule products for early phase studies to help expedite drug development activities. In addition, we have expanded our onsite analytical capability and capacity to help clients expedite drug development activities. We have also bolstered our breadth of manufacturing capabilities to include roller compaction technologies. In the United States, PCI has made significant internal investment into new equipment to expand capacity. Our Philadelphia site has significantly expanded onsite cold chain storage (refrigerated storage at 2oC to 8oC) and we have invested in frozen and cryogenic storage in the United States and United Kingdom. PCI can offer storage temperatures from controlled room down to -196oC.

How are requirements for serialization affecting PCI, particularly across different geographies?

PCI was an early adopter of serialization and has been serializing products for over six years. This has been particularly important in emerging countries and is becoming a more common requirement. Although the U.S. requirement has been deferred, it will likely be put in place in November 2018. We are equipped to compliantly lead the charge. In the last year, PCI has tripled its serialization capacity in order to serialize over 90 different manufacturing lines.

What other trends are driving new products and service lines for PCI?

We are seeing a rationalization of anti-counterfeiting strategies. We are encouraging our customers to take a more comprehensive approach regarding anti-counterfeiting beyond just serialization and meeting minimum regulation. This is set to become a differentiator in the future. The problem may still be regarded as small in the United States, but there remain significant examples where people have lost their lives, particularly since the products that are attractive to counterfeiters tend to be more critical, high-value medicines. Value over volume is another trend we are catering to. We have to adapt to the New Normal in the market through the presence of orphan drugs and unique high potent medicines. These more specialized and higher-value medicines require greater diligence and care and an appropriate supply chain to maximize yields. PCI has therefore invested in new, more flexible and change-over friendly equipment which allows servicing of more modest patient populations. Clinical trials are another area of focus. In response to some customers finding themselves in dire situations and in desperate need of a particularly fast service, we have launched our PCIFast-Track™ offering.

What are some of the more pronounced requirements of smaller companies with single- or few-product pipelines?

These small emerging pharmaceutical companies we see entering the market with maybe only one therapy in the pipeline need a lot of help bringing their product to market. The most pressing issue for these companies is funding. They live between capital cycles so finances must be carefully managed. Clinical trial results have a significant effect and can result in dissolution if unfavorable. We are able to service these small companies from first in-human clinical studies all the way through to commercial launch and ongoing supply, providing scalable solutions as they grow. Even if these companies are bought by a larger company, since PCI is the preferred partner for 19 of the top 20 pharmaceutical companies globally, we can provide continuity in instances where the supply chain may otherwise experience disruption. ■

Nadir Lahmeur

VP Sales and Marketing
SGD PHARMA PACKAGING

As SGD's Division of the Americas, where does SGD Pharma Packaging fit within the context of the wider company?

SGD Pharma Packaging manages all the sales, marketing, technical support and logistic operations of SGD in the Americas. Within the United States and Canada, we operate out of our office in New York City, whereas in Latin America we partner with strong local partners. We have a presence in all of the major markets, including Brazil, Mexico, Colombia, Chili, Peru, Ecuador and Argentina. North America is one of SGD's most strategic markets, because of its strong pharmaceutical industry . The United States accounts for roughly 50% of the global pharmaceutical market, so many pharma companies choose to implement their research divisions and manufacturing operations here. We estimate that about 60% of our global sales end up in finished products in the U.S. market, even though they are not filled in the United States. Many of our European customers fill products in Europe and export them to the United States. SGD Pharma Packaging therefore also offers dedicated support to the U.S. divisions of these clients with supply coordination and regulatory assistance.

Are there any particular trends or preference for certain product lines that have been observed?

The quality and patient safety aspects of the package continue to be the most critical requirements for the packaging container. As the drug products become more sophisticated, we have increased our research in understanding drug interactions with our glass containers. A highly innovative drug will not fulfil its full potential if it is stable only for a short time. SGD is working on internal treatments to further minimize the interaction between the glass and the drug product. We can already offer the capability to siliconize the internal surface of the glass container to limit the interaction between the glass and the product as well as optimize the reconstitution of the lyo or powderproducts.

Container closure integrity is another strategic focus for pharmaceutical companies, as it can impact the sterility of the drug product. To meet the ever-increasing client requirements in this area, SGD has made significant investments in highly sophisticated on-line inspection equipment to control all neck defects that could lead to seal integrity issues with the closure. ■

Mark Florez

Product Manager –
Business Development and Marketing
CLARIANT HEALTHCARE PACKAGING

Clariant is widely known as a specialty chemicals company. Where does the packaging segment fit into the wider business?

The healthcare packaging arm of Clariant is dedicated to manufacturing, designing and marketing a full line of protective packaging solutions for a wide range of healthcare applications, which includes pharmaceuticals, diagnostics, medical devices, nutraceuticals, health supplements and dietary supplements. All of our products have some level of protection built in to preserve the product throughout its shelf life. Often, it is an active agent, which could be a desiccant or oxygen scavenger in a form to be dropped into a container, such as a canister or packet. Otherwise, it could be a component of the packaging system, such as a closure, or the entire container closure system, with either an active agent or a passive barrier to yield the protective properties that are needed for a particular application.

Clariant Healthcare Packaging has five plants around the world. We have a major manufacturing facility here in the United States in New Mexico and others in France, China and a new site in India. We do not necessarily produce every line of products at each plant, but we do have a certain amount of redundancy at each site. We get more and more requests from the market for business continuity planning, so we have this built in to our supply chain. All of our sites are ISO: 15378 compliant, which certifies that we maintain GMP standards for the production of primary pharmaceutical packaging.

Are there any notable new technologies recently launched, such as Clariant's EQIUS brand?

Although we have had this technology for some time, this is somewhat of a new launch for us. We now offer a full range of configurations, which we have grouped under an umbrella brand, EQIUS. This product helps to maintain a specific relative humidity inside the packaging. The vast majority of drug products that require desiccation should be kept in a very dry environment inside the package – this is a requirement for most formulations. However, there are some applications in which the drug product must not be too dry. With gelatin capsules for example, excess humidity may cause drug degradation, whilst an environment that is too dry could introduce brittleness to the capsule itself. EQIUS maintains a specific relative humidity within the package – 20% is ideal for many applications. Clariant is a very innovative company with a full innovation team dedicated to the healthcare packaging business line. We have three R&D centers: one in the United States, one in France and the other in China. Drugs continue to become more sophisticated and more sensitive. We continue to investigate what is needed in the market and what customers are demanding. ■

External innovation: outsourcing research

In response to rising pressure to identify new drugs and competition from generics along-side increasing R&D costs, outsourcing of research is increasingly common. Grand View Research expects the global healthcare Contract Research Organization (CRO) industry to reach US$45.2 billion by 2022, highlighting stringent timelines as a key driver for increased demand for outsourcing of research activities. Universities are also benefitting from this trend, more able now than ever to collaborate with industry and eager to have the opportunity to commercialize research.

Covance, a global leader in the CRO field, worked on all of the top 50 best-selling drugs available today through its full spectrum of nonclinical, clinical and commercialization services. Today, the company acts as LabCorp's drug development arm since the acquisition in 2015. LabCorp, now the world's leading healthcare diagnostics company, acquired assets of Mount Sinai's Clinical Outreach Laboratories, giving more direct access to the New York metro market health system in January 2017.

QuintilesIMS, formed through the merger of Quintiles and IMS Health in October 2016 is now IQVIA as of November 2017. The company's extensive service offering is a prime example of capability integration, spanning healthcare information, technology and service solutions, with the intent to drive efficiencies and insights across the entire life sciences product lifecy-cle, from R&D through commercial execution to real-world patient outcomes. Following the trend for integration, inVentiv Health's business model is built around a CRO combined with a global Contract Commercial Organization (CCO). In the past five years, inVentiv Health has helped to develop or

> "Big pharma still tends towards carrying out processes internally as much as possible. In biologics, there are many patents surrounding various technologies and advancement is rapid. As a highly IP-protected space, large pharma companies feel more comfortable having exclusive access to these technologies, which restricts them to internal use. For this reason, big pharma companies tend to build out their internal capabilities. However, this has begun to change in the last few years, particularly as patents have begun to expire or some non-patented alternative technologies are finding acceptance. Biosimilars are also changing the landscape, which has opened up space for outsourcing. The general environment has therefore become more conducive to outsourcing, even by large pharma."
>
> **- JB Gupta, CSO, GVK BIO and Member, Board of Directors, Aragen**

commercialize 81% of novel new drugs and 79% of novel new oncology drugs approved by the FDA, as well as 70% approved by the EMA.

Whilst the advantages of different geographies may make some contract service organizations more attractive to their partners, proximity remains important for others and valued by clients in some cases. In the CRO space, for example, proximity can be hugely important when dealing with biospecimens and patient samples. "In the last 10 years, there has been a greater demand for more information about the patient, and more rapid access to the sample," explained Luke Doiron, CCO at Alabama-based Conversant Bio, which was formed in response to an announcement by the National Cancer Institute that the number-one impediment to the discovery of new drugs was the lack of well-annotated specimens. "Our ability to collect blood samples at a particular point in time, at a particular point in treatment, from a particular patient, is unique. The capability stems from having access to medical records that enable us to find the right patients. Similarly to how CRO's might recruit patients to participate in a drug study, we recruit patients to participate in a blood-collection-only study. As well as being able to carry out overnight delivery in the United States, we also work to ensure that same availability in the other regions that we service."

> "The disadvantage of commercial research, especially in the United States, is the lack of major universities with both clinical capabilities and research capabilities in the same place...Custom procurement and sample processing requires the unique combination of a big clinical center and a research center next to it. Some of our most complex projects are carried out overseas because we need centralized locations to attract patients with rare indications or select patients with difficult criteria – we need a strong patient flow. No single hospital in the San Francisco Bay Area would have sufficient patients for an oncology study. We try to fuse the patient presence with the capability of the center, the presence of the science and the availability of the right scientific talent.
>
> **- Olga Potapova, Founder and CEO, Cureline**

Conversant Bio plans to expand its cell-based services and conduct biospecimen analysis on behalf of its customers, providing those insights as part of an integrated service.

Just as large pharma companies are looking to universities for early-stage research, CROs are also benefitting from increased interest as the rate of technological change only increases, meaning that companies are more challenged to keep up. At the other end of the spectrum, many small biotechs are choosing to remain virtual or lack the capital to invest in more extensive infrastructure. CROs are therefore well positioned for growth going forward. ■

Olga Potapova

Founder and CEO
CURELINE

Cureline, Inc., is a global commercial biobank and human biospecimen CRO.

Founded almost 15 years ago, Cureline operates globally. How extensive is the company's reach and scope of services?
Cureline became a global fusion CRO growing from a simple tissue procurement group. The company originated in 2003 from SUGEN, based on our expertise in translational medicine and biomarker development programs. When Pharmacia and SUGEN were purchased by Pfizer in 2002, we decided that this service might be of interest to other companies. Sure enough, we were encouraged by several San Francisco Bay area biotech companies to start the business. In July 2003, we incorporated Cureline Inc., and in September we signed our first project with Genentech. We continued that protocol for about a year and a half.

We started a histology laboratory in 2008 to complement our services in tissue processing, and acquired majority shares in a glycoproteomics startup Biocrypton in 2014. The core expertise remains human biospecimen procurement and processing. In 15 years of existence, we have distributed approximately half-a-million high quality human samples, enrolling tens of thousands of patients in these studies. With the addition of the histology laboratory, we added an analysis component. We also have a molecular laboratory, which enables us to study DNA-RNA-proteins and cell-free DNA; we provide services in cell culture and tissue culture and have a specific section for immuno-oncology services.

Having initially focused on the oncology space, how diverse is Cureline's client portfolio today?
The company's initial oncology focus stemmed from the team's expertise. We now work in all major therapeutic areas, including inflammatory conditions and autoimmune disorders, cardiovascular diseases, metabolic conditions, infectious diseases and HIV, and other areas.

What challenges does Cureline face in bridging several segments of the industry?
The disadvantage of commercial research, especially in the United States, is the lack of collaborative enthusiasm from major universities that have both clinical capabilities and research capabilities in the same place. It is very difficult to find a clinical center next to a research laboratory unless the clinical center is part of the university campus. Whilst hospitals have samples, they only have the clinical laboratory, which cannot handle specialized services like those in immuno-oncology – their focus is to provide specimen analysis for clinical diagnostics and patient evaluation. Custom procurement and sample processing requires the unique combination of a big clinical center and a research center next to it. Some of our most complex projects are carried out overseas because we need centralized locations to attract patients with rare indications or select patients with difficult criteria – we need a strong patient flow. No single non-university hospital in the San Francisco Bay area would have sufficient number of patients for an oncology study in a provided timeframe. We try to fuse the patient presence with the capability of the center, the presence of the science and the availability of the right scientific talent. We are bringing cutting-edge science to hospitals, and encouraging big clinical centers and research labs next to them to collaborate, establish biobanks, participate in international consortiums, to provide their research and medical professionals and students the ability to be a part of world-class research.

While universities may be placing greater emphasis on real-world applications, their strength lies in research. They are funded to provide world-class research and data, and they are well-equipped for this. Collaborations are good, but a scientific laboratory cannot become a CRO. Recently, some US universities explored an idea to start biobanks with a commercial focus for internal and external researchers. However, they soon ceased this activity when they realized they could not run the core facility as a business without sufficient funds and workforce and lack of marketable interest. Universities are a place to develop new technologies, and pharmaceutical companies are a place to develop products – they need each other, but should not try to replace each other. CROs are a bridge between clinical and research sites and pharma companies.

What are Cureline's plans going forward?
The space we are in is quite fragmented and we are seeing a number of consolidations. We are interested in partnering with companies and combining strengths. We are very unique in our combination of clinical and research capacity, and our range of capabilities extends beyond what any other company can do. Outsourcing is a great model. Our job is to make sure that we bring the best hospital capabilities together with the best research center capabilities. ■

J. B. Gupta

CSO, GVK BIO and Member, Board of Directors
ARAGEN

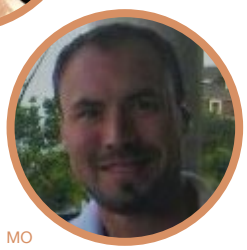
What have been the major developments at Aragen since its acquisition by GVK BIO?
GVK BIO acquired Aragen in 2014 and took full control in 2016. At the time of acquisition, Aragen was focused mainly in the West Coast area. Since GVK came on board, as a global company with a global client base and therefore global aspirations, the sales and marketing team has been strengthened.
Aragen's core capabilities are within two areas: one is the biologics drug discovery side, comprising antibody discovery, protein production and cell line development. The second pillar is preclinical efficacy testing, which involves animal testing.

Could you elaborate on any recent expansions into new service areas?
Our focus is on strengthening the infrastructure and services offering. Our vivarium was at a distant location and in a very old building. We relocated the vivarium close to our current site, and converted it into a state-of-the-art facility. We are also upgrading our Wood View facility for biologics and altogether, will now operate over 40,000 square feet. We have also improved our technology capabilities. We re-engineered the entire cell line development process. We have integrated our process with one of the leading manufacturers on the West Coast and reduced cell line development timelines from 10 months to six months, and increased titers from 1 - 2g/l to 3 – 5 g/l. We have recently partnered with Horizon to license their CHO-GS cell line and now we are providing those services as well.
We have also expanded within protein analytics having realized that while most of our customers understand molecules very well; they need more support for protein and antibody characterization. ■

Dr. Peng Jiao & Michael Osborne

PJ: CEO
MO: Director – Business Development,
BOSTON INSTITUTE OF BIOTECHNOLOGY

PJ



MO

How extensive is the Boston Institute of Biotechnology's service portfolio and involvement in the Massachusetts life sciences sector?
As a CRDO, we provide research and development services on clinical drug projects, specializing in microbial fermentation and mammalian cell culture processes. We offer a truly full-spectrum range of services. On the microbial side, we could start with the strain development and on the mammalian side cell-line development. The clear differentiator from our team versus almost any other team globally is our process characterization and in-depth studies. The institute was founded in 2015 by Dr. Peng Jiao, and the laboratories became fully functional and operational in the Spring of 2016. Our Shanghai facility opened in August 2017 and we began manufacturing in December 2017 as a CDMO.

How is the Boston Institute of Biotechnology's client portfolio segmented in line with its capabilities?
We have a 6,000 square foot facility and work across the spectrum of large multinational organizations and small biopharmaceutical and biotechnology companies, down to virtual VC-backed companies.

In what ways will the institute's operations in the United States and China complement each other?
A lot of organizations in China and in Asia at large are also looking to make big plays in the United States. The cost of development and manufacturing is approximately 40% to 50% less than in the United States. This alone clearly demonstrates why some U.S. companies might choose to partner with us on some initiatives overseas.

What are the priorities for the institute moving forward?
In the United States, the expectation is that we will acquire an existing facility that was previously managed by a CMO, so we are currently scouting locations. We are confident that we can get the facility up and running within 12 to 18 months. ■

Image courtesy of UPS

Supply Chain, Distribution and Logistics

"Third-party logistics providers will be challenged more and more to keep pace as healthcare and life science businesses continue to develop new treatments, clinical trials increasingly become multi-regional, and healthcare delivery models continue to evolve. In today's dynamic marketplace, healthcare companies and supply chain providers have vast opportunities for collaboration to gain cost savings while improving the quality of lives for populations globally."

- Dirk van Peteghem,
Vice President of Global Healthcare Strategy,
UPS

From Factory to Patient: Distribution and logistics

The logistics space has become highly consolidated, with key players such as DHL, UPS and Fedex continuing to make acquisitions. Even more consolidated is the distribution and wholesale industry, with Amerisource Bergen, Cardinal Health and McKesson Corporation accounting for over 80% of drug distribution revenue in the United States. Other players include Morris & Dickson, H.D. Smith, Smith Drug and Rochester Drug Cooperative. The HDA Factbook for 2016 to 2017 marks an increase in sales through pharmaceutical distributors by 16% from US$349.9 billion in 2014 to US$407.6 billion in 2015. The report cites continued growth of specialty pharmaceuticals as the driver for this growth, alongside distributors capturing a greater share of chain drug store sales, also claiming that 94% of all U.S. pharmaceutical sales volume came to the market through pharmaceutical distributors.

In light of increased M&A activity in the life sciences industry, the role of logistics providers in managing supply chains is critical. "M&A activity is incredibly disruptive," commented Scott Cubbler, COO life sciences & healthcare, global, DHL Supply Chain. "It is our responsibility to help customers fix their supply chains given the new product portfolio that they have either created or divested themselves of. Often, this means changing the footprint or location of the company's distribution services. We can help companies to reach synergies much faster because of our experience in helping companies integrate new product lines and new facilities into their operations and supply chains. Some companies make an acquisition and end up with redundant supply chains, perhaps with two facilities with similar capabilities in the same state. We can help those companies consolidate those operations and optimize the cost structure. Between our solutions design team, our real estate team and operations group, we have a full suite of tools that can help our customers to eliminate those redundancies, reduce or increase footprints when needed and get them to a stable supply chain platform as quickly as possible."

As the market continues to move towards higher-value products, technology requirements regarding their handling are also increasing. Temperature and time sensitivity are two main factors coming into play with delivery. According to Pharmaceutical Commerce's Biopharma Cold Chain Sourcebook, cold chain will rise from representing 19% of a US$12.6-billion industry to 22% of a US$93.8-billion industry by 2020, valued at US$16.7 billion. The bulk of spending is expected to be on refrigerated products at 2°C to 8°C.

Referencing the need to adapt to these market trends, Cubbler noted: "The wholesale models that have been traditionally dominant in the United States can no longer be relied upon. There has been a significant shift in the way these products are handled, the way they are shipped and delivered, and

Image courtesy of UPS

where they are delivered. We are putting a lot of our creativity and solution-design efforts into improving those temperature control hand-offs and the way products get delivered, ensuring there are better options out there."

In response, DHL is driving direct-to-patient and direct-to-pharmacy initiatives,

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Cold chain packaging and shipping trends continue to evolve, as pharmaceutical and life science organizations increasingly move toward more secure temperature-sensitive shipping solutions, particularly during last-mile transportation... An increased number of pharmaceutical companies are also innovating and collaborating with 3PLs to create better efficiencies, de-bulk shipments and reduce dimensional weight costs.

- Dirk van Peteghem, vice president of global healthcare strategy, UPS

Robyn Frisch, Matt Thiel & Charles Dods

RF: Founder and CEO
MT: President
CD: Executive Vice President
ROCHEM

Rochem is a global leader in developing, sourcing and supplying pharmaceutical, food, nutritional and animal health ingredients of Chinese origin.

RF

MT

CD

What have been some of the largest focus areas for investment over the last 12 months?

MT: We have made good progress over the past year in moving products from R&D development into the approval stages. We have seen a good uptick in the number of FDA inspections that we have been hosting because of that activity – getting out of the R&D file stages and getting to the point where customers are actually referencing Drug Master Files from our development investments and are now waiting for approvals. The next key step is having regulatory authorities both from Europe and the United States coming in and approving facilities as a part of reviewing the API or finished dosage dossier that has been filed.

CD: Our primary focus is on pursuing challenging and complex molecules, whether that be fermentation on a large scale or complex peptides.

In bridging the gap between China and the United States, what are some of the primary challenges?

MT: There is a heightened awareness across many executives within China about how seriously they have to take GMP compliance. When stories of falsification and data destruction lead to manufacturers both in China and India getting warning letters, people take notice – these companies immediately receive negative publicity and are restricted from doing business in the United States. As well as the embarrassment, there is a major financial impact on the business. Well-known names thought to have solid compliance procedures have been caught up in this heightened scrutiny. Rochem is well positioned to meet regulatory requirements, as our inspections have shown.

Do you see your client base moving away from single-sourcing in order to mitigate risk?

MT: Many companies are moving away from single-sourcing, but this is difficult to do when very niche APIs are required. The cost to deal with alternate sources is very high. However, in many other commodity areas requiring mainstay APIs, such as nutritional products, we see the multisourcing trend continue.

Rochem works with a large number of Chinese manufactures – what do you look for in a partner?

RF: Quality control is extremely important, especially due to stringent regulatory requirements, so having our own in-house regulatory compliance team adds great value when selecting the right partners in China. It is important to be very selective and identify, train and coach the right partners and bring them to the right level to support our customers' needs. The zero-tolerance policy of China's EPA will continue and only get stricter. Pharmaceutical and chemical companies, in large part the focus of the government, are expected to move out of the cities and into industrial parks. This will definitely cause delay in supply, but will bring benefit in the longer-term.

MT: Businesses must also be well financed. It will otherwise be very difficult for companies to invest in the things they need from a human resource and hardware standpoint. The right mentality at the top management level is also critical in implementing strict regulatory practices to ensure a compliant business.

As more companies establish their own bases in China, do you see increasing levels of competition?

MT: Many pharmaceutical companies are trying to open or establish offices in China and build their own expertise. Some companies are even trying to take finished dosage formulations into the Chinese market now as part of their long-term strategy and will likely continue to develop that capability. We have positioned ourselves as one of the leaders with strong technological expertise on the ground in China. Even large companies with their own offices in China still work with us because we have been the regulatory compliance arm that has helped build our Chinese suppliers – we have earned that protection and respect from our manufacturing partners. As the world gets smaller and smaller and communication gets easier, we will continue to see increasing competition, but we maintain a strong advantage with our established partnerships and experience.

What are the next areas of focus for Rochem?

RF: We are determined to grow our generics line for animal health and human health. We plan to continue to diversify our market presence, stepping from North America and Europe into the South American market as it becomes more regulated. ■

> In terms of data storage, blockchain technology is an area of great interest to Antares Vision and the industry as a whole. Serialization will create critical information, and blockchain presents an interesting platform to manage that data.
>
> **- Emidio Zorzella, CEO, Antares Vision**

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pivoting on the patient-centric approaches now commonly influencing drug development.

Digitization of supply chains and greater use of analytics is helping to drive efficiencies in supply chain management, while serialization and blockchain are greatly contributing to supply chain visibility. According to UL, an estimated 10% of all medicines and high-tech products sold worldwide are counterfeits. Although serialization requirements have been postponed in the United States, they are expected to be put in place by mid-2018, posing a challenge to many companies that have been slow in implementation or lack the investment capability. Serialization is also just the first step towards the goal of transparency and traceability. "Serialization is only a serial number on a product, but many other elements must be considered – control, weight, how it has been handled, where it has been stored and at which temperature," emphasized Emidio Zorzella, CEO & co-founder at Antares Vision, a provider of serialization-based track and trace solutions. "One of the big trends is implementation of technology to generate and analyze more data. To leverage this opportunity, a large investment must be made and new architecture and infrastructure must be created. Due to regulatory requirements, companies will have to implement an infrastructure to connect the digital world with the physical world. Generated information will be applied in two directions – first, backwards, looking at the efficiency of the production environment and back to the raw materials; on the other side, greater visibility will be given to the supply chain, following distribution up to the pharmacy and the consumer."

Antares Vision's platforms include the recently-launched ATS4 and tools such as Avionics, a control panel focused on production efficiency and Follow For me, which follows the life of a product along the supply chain.

Emphasis on supply chain visibility and tracking measures will only increase as drugs become higher in value and more steps are taken to mitigate any sort of risk that could lead to disruption and loss of revenue. Logistics companies are therefore constantly innovating and adapting to ensure ultimate reliability, flexibility and effectiveness. ■

Scott Cubbler

COO Life Sciences & Healthcare, Global
DHL SUPPLY CHAIN

DHL Supply Chain is the Americas' leader in contract logistics and part of Deutsche Post DHL Group, headquartered in Germany.

How is DHL Supply Chain progressing along the lines of its 2020 strategy?
Our Strategy 2020 focuses on three main pillars: Focus, Connect and Grow. "Focus" drives our operational and quality excellence, plus best practices and global standardization. "Connect" centers around bringing together customers and industry experts and sharing information and best practices to drive better solutions and collaboration across the globe. "Grow" is providing new services that are in demand to make our customers more successful. We have a banner in each life sciences facility, which reads "Improving lives one case at a time." This statement reminds us that the key initiatives within Strategy 2020 are ultimately designed to help the industry improve patient outcomes. We continue to be the fastest-growing sector within DHL Supply Chain, which we take as a sign that our customers value the services we provide.

DHL Supply Chain operates across different stages of a drug life cycle. How extensive is DHL's service offering?
One of our key growth areas is the clinical trials segment of the industry, so we have a global network to provide clinical trial distribution services to our customers. Beyond that, warehousing and distribution is the bulk of the work that we do. We also provide transportation management solutions, from individual truck loads and deliveries to lead logistics provider (LLP) services. In addition, we provide serialization services for our customers, and offer last-mile delivery of medicines to pharmacies and hospitals. Other areas where DHL Supply Chain is growing include secondary packaging.

How is DHL Supply Chain adapting to the shift towards higher-value drugs?
Our direct-to-patient and direct-to-pharmacy initiatives are all in reaction to the changes from volume to value, and what we refer to as a shift to a patient-centric approach to drug development. These products tend to be a lot more temperature-sensitive and time-sensitive in terms of delivery. The wholesale models that have been traditionally dominant in the United States can no longer be relied upon. There has been a significant shift in the way these products are handled, the way they are shipped and delivered, and where they are delivered.

M&A activity remains on the rise – has this led to a consolidation in DHL Supply Chain's customer base?
M&A activity is incredibly disruptive. It is our responsibility to help customers fix their supply chains given the new product portfolio that they have either created or divested themselves of. Often, this means changing the footprint or location of the company's distribution services. We can help companies to reach synergies much faster because of our experience in helping companies integrate new product lines and new facilities into their operations and supply chains.

In what ways is DHL Supply Chain embracing digitalization to improve its logistics solutions?
We have a very aggressive digitalization strategy. This means using analytics, data and technology in a lot of different ways that can make us much more efficient, provide much better visibility of information and improve decision-making processes. Blockchain, for example, is an incredibly complicated offering. We have recently partnered with Accenture to develop an approach to improve serialization requirements and eliminate counterfeit drugs and any kind of tampering within the supply chain.
Driving these new technologies offers many advantages, both to DHL Supply Chain in terms of improving operations and driving productivity and to our customers, by providing better information and enabling them to make better decisions in areas such as inventory levels and ordering patterns. In one of our customer's facilities in Memphis, we have recently been piloting the use of automated robots, which have improved productivity by nearly 80% and helped integrate a new product line that our customer acquired. It is our responsibility in this space to drive these uses of technology in order to reduce overall costs and drive productivity, allowing our customers to focus their resources and energy on developing new drugs that will save lives and improve patient health.

What are the next steps for DHL Supply Chain in the healthcare space?
First and foremost, we will focus on the three pillars in our Strategy 2020. We strive to be number one in our quality management systems and performance, and drive operational excellence through standardization and best practices. ■

Dirk van Peteghem

Vice President of
Global Healthcare Strategy
UPS

Founded in 1907 in the United States, UPS is a leading global provider of specialized transportation and logistics services.

Could you start with a brief update on UPS' healthcare logistics division?

Healthcare continues to be a fast-growing sector and a top-tier priority for UPS. As more pharmaceutical and biopharma manufacturers look to outsource supply chain operations to reliable 3PLs, UPS knows that having a nimble, scalable and integrated global supply chain is critical to meet demands of the healthcare and life science sectors. Manufacturers and clinical organizations are relying more on companies like UPS that have extensive logistics experience, regulatory expertise, and cold-chain capabilities – in addition to value-added services. We will continue to make the right investments for timely, secure transportation and storage of sensitive, high-value products, including lab specimens and other time-and temperature-sensitive goods. These are the types of services healthcare and life science companies rely on as therapies become increasingly sensitive, sophisticated and valuable.

What is the significance of UPS' recent acquisition of Marken to its clinical trial logistics services?

Marken is the clinical supply chain subsidiary of UPS and is the global leader in providing patient-centric supply chain solutions for the life science industry. It was recently announced that Marken launched a new service allowing nurses to drop off clinical trial samples at UPS Store locations within the United States. This expanded service is a direct result of the exponential growth of home-based clinical trials in the past few years. Marken worked closely with UPS to set up the unique service, which provides patients and nurses greater flexibility for home care during clinical trials. Other developments include the launch of a hybrid service that enables the booking of Marken shipments in its proprietary Maestro operating system, managing them from origin to destination, while using the UPS network in a seamlessly effective manner. The service provides more flight options and integrated tracking to and from major airports. At the same time, Marken draws on UPS's experience with temperature-sensitive transportation which, when combined with Marken's experience with clinical trials, forms a powerful combination. Marken expanded its geographic reach and product portfolio in 2017, including announcements of new locations in Stuttgart, Germany; Shanghai, China; and Ahmedabad, India.

How does UPS incorporate technology in its healthcare packaging service offerings?

UPS constantly innovates and implements new technologies. As a matter of fact, we are finalizing the launch in 2018 of a new, innovative packaging service for healthcare and life science customers. Through UPS's package design and test lab, our engineers put packages through rigorous testing to make sure they hold up to real-world conditions, from heat and humidity to impact and vibration. UPS also has done extensive mapping studies of our shipping lanes during the coldest and warmest parts of the year to create a comprehensive set of systematic ambient temperature profiles. This data help our engineers identify the most appropriate packaging for items such as biologics and specimens to help prevent damage and spoilage, remain within required temperature range, and ensure critical healthcare products get where they need to be to do what they are intended — improve the quality of lives. Our high-tech package testing facility is one of fewer than 400 labs worldwide certified by the International Safe Transit Association (ISTA), and is ap¬proved by the National Motor Freight Traffic Association (NMFTA).

Do you have a final message regarding UPS's overall outlook on the industry?

The increase of temperature-sensitive pharmaceuticals and biologics entering the global marketplace is changing the game on how products are packaged, stored and shipped. Also, enhanced technologies (think 3D printing and cryogenics) and patient-centric trends (think kidney dialysis and cancer screenings performed in the home setting) are shifting the status quo. Third-party logistics providers will be challenged more and more to keep pace as healthcare and life science businesses continue to develop new treatments, clinical trials increasingly become multi-regional, and healthcare delivery models continue to evolve. In today's dynamic marketplace, healthcare companies and supply chain providers have vast opportunities for collaboration to gain cost savings while improving the quality of lives for populations globally. A healthcare product's journey is equally as important as its destination. As the industry continues to innovate, so too must logistics providers in order to provide best-in-class supply chain solutions that ensure product integrity and safety. ■

Dwight Mutchler

Strategic Manager
IMCD US PHARMA AND IMCD PUERTO RICO
(previous owner of Mutchler Inc. Pharmaceutical Ingredients)

IMCD US Pharma supplies a comprehensive range of excipients, API's, specialty solvents, process chemicals and intermediates for formulation and chemical synthesis.

IMCD is historically a distributor of specialty chemicals. Could you outline the company's growth in the pharmaceutical industry?

IMCD's pharmaceutical business unit is probably the business unit with the most global coverage. However, until relatively recently, IMCD was absent from North America's pharmaceutical segment – the most important market in terms of consumption, manufacturing and development. In 2015, IMCD bought Select Chemie Brazil, a European company with a significant presence in Brazil, focusing on APIs. IMCD then approached Mutchler Inc. in North America, which had been around for 71 years. Originally a general-chemical distributor, Mutchler had transformed over the years into a pharmaceutical ingredients company, addressing a large unmet need for distribution solely focusing on specialty and high-performance excipients for final dosage manufacturing. Distributors wear many hats, and they often struggle to meet the regulatory requirements as well as the quality and supply chain compliance levels necessary within the pharma industry. Many companies run away from the high-level of service required by the pharmaceutical industry, where orders tend to be slow in coming and smaller in volume. This created a gap in the market that Mutchler decided to fill.

Now IMCD Pharma, Mutchler was originally founded in New Jersey before opening another base in Puerto Rico, which was one the largest concentrations of pharmaceutical manufacturer in the world. We used Puerto Rico as a logistical hub to develop that attracted the best portfolio of suppliers in the industry. Many of these relationships migrated with us to the U.S. mainland. The IMCD strategy was completely in line with Mutchler's, and the merger made perfect sense for both parties. Since IMCD acquired Mutchler in 2016, there has been robust growth and supplier continuity on a global basis. More recently, Canadian L.V. Lomas came on board. IMCD how has extensive connectivity throughout the Americas, supporting the company's strategic focus on development in this region.

Considering the industry emphasis on both quality and cost, does IMCD US Pharma tend to source from lower-cost countries or more locally?

We do not see our suppliers sourcing raw materials from lower-cost countries. Our suppliers for the most part are based in the US, Europe and Japan. They all manufacture their excipients from the highest quality materials and under strict cGMP's. We even see many companies in South and Central America seeking for cGMP U.S.- or European-produced excipients and are willing to pay a premium price. Many also buy from brokers that we sell to. When purchasing from countries with lower-cost ingredients, the supply chain can become very muddy. The distributor needs to know exactly where the goods are being shipped to, who is picking the product up and how it is being transported. IMCD is particularly strong in this regard, because it has offices all over the world.

In what ways is IMCD able to support its clients in meeting technical requirements?

IMCD Pharma has developed strong regulatory and technical support departments. We also have our Added Value Services (AVS) business unit, which includes dispensing many types and sizes of packages for production-ready excipients, following strict cGMP protocols. IMCD Pharma's goal is to integrate its value further into its suppliers' and customers' supply chains. The objective is to provide production efficiencies and to become a solid link in the supply chain rather than just simply passing on a packaged product. IMCD Pharma has an applications development lab in Cologne, Germany, which trains our sales team and explores new formulation ideas for our suppliers and customers. IMCD US Pharma has begun construction on a new applications laboratory in New Jersey scheduled to be ready by October 2018. In addition, approval has recently been granted for three more labs across the globe.

Traceability is a growing concern within the pharmaceutical industry. What measures does IMCD have in place to support a move towards greater supply chain visibility?

We are launching a brand-new state-of-the-art IT system globally throughout the company this year, which will add a lot of value to IMCD Pharma's services. We have also developed an effective sales tool, which ties all possible application and functionality aspects to excipients in our portfolio. Implementation of this software will give us even better access to information and guidance. Driving efficiency within the supply chain is of great value to IMCD's customers.

What are the next steps for IMCD Pharma?

One of our primary objectives is to take our state-of-the-art dispensing services (AVS) to the global market. The progression and application of formulation development work is another key area of focus. Global connectivity with suppliers is vital, and IMCD Pharma is proactive in growing that side of the business and constantly improving its capabilities to recognize opportunities for new applications and new products. We are true marketers. Proactive sales, marketing and value-add are the essence of effective distribution, not just moving pallets. ■

Julien Faury

Vice President – Operations
ADENTS

Adents is a provider of premier serialization solutions for unique product identification and traceability.

How has Adents progressed since its establishment in 2007?

Adents was first created to explore the new generation of serialization software. The major challenge with serialization is not the actual marking or reading of serial numbers but rather the data management expertise that backs up the serialization. Over the last years, Adents has created a solution in the form of a new software suite, which has been developed from the ground up with innovative technology and an open architecture. The first part of this software was released in 2010. This software driven serialization solution took off very quickly in the European market. The solution is not only used in the pharmaceutical sector but also in the wine and spirits, and health and beauty.

In 2012, pharmaceutical companies in the United States and Europe started to implement these processes and began to look into cloud-level solutions. Many of the vendors used by pharmaceutical companies were not well-equipped to ensure strong long-term relationships. Adents became aware of this challenge and created its own cloud-based solution for these companies, which would allow trading partners to exchange data. In order to manage this data, Adents partnered with Microsoft, a strong cloud expert, in 2014. The Adents/Microsoft co-developed cloud solution, Adents Prodigi, was released in 2017. Adents has now grown to nearly 100 employees and has onboarded numerous certified partners in current commercial markets. More than half of our customer base consists of life science companies.

In what ways are new technologies such as cloud infrastructure and blockchain likely to impact the supply chain?

Cloud architecture is the only viable method of exchanging large amounts of data between partners. Adents' task is to support its customers in making the most of the massive amounts of data collected during the serialization process. In partnership with Microsoft, we are currently bringing Artificial Intelligence capabilities into the supply chain. This allows companies to track products in the cloud, analyze the processes, and track where the product is going, or if it has been damaged.

Adents customers can take advantage of the Adents Prodigi marketplace to enrich their serialization data with additional applications. For example, businesses using cold-chain data to precisely track where the shipment is located and provide very in-depth details about the shipment, such as the product's temperature and even on the location of the product in the warehouse. With blockchain, we have some initiatives in place right now, but we believe there is still some way to go regarding chain of custody. We are still unsure what the final business case will be.

What is the significance of Adents' relationships with both Microsoft and Siemens?

The relationship with Microsoft and Siemens stemmed from the same point. Adents has an extensive understanding and knowledge of serialization and the regulations that come with it. Automation, the manufacturing of quality pieces and system integration are not core aspects of Adents' expertise. Adents therefore partnered up with Siemens to take advantage of their expertise, utilize some of their equipment to develop innovative solutions, and to utilize their network of system integrators around the world. This partnership led to a point where 2 years ago, Siemens retired their own serialization solution and included Adents solutions when they sold a serialization project. With Microsoft, Adents chose to partner up with the leader in enterprise cloud. The future of cloud are very innovative solutions like micro services and scalability. Both Microsoft and Siemens also cross sell Adents solutions.

Where does Adents see the most opportunity for serialization implementation, both in the United States and overseas?

The major hubs in the United States are the San Francisco Bay Area, the Northeast and of course Research Triangle Park. Additionally, we see a large opportunity for external manufacturing in the mid-west. The beauty of cloud solutions is that they have unlimited scalability, so we are able to work with companies of all sizes and customize our solutions according to the size of the business. Further, Colombia and Brazil are emerging markets, while Canada will adopt serialization within the next five years due to changes in regulations. Adents relies heavily on our solutions partners. Through our partner network, we are able to reach any market worldwide.

What are the upcoming milestones for Adents over the next 12 to 18 months?

We aim to capture more of the untapped customer base in Europe and the US. Additionally, it is our objective to further implement solutions for U.S. distribution and supply chain management, and also proposing new specific features for the trading partners and capture market share.

Long term, the goal is to ensure that every product will have a unique identification, becoming the most personalized way to connect brands and consumers. ■

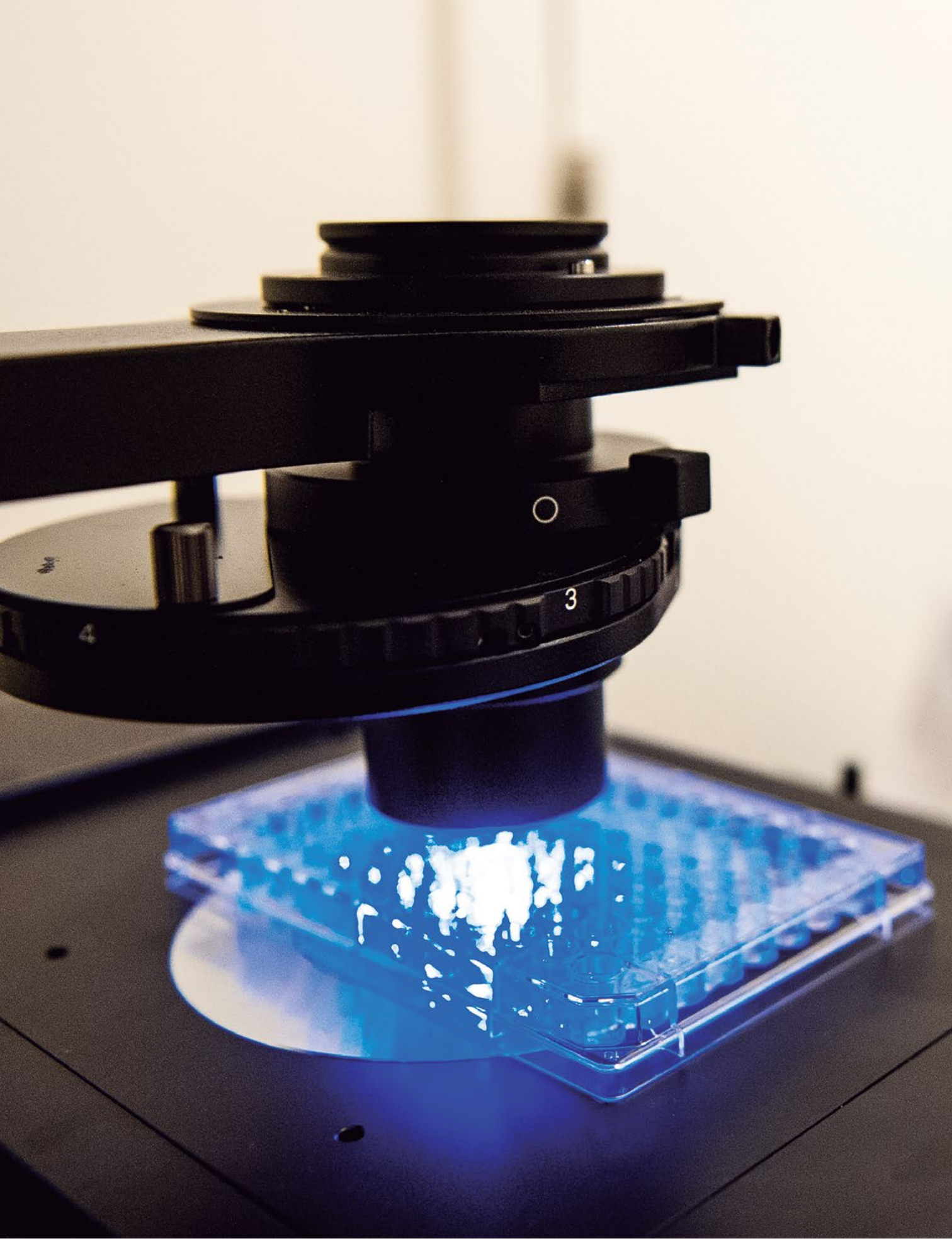

Image courtesy of Batavia

Industry Outlook

"Pharmaceutical companies setting up innovation labs are heading to Boston, San Francisco, Shanghai and London – most of the innovation will be centered around these hubs in the next few years. Data science is playing an increasing role in innovation moving forward, explaining why areas such as San Francisco and Singapore are starting to attract more life sciences organizations, offering that blend of wet lab research and technology to drive their innovation."

- Richard Harrison,
CSO,
Clarivate Analytics

The Winning Formula: Improving patient outcomes

The U.S. innovation landscape is undergoing a fundamental shift in focus away from the blockbuster models that have long been the norm. Improving patient outcomes through a deeper understanding of disease areas and better-defined addressable patient populations is revolutionizing the approach to drug discovery. By not only developing more effective treatments but also matching the right drug to the right patient, companies are reaching for a new phase of medical progress.

Nevertheless, while these new trends feed into a much more favorable environment for the treatment of diseases, the life sciences industry remains a commercial business and reimbursement models are hugely important in maintaining incentives for innovation. Therefore, as the industry moves towards more effective treatments and even cures, it is paramount that the framework evolves in conjunction. Whilst the FDA has in many instances recognized the need for addressing unmet need and accelerating approval timelines, the current U.S. healthcare system's ability to absorb some of these therapies is questionable. "What makes us nervous is the inability of the healthcare system to absorb and measure the costs of curative therapies – both short-term costs and long-term savings," highlighted Bob Coughlin, president and CEO at MassBio. "Currently, we do not have a healthcare system; we have a sick-care system. It is designed to treat chronic sickness with therapies over the life of a patient. If we are going to live in an age of cures, we need a healthcare system and a payer system that can ensure access to these breakthroughs. The way to save money in a healthcare system is by keeping people healthy and out of hospitals and having an accounting system that tracks costs avoided when new drugs come to market. The clock is ticking, and we need to continue to work together as an industry to come up with a new system, or the government will do it for us and get it wrong. We need the payer system to innovate at the same rate at which we innovate on the discovery and manufacturing side."

In response to this flaw in the system, MassBio has initiated a working group with payers and market access representatives from its member companies to continue to build value-based partnerships and other innovative methods of paying for new therapies. Coughlin added: "We are taking the argument of drugs being too expensive off the table; drugs save money by keeping people out of the hospital and actually only account

Image courtesy of Batavia

for 12% of the total cost of healthcare. Restricting access to patients is not an option, so the only solution is to find new ways to cover the costs of these drugs."

In an industry that holds the improvement of patient health and quality of life at its core, working together towards a common goal is a logical step in advancing treatment options and discovering cures. This includes dialogue across all aspects of the industry, from the commercial players to the associations in many instances acting as policy advocates and the policy makers themselves. For this reason, prominent hubs such as Boston/Cambridge and the San Francisco Bay Area will continue to flourish – with such a high concentration of activity, they will likely be the driving force behind the conversation and implementation of change. ■

Without question, outcome analysis is where the industry must become more stringent. However, we have seen problems in Europe when tenders and price controls were implemented and innovation was stifled. German chemical companies were really the foundation for modern pharmaceutical companies and yet the country's pharmaceutical presence has very much diminished. There needs to be an economic environment where companies can profit through innovation. It is likely that pharma companies will begin to price their products based on outcomes and insurance companies will pay based on success of the treatment.

- James Gale,
CEO,
Signet Healthcare Partners

California is not only the most established life sciences sector, but also has an extraordinary tech sector. Major tech companies like Google, Apple, Facebook and Fitbit are really looking at how they can make alliances in the healthcare space. Some are looking at new apps and others are looking at patient monitoring or consumer-facing ways to improve health or monitor how patients take drugs. Our nexus with the tech sector is definitely an influencing factor in driving larger companies to increase their presence here in California.

- Sara Radcliffe,
President & CEO,
California Life Sciences Association

Despite decades of medical innovation, the global prevalence of cancer continues to increase and cancer treatment remains a priority for patients, physicians and the biotechnology and pharmaceuticals industries. Novel and effective oncology products are in great demand. The oncology market may seem crowded but there remains a very real unmet need; as a result, there has been and will continue to be significant investment in the development of new anticancer therapies that benefit the lives of cancer patients.

- Christian S. Schade,
President and CEO,
Aprea Therapeutics

Rather than a shift in focus, large pharma companies are extending their capabilities across the country. It is a global industry, which has morphed to focus on collaboration between large and small companies to a much greater extent – it makes sense that companies would pursue these opportunities.

- Debbie Hart,
President & CEO,
BioNJ

Both the Bay area and Boston will be the two main centers of gravity both for venture dollars and for pharma dollars. The numbers in terms of which hub is attracting more investment are irrelevant. The density of the Boston area is very unique and San Francisco has the benefit of a larger geographic footprint. We see a lot of capital flowing into both ecosystems. It is a lot easier to recruit into Boston from the West Coast and into other areas now than it was five to ten years ago.

- Kevin Bitterman,
Partner,
Atlas Venture

There is a significant opportunity around convergence. Today, unlike ten years ago, the lines between different industry segments such as biotechnology, pharmaceuticals and medical devices are becoming much more blurred. A decade from now, we hope to be the best location in the world for all things life sciences across areas such as drug discovery, cures, combination therapies and companion diagnostics.

- Robert K. Coughlin,
President & CEO,
Massachusetts Biotechnology Council

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EDITORIAL AND MANAGEMENT TEAM

Project Director/Journalist: Catherine Howe (chowe@gbreports.com)
Project Coordinator: Neha Premjee (npremjee@gbreports.com)
Project Coordinator: Emma Johannes (emma@gbreports.com)
Journalist: Ben Cherrington (bcherrington@gbreports.com)
Editor: Mungo Smith (mungo@gbreports.com)
Designer: Gonzalo Da Cunha (gonidc@gmail.com)

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