Building The Biotech City

IS LOS ANGELES THE GO-TO HUB FOR INNOVATION?

BY WILLIAM LOONEY
Could The Gut Cure Brain Disease?
MELANIE SENIOR
Scientists now understand that there are multiple, bi-directional links between gut and brain. They are using this knowledge to develop new treatments for some of the most challenging chronic conditions, including Alzheimer’s disease, Parkinson’s disease and obesity.

A New Definition: The EU Answer To Medicines Shortages?
IAN SCHOFIELD
What is a medicines shortage? The answer may seem obvious, but the fact that European regulators have only now come up with a commonly agreed definition suggests otherwise.

MedTech Forum 2019: Building Growth In The Outcomes Era
ASHLEY YEO
The European MedTech Forum’s CEO panel set out to address high-level global, long-range issues, but from the start it got log jammed in regulatory issues. Not in the script perhaps, but wholly understandable, as new EU regulations will have huge strategic importance for how companies do business – and in the case of start-ups, if they can continue to do business.

How To Negotiate With Public Payers
WILLIAM LOONEY
In Vivo speaks to the UK branded industry’s negotiator for the latest five-year joint pricing pact with the government, Richard Torbett, who outlines, among other topics, five widely applicable precedents from the talks that can work in “getting to yes” – despite the fractious budgetary climate for health care evident in all major country markets.

Building The Biotech City: Is Los Angeles The Go-To Hub For Tomorrow’s Drug Innovations?
WILLIAM LOONEY
The complexity of producing viable drug candidates is increasing as an abundance of new science keeps extending the range of possible targets and fragmenting disease subtypes. Proximity to novel exploratory research is a driver of pipeline productivity – so can physical location within a communal geography of well-resourced intellectual firepower raise the odds for R&D success?
Summer 2019 started with a deal-making boom for the biopharma sector. In June, AbbVie announced it would acquire Botox developer Allergan for $63bn. AbbVie CEO Richard Gonzalez said repeatedly when describing the company’s rationale for buying Allergan that very little value was ascribed to the latter’s research and development pipeline. However, the pharmaceutical firms combined have 62 drugs in clinical development – with 38 in Phase II and III or awaiting regulatory approvals, including new indications for marketed products – requiring substantial ongoing investment.

Elsewhere, Gilead Sciences has agreed to a new deal worth $5.05bn with existing partner Galapagos, which will see the US firm increase its stake in the Belgian biotech. Gilead will pay $3.95bn in cash and $1.1bn for an equity investment, plus additional milestones and royalties. The deal gives Gilead access to six clinical compounds, including GLPG1690, which is in Phase III for idiopathic pulmonary fibrosis (IPF), GLPG1972 in Phase Ib for osteoarthritis and more than 20 preclinical programs as well as Galapagos’ drug discovery platform. It also gains an exclusive option to develop and commercialize all the products outside Europe.

In June, we also saw Pfizer pay $11.4bn to purchase Array BioPharma for its recently approved Braftovi/Mektovi drug combination and pipeline of targeted cancer therapies.

In a recent exclusive interview with In Vivo, which will be published in August, biotech CEO and UK Bioindustry Association board member Charlotte Casebourne commented on this trend of buying innovation. She said: “It is evident that over the last five years major pharma companies have increasingly outsourced their R&D activities. An example here would be Gilead; most of their lead products are the result of licensing deals.”

“Where companies are doing well in terms of having fresh pipelines, a lot of those products are coming from licensing deals and acquisitions. It shows how the different stakeholders within the R&D sector are capitalizing on what they are good at. For some of the bigger players, that might not necessarily be doing innovative R&D in-house,” she added. Casebourne is CEO of emerging oncology biotech, Theolytics.

Details about other recent alliances and acquisitions can be found at the back of this month’s issue in our regular “Deals Shaping The Medical Industry” column.
A larger issue is changing the cultural mind-set, by tackling up-front the myths that others in biopharma seem to have about Los Angeles. For example, I still hear from outsiders that it’s hard to recruit talent. That’s the mantra. I just smile and try to ignore it. It might have been true.”

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The possibility of shortages in a no-deal Brexit scenario is a real worry, and the UK government has produced a number of documents advising pharmaceutical companies on what to do to mitigate the risk, including building up an additional six weeks of stock over and above normal levels.

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Future medtech CEOs will have different values, digital nativity and the ability to think agile and find creative solutions to issues.

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A distinguishing feature of the UK biopharma landscape is the structured and predictable approach to managing the cost of medicines. There has been a voluntary arrangement to secure this objective since 1957. However, as globalization of supply chains and trade liberalization took hold, such an explicit connection between pricing and profits became harder to implement.  

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Around The Industry

MedTech Forum 2019: Consumers And Wellness, Or Patients And Health Care?

As health care transitions to digitally enabled wellness, medtechs will be missing a trick if they persist in holding onto the delivery, business methods and models that were the standard of the early 2000s. Heightened expectations of the new options for dealing with personal health mean that new opportunities are there for the taking – but industry shouldn’t let the tech companies have it all their own way, advised ZS principal Brian Chapman.

The MedTech Forum, Medtech Europe’s annual conference, was uprooted for the first time in its history, shifting from Brussels to Paris for 2019. The change of location worked well: by tackling the already populous event onto the back of the French industry’s annual start-ups forum (Start-up innovantes du dispositif médical or Snitem), attendee numbers swelled nicely.

And the French delegates offered fresh ideas on innovation and uptake, especially on digital innovation, as the health care and medtech worlds turn – albeit slowly – to face the new realities and opportunities of digitized health care.

The MTF has traditionally focused on market access, risk sharing, regulatory challenges and modern methods of partnering. Now it is also, inescapably, about integrating and exploiting digitization to deliver care at the right place, at the right time, and affordably. The potential for disruption to the existing model of care delivery still cannot be quantified with any accuracy, but that’s the aspiration in the sights of many stakeholders – even if the picture up ahead is still out of focus.

ZS principal Brian Chapman put his finger on the worry that most MTF delegates were probably reflecting on, but were perhaps not sure how to articulate. Speaking to In Vivo at the event (May 15-16), Chapman observed that the word “digital” had been heard hundreds of times during the conference, and yet “we’re all still trying to figure out what it means ... We don’t know which rules apply, and which don’t, and all of industry wants to know how to disrupt without disrupting.”

It is perhaps sobering to discover that, regarding digital, industry players are still trying to define it and are all grappling with its implications in health care. And this goes right to the top of organizations and to the forefront of leadership. One of the issues to factor in is, how does medtech stay true to privacy and data protection standards, with digital, that are well above traditional levels, and yet not act so conservatively at this time of change that it risks losing the opportunity ahead?

Exploiting it properly will probably call for new talent – which is arriving – and the kind of staff that are not fazed by working to unfamiliar strategies, while also being very familiar with the cutting edge of business.

NEW TALENT

The combination of digital and new talent pools is changing the industry. The medtech leaders of the future are people who want to be on the team, not just (usually) older people wanting to sell. “The threshold has been crossed, and the change is happening now. Whether it’s enough of a change remains to be seen,” said Chapman. The stakes are high though, in terms of talent retention. “If you can’t keep your team, it now starts to have economic implications.”

The new talent’s eyes do not glaze over at the mention of codes of ethics. They work increasingly to sets of ideals, transparency, ethics, openness, honesty and trust. These are top-of-the-bill considerations for the new intake of future leaders, which wasn’t so much the case as little as five years ago. These individuals are ready to take on board the potentially disruptive findings of lobby groups such as the International Consortium of Investigative Journalists (ICIJ), whose actions last year quickened medtech’s heartbeat – if only for a brief moment. The ICIJ’s weakly assembled research did not get the traction its architects evidently were seeking, other than some one-off story themes in a few, albeit upstream, European dailies. It had been anticipated that ICIJ representatives would have a big presence at MTF 2019, just as they had at medtech regulatory meetings in Brussels last fall. But if they did send any delegates, no one noticed.

ICIJ INITIATIVE – NOT A TOTAL MISSED OPPORTUNITY

Their media investigations in 2018 made more impact in Europe than in the US, where the Bleeding Edge Netflix documentary was aired, Chapman observed. But there has been some spillover into day-to-day medtech operations, with the realization that there are – probably always – ways of tightening up on compliance and transparency. Did the ICIJ initiative provide any long-term benefit? Chapman answered his own question: “I think so.” Often there has been collateral damage from such initiatives, and some areas of industry have been painted in an unfair light, he observed. “But the overall attention being paid to ensure processes are working does make sense, and if we redouble our efforts, then it has to be good.”

He added, “No one feels good about working for a company that operates on the ‘ethical edge,’ which is an important consideration when attracting new talent to a company.” It is even more important when talent is in short supply. “Feeling good about what you’re doing is something people are much more aware of now.”

The notion persists that the pharma industry is strongly regulated, and that medtech is far from comparable. It is an
unfair assumption, but one the industry has had to live with. Yet it is an advantage to have clear and unambiguous guidelines around transparency, and this new crop of staff is expected to build higher standards of responsibility, as well as ethical and environmental goals, into their working lives. They tend to think more about the worker’s – not just the consumer’s – view of business. And they are aware that they, too, are consumers, who use online naturally and feel good about doing so.

PATIENT OR CONSUMER?
If “consumer” is an underused word in health care, then it’s because “patient” is, implausibly, overused. And maybe “health care” is a term that is also getting too much mention still, when “wellness” conveys a more accurate picture of where the sector is moving to. These alternate – some might say modern – tags, reflect positive notions, and are a small world away from the current focus on sick people. Medtechs from the established world should reflect seriously on how they pitch themselves now, Chapman recommends.

The upstart competitors, Amazon, Google, Apple, etc., have opted to focus on people who are not sick. They also have an affinity with the language of the consumer. This, Chapman observed, should bring more people into the system, and will serve as the basis for longer relationships.

The implication here is that, if medtech focuses only on the patient, it is going to miss out on a huge opportunity. The word “patient” is itself part of the issue as it targets only those who are unwell, and does nothing to engender any form of business relationship outside of the clinician’s office. That was not “health care’s” business in the past century; now it should really be just that.

Chapman noted in a recent blog post for *The Pacemaker* that about five years ago, “we awakened to this new perplexing constituency called ‘the patient’ and, of course, created a slew of patient marketing, patient research, patient engagement and outreach programs in response.” This seemed right, being an industry driving to be increasingly patient-centric. But then a new hurdle popped up. It is not just semantics, but the word “patient” seems to have negative connotations, “using a narrow set of language and interactions that undermine the strategies used to engage the general public.” It’s a policy that may be harming the futures of traditional medtechs, who might have felt confident that they were creating the future, but now have to think harder.

It goes further. Payers in the US are now focusing more on wellness than on health care. A lot of this focus is on mental health (which, unaddressed, can lead to further physical problems) and nutrition. Health is being viewed more broadly than simply as the health delivery system. “Thinking about people as patients alone impedes medtech’s ability to engage with them outside of the clinical setting. They are humans 365 days, and maybe patients, say, three days.”

Chapman concluded, “It’s a mentality we have to bring into medtech, and if we don’t do it, we’ll lose out to consumer-oriented people who design products for consumers and know how to interact with them.”

NEW LEADERSHIP
This would chime perfectly with the new generation’s view of necessary leadership qualities and visions for the future in medtech. Similarly, environmental concerns, diversity and inclusivity: they are all on the list for aspiring leaders. In a talent-constrained environment, having a vision of inclusiveness will pay returns. “It’s the right thing to do, but it’s even more important for engaging the next generations.”

It is not all upside, however. A lot of value is in understanding the rules of the game in what is a highly regulated industry. “The notion of ‘go fast and break things’ may work in certain environments, but it could be the ultimate risky thing to do in medtech.” In order not to bring a business model to a sudden end, a balance is usually the aim to strive for. “Ignore it at your peril – but don’t miss the disruption!”

Nevertheless, medtech is an environment of slow change. Value-based health care (VBHC) is a case in point. It would not work right on cue because the system was not ready and no one could make it pay. “VBHC makes sense, of course, but there are so many variables that make it hard to do in practice.” It may be more meaningful if medtechs started with small innovations, instead of aiming too high. “A lot of agile thinking has to do with small experiments, building capabilities, and thinking differently.” In short, there was more than one method of buying and selling, said Chapman. Smart medtechs may succeed faster by figuring out how to “bite off” enough of a transformation without trying to change everything, and thereby risk losing their core business.

ALWAYS A RISK
The risk to medtech is not merely theoretical. In spite of the amount of money being spent, a lot of inefficiency remains in the system. Chapman said there was a real fear of medtechs finding themselves pushed to the periphery of their own industry. “I’m worried about some legacy companies becoming mere parts suppliers.” To avert this worst-case outcome, medtechs today need to come up with robust solutions, wrapping services around them. Digital creates network effects, adds to the robustness of a product and addresses inefficiencies.

Some are on the way, with solutions that yield better outcomes while reducing the need for GPs to spend time with people, allowing them to prioritize patients as necessary. Funding these solutions – that is, how the originator medtech company gets paid for its efforts – remains a work in progress. It is a case of expectation management: medtech expects a return on each patient solution they provide in real time.

CREATIVE THINKING
But being paid immediately for everything supplied is maybe unrealistic. “Medtech has deep pockets, but it is not using this,” said Chapman, issuing a challenge for creative thinking among medtechs on payment schedules and methods. Moreover, the creative thinking needs to be ecosystem-wide. For example, hospitals may have to rethink their roles if they do not want to end up being maternity and ER-oriented – the two worst “businesses” from a predictability and liability standpoint.

Even if the view ahead is still blurry, digital solutions will provide the bulk of the answers for health care systems heading for demand overload, staff shortages and, in some cases, bankruptcy. But first, the ecosystem must define the parameters of what is needed, who will be responsible for providing it, and how that will be rewarded.
European SPC Manufacturing Waiver Comes Into Effect

On July 1, European Regulation 2019/933 entered into force, marking the end of a long journey for the generics and biosimilars industry in its pursuit of a waiver to allow manufacturing for export outside the European Union – as well as stockpiling for day-one launch within the EU – during the term of supplementary protection certificates.

Amending the European SPC Regulation 469/2009, the waiver Regulation, is the culmination of more than a decade of lobbying efforts on the part of the European off-patent industry – including most prominently industry association Medicines for Europe, formerly the European Generic medicines Association (EGA). This comes despite efforts from the originator industry to limit the scope of the mechanism.

While the off-patent industry has long campaigned for a “Bolar” style manufacturing exemption during the SPC period, it was only in the second half of this decade that the possibility of introducing a waiver truly started to pick up steam. In October 2015, the European Commission published a single market strategy for Europe that mooted a “targeted SPC waiver for export purposes” that it said would allow EU manufacturers of generics and biosimilars “to compete on equal footing with competitors from non-EU countries,” where producers are able to manufacture versions of products still benefiting from SPC coverage in Europe, because no equivalent protection exists locally.

Then in mid-2016, the European Council’s conclusions on “strengthening the balance in the pharmaceutical systems in the EU and its member states” invited the Commission to revise incentives for industry development. “Among those incentives,” the Council urged, “particular attention should be given to the purpose of SPCs as defined in the relevant EU legislative instrument and the use of the ‘Bolar’ patent exemption.”

But despite these developments – which happened alongside the implementation of the EU’s Comprehensive Economic and Trade Agreement (CETA) with Canada, which itself included a local counterparty to SPCs along with a waiver for manufacturing in Canada during the patent-extension term, adding pressure on the EU to reciprocate – progress for the off-patent sector was slow.

**ATTEMPTS BY EFPIA TO BLOCK WAIVER**

In 2017, Medicines for Europe pointed the finger at European brand industry association EFPIA, spotlighting “particularly shameful” efforts by the originator body to block the introduction of a waiver by lobbying the authorities on the basis that such a measure would “weaken the SPC regime in the EU.” The delay in the European Commission kicking off a consultation had been a direct result of EFPIA’s lobbying, Medicines for Europe claimed, even though the brand industry body had insisted in response that it supported initiatives to broaden access to medicines in developing countries.

However, Medicines for Europe continued to encourage the authorities to make the SPC waiver a priority, until the Commission unveiled in late 2017 a public consultation on SPCs and research exemptions – including questions on a potential waiver – which was open for comment until early January 2018.

Shortly after the consultation closed, originators appeared to be more concerned about a potential waiver. US brand industry association PhRMA told the US Trade Representative that such a mechanism “would have significant detrimental economic impact on research-based companies both in Europe and around the globe” and should lead the USTR to place the EU on its “Special 301” intellectual property watch list.

However, almost immediately after PhRMA’s intervention, European Commissioner Elżbieta Bienkowska of the directorate-general for the internal market, industry, entrepreneurship and small- and medium-sized enterprise renewed the EU’s commitment to the waiver. “We are looking to make sure that EU generics [companies] are no longer at a competitive disadvantage with non-EU players,” Bienkowska emphasized during a speech on the single market and the industry of the future on European industry day.

**COMMISSION’S INITIAL PROPOSALS NEEDED WORK**

It was not long before the Commission announced tangible proposals, which were welcomed by the off-patent industry with one important caveat. While they allowed manufacturing during the SPC term for exports to non-EU markets, the proposals did not include a stockpiling provision to allow firms to prepare for day-one launch within the EU upon SPC expiry.

Medicines for Europe’s then president, Marc-Alexander Mahl, insisted at the time that the only way the waiver would represent a step forward for industry would be if it allowed both manufacturing for export outside the EU and stockpiling for day-one EU launch. “Both are important,” he insisted, adding that “one alone does not really do the trick.” A compromise position of allowing export but not stockpiling would be “a poisoned compromise” he said, that would “kill the idea.”

This tension between welcoming incremental progress on one hand but stressing the need for refinement and revision on the other would prove to be a recurring theme as the SPC waiver made its way through the legislative process. Once a formal proposal was published by the Commission, Medicines for Europe was disappointed to find that it did not go far enough in allowing production for day-one launches within the EU, with the Commission stating outright that the waiver would be “for the exclusive purpose of exporting products to non-EU markets where protection does not exist or has expired.” The Commission had claimed that the waiver would nevertheless “indirectly” put manufacturers in “a better position to enter the EU market immediately after expiry,” thus addressing “to a certain extent” the day-one entry issue.
But Medicines for Europe was not satisfied—and at the same time, had to cope with renewed opposition from EFPIA, which said it was “deeply concerned” by the waiver as proposed. According to EFPIA—in comments that would be echoed by the brand industry association throughout the legislative process—the waiver “reduces IP rights and thereby jeopardizes patient access to innovative treatments,” thus discouraging investment.

“It also sends a global signal that Europe is weakening its commitment to IP,” EFPIA said, which was “all the more striking given the extent to which other geographies, notably China, are moving in the opposite direction by strengthening their IP frameworks, aiming to become the Europe of tomorrow.”

**IMPROVEMENTS MADE THROUGHOUT LEGISLATIVE PROCESS**

The off-patent industry was not without allies among European legislators. Spanish member of the European Parliament (MEP) Soledad Cabezón Ruiz—a rapporteur for a Parliament committee report on improving access to medicines—had insisted that her colleagues needed to work to improve the proposals. The Commission had shown “not enough ambition,” she said, pledging that improvements—including adding a stockpiling provision—would be “the focus of my work over the next few months.”

Then, in late September 2018, the off-patent industry’s concerns were eased when a rapporteur for the European Parliament’s committee on environment, public health and food safety (ENVI), Tiemo Wölken, recommended a stockpiling provision as part of formally proposed amendments to the waiver. Wölken’s proposals also included limiting the extent to which commercially sensitive manufacturing information provided by the generics industry must be published and shared by national authorities: another sticking point for off-patent producers.

**TWO STEPS FORWARD, ONE STEP BACK**

There was often a sense of taking two steps forward and then one step back as the waiver progressed through the legislative process. And in October 2018, Medicines for Europe got wind of plans to apply the waiver to SPCs for which the basic patent expires after the entry into force of the Regulation “shifts the goalposts for those who have already invested in life sciences under the existing

with the US Patent and Trademark Office and the USTR—held a dedicated “government-official only” briefing in Brussels on the waiver proposal, which Medicines for Europe claimed was an attempt to “influence the outcome” in line with “consistent efforts from US commercial interests to close the US health care market to biosimilar medicines.”

“Unfortunately, the organizers have had no regard for transparency about the details of the meeting, the participants, nor the agenda,” the association observed, slamming the US for “interfering in an EU domestic policy matter by trying to manipulate and influence the current debate, in order to influence non-better specified interests.”

Adrian van den Hoven, the off-patent industry association’s director general, insisted that “Europe cannot be intimidated and will not capitulate before the defence of the economic concerns of US commercial interests.”

By the end of 2018, a series of EU-level endorsements provided fresh momentum for the waiver proposals.

**LATE-2018 SEES A BOOST FOR PROPOSALS**

A vote by the European Parliament’s international trade committee, INTA, endorsed the proposed waiver, shortly after the EU’s competitiveness council recognized the measure at the same time as “constructive amendments” to the proposals were offered by the European Parliament’s health committee.

EFPIA doubled down on its objections. “The proposal to introduce an export manufacturing waiver to the SPC Regulation sends a signal to the world that Europe is weakening its commitment to IP incentives and innovation,” the brand body argued. “Weakening IP means less investment in new medicines, which ultimately limits patients’ access to new treatments and cures.” Many medicines available today and in the pipeline “would not be there without the EU’s robust standards of IP protection,” the brand industry association said.

Applying the waiver to SPCs for which the basic patent expires after the entry into force of the Regulation “shifts the goalposts for those who have already invested in life sciences under the existing

**“Weakening IP means less investment in new medicines, which ultimately limits patients’ access to new treatments and cures”**

– EFPIA
Europe's SPC Manufacturing Waiver: A Timeline

Key events in the history of the European Union’s development of a waiver to allow manufacturing and stockpiling for day-one launch during the term of supplementary protection certificates

- **OCTOBER 2015**
  The SPC waiver is mooted in the European Commission’s single market strategy

- **JUNE 2016**
  European Council publishes conclusions on strengthening the balance for pharmaceuticals

- **MARCH 2017**
  European Parliament adopts resolution calling for SPC waiver

- **MAY 2017**
  Canada passes legislation for SPC counterpart, including waiver

- **OCTOBER 2017**
  European Commission opens consultation on SPC waiver

- **JANUARY 2018**
  Consultation period ends

- **FEBRUARY 2018**
  US brand industry association PhRMA asks USTR to put pressure on Europe over waiver plans

- **MAY 2018**
  European Commission college discusses form waiver should take; formal proposal published

- **SEPTEMBER 2018**
  Rapporteur for the European Parliament’s committee on environment, public health and food safety (ENVI) proposes amendments

- **NOVEMBER 2018**
  European Parliament’s health committee offers further amendments

- **DECEMBER 2018**
  European Parliament’s international trade committee, INTA, endorses proposed waiver

- **JANUARY 2019**
  European Council approves a mandate for negotiations with the European Parliament

- **JANUARY 2019**
  European Parliament’s legal committee, JURI, proposes two-year stockpiling provision to prepare for a “day-one” launch

- **FEBRUARY 2019**
  A deal on the European SPC manufacturing waiver is agreed by the European Council, Parliament and Commission, providing a concrete path for a Regulation to move forward; stockpiling period is reduced to six months

- **APRIL 2019**
  European Parliament approves the SPC waiver Regulation

- **MAY 2019**
  European Council formally adopts SPC waiver Regulation

- **JUNE 2019**
  SPC waiver Regulation published in Official Journal

- **JULY 2019**
  SPC waiver Regulation comes into effect
IP framework,” EFPIA argued. “If Europe wants to be at the forefront of medical innovation and be taken seriously as a destination for life sciences investment, any waiver should only apply to SPCs applied for after the amended regulation comes into force,” EFPIA insisted. “Devaluing investments halfway through their lifecycle via ill-thought-out policy changes will drive investment to other locations around the world.”

**VICTORIES AND COMPROMISE IN 2019**

The start of the new year saw the proposals take yet another step closer to being realized after the European Council in January approved a mandate for negotiations with the European Parliament over the waiver Regulation. However, even at this stage, there was still significant uncertainty over the eventual form that key elements, including the stockpiling provision, would take. Still, the European Parliament’s legal committee later that month voted to allow firms to stockpile for two years ahead of SPC expiry to prepare for a “day-one” launch.

Against a backdrop of continuing US pressure, the EU persisted with pushing the measure through the legislative process, with the European Council, Parliament and Commission ultimately reaching a compromise agreement that the generics and biosimilars industries found acceptable, if not ideal – not least because the two-year stockpiling period had now been reduced to six months.

Medicines for Europe’s van den Hoven acknowledged the six-month period was not ideal. While he said this period was just about adequate for the measure to be effective, he suggested that “for a lot of complex products, this is going to be challenging.” It would also be a challenge for manufacturers who were producing only for local European markets – rather than also producing for export to countries where SPC protection does not exist – to ramp up production in such a short period of time, he observed. Even a compromise period of a year would have been preferable for the generics industry, he added. Nevertheless, the association pointed out that “the compromise foresees a review in five years, specifically of the day-one launch duration, which provides us with an opportunity to assess its benefits.”

After much back and forth, the EU Council, Parliament and Commission’s agreement also settled on implementing the waiver from 2022 – rather than the previously mooted 2020 or 2021 – and retaining notification requirements that will force generics firms to publish commercially sensitive information, which again was not exactly what the off-patent industries had desired.

By this point, it was looking increasingly unlikely that the waiver would be knocked off course, despite continued concern from EFPIA that the agreement would “significantly weaken Europe’s research and development offering, risking investment and jobs from our SMEs, our companies, our academic institutions and our health care systems.”

By March, the Regulation was nearing the finish line, and the European Commission was clearly looking ahead to how it would function in practice, revealing plans to closely monitor the use of the mechanism as part of ongoing evaluations after it entered into force.

**ORIGINATORS NOW PREPARING FOR IMPLEMENTATION**

Once the Regulation had been approved by the European Parliament – via a large margin – the remaining steps were a formality. The Council formally adopted the Regulation in May, with publication in the *Official Journal* on June 11. The Regulation came into force on July 1, with companies able to start manufacturing under the waiver from July 2022.

The waiver will apply to all new SPCs filed on or after July 1, 2019, so any certificates already in effect on that date will not be affected. However, where an SPC has been filed before July 1 but has not come into effect by then, the manufacturing waiver will initially not apply, and will instead become applicable three years after the regulation’s entry into force – that is, July 2022.

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**DAVID WALLACE**

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*This article was provided by our sister publication Generics Bulletin*
Building The Biotech City:

IS LOS ANGELES THE GO-TO HUB FOR TOMORROW’S DRUG INNOVATIONS?

BY WILLIAM LOONEY

As the global battle for high-value life sciences investment heats up, Los Angeles is emerging as a locus for next-generation technology and therapies. An In Vivo Roundtable of prominent players in LA biopharma met at the University Of California Los Angeles second annual Biosciences Innovation Day to assess what’s good about this market metropolis of 10 million potential patients - and what needs to improve.

Identified as positives are LA’s extensive university network, with a strong entrepreneurial orientation; a deep presence in adjacent sectors like digital health; clinical expertise in managing trial work in diverse populations; and ready access to funding for early-stage science. Deficits include the absence of a single center of gravity in a region where transport links are tenuous; a shortage of homegrown management talent; and lack of a local VC community committed to late-stage funding.

So what? The city’s successful bid for the 2028 Olympics and Paralympics provides a global spotlight and rallying point for outsized rebranding initiatives that could prove more enduring in terms of human impact than the games themselves – like positioning LA as the biotech hub of tomorrow. Is big pharma ready to step up to the plate?
In Vivo: Los Angeles is the geography of destiny, with an expanding and diverse economy whose output now exceeds $900bn annually, placing it third, after Tokyo and New York, among world metropolitan areas with the biggest economic footprint. As a scene setter, how did you land in Los Angeles – as a knowledge leader, what is the value-added to being in this part of the country?

Arie Belldegrun, co-founder and executive chair, Allogene Therapeutics: I received my medical degree in Israel and did my residency at Harvard University followed by a surgical oncology fellowship at the National Cancer Institute (NCI) under Dr. Steve Rosenberg, a mentor who stirred my early interest in immunotherapy as a treatment pathway for cancer. Back in the 1980s, few institutions were either attracted to this area or had embraced its potential, but I learned quickly that UCLA was the exception. As a result, I joined the medical school faculty as an assistant professor in urologic surgery and signed on as a researcher at the university’s Jonsson Comprehensive Cancer Center. With several colleagues who, like me, remain on the UCLA faculty today, we worked to raise the profile of cancer immunotherapy and gene therapy research by soliciting joint grants from the National Institutes of Health (NIH) and other granting agencies.

The funding we received helped set the stage for the discovery of revolutionary new medicines that use the body’s own defense mechanisms to attack cancer cells. It also gave me the confidence in our science and the ability to take the calculated risks of investing in and founding several business ventures here in Los Angeles aimed at bettering the lives of patients with advanced or incurable cancers.

As an aside, what led you to make that decision to combine the practice of medicine with business entrepreneurship? What was the chronology of your success as arguably the man who made Los Angeles a magnet for research on new ways to fight cancer?

Belldegrun: The NCI grant money was great, but I realized that academic research had limitations. Even assuming your work could get published, the immediate impact on patients was negligible. So, in 1996, I decided to start a biotech company, called Agensys, with a mission to discover and commercialize novel monoclonal antibodies to treat solid tumor cancers. In launching Agensys, I relied on support from a group of fellow professors at the UCLA Medical School who joined me as the scientific founders of the company. It was the reason why we chose nearby Santa Monica as the site for our headquarters. The decision proved fortuitous when, in 2007, Japan’s Astellas Pharma tendered a buyout offer. The new owners subsequently made a significant new investment in research and manufacturing at the Santa Monica location. This was a big win for the...
Los Angeles biotech community and Agensys grew from 120 employees, with 50 PhD researchers, to over 300 employees.

A decade later, after Astellas decided to relocate its operations in Santa Monica to Chicago, we convinced Gilead Sciences to acquire the Agensys facilities, widening a top-10 biotech company’s stake in the Los Angeles life sciences ecosystem. It really put us on the map.

In 2004, we also founded another biotech start-up, Cougar Biotechnology. At Cougar, we developed a novel small molecule, Zytiga (abiraterone) a potent drug for castration-resistant prostate cancer. We located the company literally across the street from UCLA Medical Center. At the same time, right next door to my own lab at the Jonsson Comprehensive Cancer Center, Professors Charles Sawyer and Michael Jung were actively engaged in collaborative research on prostate cancer that produced much of the discovery work on what became Pfizer’s drug Xtandi (enzalutamide), a blockbuster for which UCLA continues to receive royalties to this day. Cougar was acquired by J&J in 2009 to gain access to abiraterone, which was subsequently approved as Zytiga by the FDA in 2011. Zytiga earned J&J US sales of $3bn in 2018.

By the time we sold Kite to Gilead Sciences in 2017 for $11.9bn in the largest pre-commercial biopharma acquisition to date, we had 800 employees and a local good manufacturing practices (GMP)-certified commercial manufacturing plant scaled for the imminent approval of Yescarta. Under the new management at Gilead, Kite’s workforce has more than doubled, to 1,850 employees, located in Santa Monica and in El Segundo, the site of a manufacturing plant that oversees the customized biology required to deliver Yescarta to each individual patient.

That Yescarta is made here is another sign that Los Angeles has come into its own as a leader in biotech, combining top academic talent and business know-how to produce world-class medicines that advance patient care. The opportunities that came from my academic connections to UCLA have instilled in me a deep confidence in the city’s future as a bench-to-bedside
powerhouse in medical innovation.

My newest and most ambitious project is Allogene Therapeutics. This company is pursuing an off-the-shelf CAR-T therapy against cancer. I am joined in this project by another colleague and former UCLA professor, David Chang, who has moved from heading Kite’s R&D program to his new post as Allogene’s president and CEO. For now, we are based in South San Francisco due to our history with Pfizer, from whom we acquired the asset. I am keeping my roots here in southern California by taking the lead in opening a new office in Los Angeles for Vida Ventures, a Boston-based boutique VC I co-founded and helped launch in 2017 with more than $350m to support emerging and breakthrough science. We will work with other geographically focused VCs, including Westlake Village BioPartners, which is also here today, to provide hands-on expertise with a focus on start-ups that are making the Los Angeles metropolitan region their preferred home base.

You see that all of us here today are deeply interconnected in pursuit of the same goal. I am interested in hearing from the others on the panel.

David Reese, executive vice president R&D, Amgen: I am a refutation of the notion that Los Angeles is a transient place where people don’t put down roots. I came to Los Angeles 30 years ago as a newlywed and except for a brief period on the faculty of the University of California, San Francisco, I’ve been here ever since. Both of us were looking for a place where I could do my post-med school residency and my wife could apply her new degree from Stanford Business School.

Like for Arie, UCLA proved to be an attractive place for me to start a career in science and research. I ended up doing my medical training at UCLA’s old Center for the Health Sciences campus just across the street from here. I was the chief resident in internal medicine when the 1994 Northridge earthquake hit nearby, which gave me my first exposure to crisis management. It was also during my first week as a UCLA physician intern that I met Professor Dennis Slamon, a mentor whose lab did much of the basic research on the HER2/neu oncogene that eventually produced the breakthrough drug Herceptin for breast cancer. I ended up spending a decade in Slamon’s group, and later I ran a clinical research network with him.

In 2005, I joined Amgen’s R&D program, where I have held various roles leading up to my present position as the company’s head of global R&D. To me, it was a natural transition from academic discovery to commercial development. The Los Angeles ecosystem proved fortuitous in offering me the best of both worlds. That critical mass is expanding and helps explain why I believe the area has much more to contribute in seeding innovations that work for patients.

Amir Naiberg, president and CEO, UCLA Technology Development Group: I am a relative newcomer to the region. I arrived three years ago after serving as CEO at Yeda R&D Ltd., the commercial arm of the Weizmann Institute of Science in Israel. The opportunity came because UCLA had made a strategic decision to take better advantage of the commercial development opportunities from the research taking place in its labs. The bottom line is UCLA wanted to recruit someone who was familiar with cutting-edge academic science and could build and run a technology group more like a business. On a visit to Israel, representatives of the UCLA search committee invited me to breakfast, and four months later I, my wife and three children landed in Los Angeles.

The commitment I find here to excellence in life sciences research makes my mission largely self-evident – it requires no explanation. Everyone understands the potential the university’s vast talent base has on innovations that create significant downstream economic opportunities while delivering real value to patients. The Los Angeles region has not been an easy sell, so we must work hard to establish ourselves as a significant hub. Medical innovation is a global pursuit, where the winners will be those who are most effective in creating an ecosystem that can support their scientific assets and resources.

Mike Jung, university professor of chemistry and biochemistry, UCLA: I’ve spent almost my entire professional life here in Los Angeles – 45 years to date. I arrived in 1974 after receiving my PhD from Columbia University and a post-doctoral residency at the Swiss Federal Institute of Technology in Zurich. It was simple: UCLA said it wanted me to come to Los Angeles and made me an offer. I took it. I grew up in the raucous French Quarter of New Orleans and Los Angeles presented as culturally a bit crazy too – ever since, I’ve enjoyed the city and enjoyed the work. Over the years I received numerous offers to leave UCLA and significantly increase my income. But happiness can’t be bought. And I truly have been happy here.

Steve Rosen, provost and chief scientific officer, City of Hope National Medical Center: I was trained as a medical oncologist with a background in lab work. I grew up in New York, graduated from Northwestern University’s medical school honors program and, like Arie Belldegrun, did post-doctoral work at the National Cancer Institute – also as a member of Dr. Steve Rosenberg’s lab, doing some of the important early work on cancer immunology. After that, I spent 25 years at Northwestern University, running its cancer research, trials and treatment programs. During that time, three of my four children, as well as my parents and sister, had relocated to southern California for the educational opportunities and the great climate, so when City of Hope approached me for a new position I decided to take a look. I quickly fell in love with the “succeed by doing well for others” culture of this institution and the commitment to research that benefits patients in fighting difficult, hard-to-treat diseases like cancer.

Since I joined City of Hope a little more than five years ago, I’ve been heartened by the resources I’ve been given to build on this great reputation. My initial assignment was to bolster the foundational research program at our Beckman Research Institute, investigating the biology, chemistry and pathology of cancer and diabetes. Today, my role as provost and chief science officer consists of administering all City of Hope research programs, from basic and translational science to clinical trials, most of which center on cancer but also include a diversity of conditions, from diabetes to HIV. The many personal connections I’ve made – and the common links I share with the other panelists here today – reinforce my view that Los Angeles has the abundance of human capital required to keep generating the best new ideas in medicine.
Beth Seidenberg, managing partner, Westlake Village BioPartners: I began my career on the East Coast but moved to Amgen some 20 years ago, where I served as the company’s chief medical officer and head of global development. I exemplify a common theme, moving out to California with some trepidation, then falling in love with the geography, climate and a unique way of living that is very different than other parts of the country. After Amgen, I joined the VC Kleiner-Perkins in the Bay Area where I spent 14 years and, as a general partner, helped fund the growth of 15 successful biotech companies.

All that time I kept my home in Westlake Village near Amgen’s HQ in Thousand Oaks. The irony was I was living in the LA area even though my work involved investing in companies around San Francisco and Boston. I found it amusing that, considering my own weekly commute, colleagues at Kleiner-Perkins would talk about LA as another planet – too far away to spend any time there. My consumer tech counterparts took the same view until Snapchat took off and created a new geographic hot zone called Silicon Beach in the Venice area. Los Angeles promptly emerged on their radar screen.

This is what is happening now in pharma and biotech. Finally, I happen to be living in the right place. I am now helping shape the future of the city after founding last September a new VC enterprise, Westlake Village BioPartners, jointly with Amgen’s longtime head of R&D and a close friend, Sean Harper. We’ve raised $320m so far. Our business mission is to seed the Los Angeles area’s potential in life sciences, focusing on early-stage incubator companies with interesting novel technologies as well as a few later-stage plays that together will create a diversified portfolio marked by great science – and treatments that will work for all patients, regardless of geography.

Peter Moglia, co-CEO and co-chief investment officer, Alexandria Real Estate Equities Inc.: I am a UCLA graduate, which makes me an optimist about Los Angeles. I started at Alexandria in 1998. One of the first things our company founder Joel Marcus asked me to do was establish a biotech “cluster” in Los Angeles. I went and found an old warehouse in Pasadena where we are based and retrofitted it for lab space. We called it an Innovation Center, with a focus on early-stage companies, given that Los Angeles was then a nascent market for life sciences.

We were able to lease it out fairly quickly, but soon found that these early-stagers would leave after two or three years – not just from our facility but from the Los Angeles area entirely. The reason was either they were getting investments from outside the region and their investors wanted them to move closer to where the capital was; or they had needs that were locally scarce, usually management talent. It was also true our business model focuses on “class A” facilities that are great for a company’s image for recruiting and retention purposes but carry a premium that didn’t fit local early-stage company budgets – at the time, their funding sources were “friends and family” contacts that did not value image as much as professional investors do. All this is starting to change and Alexandria is cautiously re-engaging in the market. The optimism has always been there and now it’s starting to prove out.

Ken Schultz, chair and CEO, Trethera Inc.: I wasn’t born in southern California but got here as quickly as I could. Following practice as a physician plus five years as McKinsey & Co. in Europe, I arrived in Los Angeles to support Medtronic’s artificial pancreas system for diabetes, which won Time Magazine’s 2014 Invention of the Year. Later, I co-located to the San Diego area to lead strategy, innovation and business development for Halozyme Therapeutics. Having served during that time as an active board member for Trethera, the directors recruited me last year for the CEO role as well. Trethera is a start-up whose origins link back to UCLA’s work in small-molecule DNA synthesis and repair space. Our lead candidate, TRE-515, is a first-in-class inhibitor of the enzyme deoxycytidine kinase (dCK). Today’s fellow panelist Mike Jung, along with Dr. Owen Witte of the UCLA Geffen Medical School as well as several other prominent UCLA faculty, developed TRE-515 for use against solid and hematologic tumors.

From my experience around the globe, the biggest value-added I see in Los Angeles is the access to early-stage start-up funding – though late-stage funding is not nearly as robust. We’ve raised well over $15m for Trethera locally, with many of our investors coming from outside the industry. Having the entertainment industry as one of your shareholders adds a unique wrinkle – where else can a start-up claim that one of its principal investors is the screen writer for the iconic movie Toy Story? Los Angeles also has the unrivaled physical presence of many major academic research institutions, including, in addition to UCLA, Cal Tech; the University of Southern California, including its new Ellison Institute for Transformative Medicine; LA BioMed Medical Research Lab; the seven Claremont Colleges; and several others.

TO PROSPER, STAY CLOSE

As a group, do you believe the autonomous capacity to access, transfer and interpret large volumes of information has made geography irrelevant to success in today’s research enterprise?

Jung: The Internet has certainly democratized the way we scientists exchange information. But direct human interaction is unpredictable, which is precisely why it can be so useful to the pursuit of innovation. Closeness does count, especially when you have a burning question and can simply walk over to a neighbor’s lab to find an answer.

Reese: Technology gives us the opportunity to pursue collabora-

Seidenberg: The common thread is that it’s always hard to start a new business – but harder still to contemplate doing that from afar, separated from the researchers who develop the science and understand the condition as experienced by the patient. It is true that you can import the intellectual property from virtually anywhere. But if you want to build a viable commercial business, a supportive surrounding ecosystem of other like-minded businesses as well as a familiarity with the stakeholders responsible for shaping local practice and regulation is extremely important. I’ve experienced this dynamic at work before in Boston; in Los Angeles the same thing is happening now, but at a more rapid pace.

Belldegrun: I am finding our investors – including Gilead Sci-
ences, in the case of Kite – are increasingly willing to come and work where the expertise lives. Many of Gilead’s management team responsible for the Kite acquisition are now sitting in Santa Monica. I think this trend will continue.

Reese: Looking at the future of this industry writ large, the engine of growth is the mixing of diverse platforms, technologies and talent. Multidisciplinary expertise is the entry point to all the new science, such as the “omics” field, which requires such diversity if we are to understand the roles, relationships and actions of the various molecules that populate the cells of an organism. Hence it is simply good judgment to stay close to where this research is being conducted – the pace of learning is extraordinary and cannot be evaluated from afar.

LA’S ASSETS

What’s attractive about the Los Angeles biotech landscape today? Are we at an inflection point in terms of the sector’s growth prospects?

Belldegrun: We are excelling at advanced gene and cell-based technologies that take us beyond the pill. When we sold Cougar to J&J, it was because we made a pill – it was very easy for J&J to integrate that modality to its base operations in New Jersey. It is not as easy for Gilead to relocate the manufacturing of the autologous CAR-T technology behind Yescarta. As its use by patients grows, our original $500m investment in the complex, customized re-engineering of individual cells will stay here because of the expertise this region has in this high-touch production.

The FDA is sending staff out here to understand the process of re-engineering the human immune system to deliver a treatment to patients. There are multiple, small start-ups founded by bioengineers, lab specialists and CROs (contract research organizations) all interested in being first with the next generation of medicines targeting the human immune system. It started with the low hanging fruit in cancer but is expanding beyond that to the autoimmune disorders and inflammation affecting millions of people in the US and worldwide. Such expertise is not easily replicated and transferable in the same way as can be done with a small-molecule pill.

Reese: I am biased because Amgen already has the best genetics database in the world due to our investment in Iceland’s deCODE genetics project. We now have millions of participants enrolled from around the world. We have another project underway with a Colorado-based biotech, SomaLogic Inc., to investigate how proteins impact health status and disease progression in the human body – it’s the largest, most comprehensive proteomics experiment conducted to date.

What’s driving us is the necessity to attack disease in a different way than traditional methods, where we can learn to generate new insights about targets and pathways against the hardest problems in medicine, like protein degradation or eliminating the blood-brain barrier. At present, only about 15% of the human genome is druggable. We have to push the technology boundaries to make tractable disease targets that are currently out of reach.

Expertise from many parts of the scientific community, from chemistry to biology to physics and engineering, will be necessary to solve these challenges. I am optimistic on what we can achieve collectively – and the university infrastructure we have cited as a feature of the Los Angeles biopharma ecosystem gives us that in spades. The molecular and cellular engineering capabilities that exist right here give this region a big edge in translating theory into therapy that works for patients. We have the opportunity here to put all this together.

Seidenberg: In terms of inflection point, what set things afire in the Massachusetts hub was the decision by Novartis 16 years ago to move its major global R&D operation to Cambridge from Basel, under the high-profile leadership of cardiologist Mark Fishman. That was the “big bang” that made Cambridge a destination for other big pharmas and in turn drew in a host of satellite smaller biotechs. Gilead Science’s acquisition of Kite Pharma in 2017 as well as its expanded research commitment to southern California has had a similar, if smaller impact compared with Novartis. If over the next couple of years we get some additional local investments by Amgen while simultaneously attracting a new big pharma player to relocate key R&D operations to Los Angeles, then it’s game over. We are already repairing the deficit in venture capital with the formation of Westlake Village BioPartners as well as Arie Belldegrun’s Vida Ventures, which will give us the concentration of capital assets that has been lacking to date.

Naiberg: I’d emphasize the enormous extra lift provided by our local academic institutions and teaching hospitals. There is a significant follow-on effect in the amount of funding this area gets from the federal research agencies like the NIH and
the National Cancer Institute (NCI). Los Angeles-based research institutions received $1.1bn in NIH funding in 2018, the largest amount of any county in California. Two of the top-five grant recipients from the state were based here: UCLA and the University of Southern California (USC).

Seidenberg: Yes. Academic relationships are a factor in our favor – so much so that few people realize that the biggest challenge facing Los Angeles biotech is the chronic shortage of private laboratory real estate. It’s not seen as an issue because of all these university-based assets. It’s tough getting outsiders to invest. Hence start-ups like Atara Biotherapeutics, another allogeneic T-cell immunotherapy company where I serve on the board of directors, must invest and build such facilities on their own. With help from the city of Thousand Oaks, Atara recently opened a state-of-the-art allogeneic T-cell operations and manufacturing center near the Amgen HQ.

Beldegrun: Let me add some additional context – we are all here today to participate in UCLA’s second annual Bioscience Innovation Day. The first one last year attracted about 450 people from southern California and around the country. This year I’m told the number has nearly doubled. A few months ago I participated in a similar daylong life sciences event hosted at Research Triangle Park in North Carolina, which drew about 900 attendees. I was impressed and asked my hosts how long they’ve been doing this meeting – the answer was 30 years! I took from that brief exchange that our prospects going forward are exceedingly bright. Today, we have a lot of the top people from companies, research institutions and VCs throughout the country. Next year, they will bring their teams with them too. People will have figured out what great things are going on out here – and they will be ready to do business. And it has happened in just two years, compared with three decades.

Reese: Another favorable trend is the market for scientists and researchers is very strong. The recruitment field is highly competitive. Amgen is not experiencing any down cycle in wage expectations of the people who come here.

Jung: David is right. The young people we hire today are getting offers from everywhere. No one feels compelled to stick to one track in academia and ignore the possibilities that can come from partnering and entrepreneurship. Arie is a prime example of those possibilities and what can be achieved in applying a medical or science background to build a great enterprise.

Beldegrun: Most biopharma scientists in academia today are highly opportunistic and this has rebounded in favor of Los Angeles due to its top-rank institutional assets. No one is in an ivory tower or giving anything away. My friend Mike Jung is not the man I knew 20 years ago. He’s not only a distinguished scholar – he’s a savvy and successful businessman.

How strong is the CRO and contract development and manufacturing organization (CDMO) presence in Los Angeles?

Seidenberg: It’s a key variable that will take a bit more time to develop. Cell and gene therapy, including gene editing, are going to compose the major source of therapeutic opportunities in the next decade. Right now, there is no truly robust capability in the contract research world to meet the production challenges around these complex, highly personalized therapies. The result is that developer companies like Kite (now Gilead) are doing it themselves. They are building their own facilities. There are also the companies like Allogene, which are working on allogeneic standardized, off-the-shelf approaches to cell/gene therapy rather than the prevailing autologous one-off model, a trend that offers a less cumbersome and possibly cheaper way to deliver treatment.

The point is we now have at least one big pharma in Los Angeles expert at this type of manufacturing. From that base many CDMOs will start to form around it. The precedent is Genentech and how its leadership in production of monoclonal antibodies spurred the growth of multiple new suppliers of this technology in the Bay Area. It’s entrepreneurial metastasis – and I expect Los Angeles will come into its own as a national locus for expertise in cell and gene-based manufacturing. Like VC capital, it’s another key element to add to the biopharma ecosystem now coming to life in Los Angeles.

MIND THE GAPS

What are the challenges – the gaps that must be addressed to bolster Los Angeles’ credentials as a world-class biotech hub?

Schultz: One thing I am not sure we can tick the box on is access to venture capital. Funding for the early stage is there – my own company secured non-VC money right at the start – but at the crucial later stages when the challenge is funding proof-of-
concept trials, local investors seem more reluctant. I don’t see as many of the globally integrated VCs opening branch offices in Los Angeles and I noticed a recent $40m VC deal with City of Hope that made the investment contingent on re-locating the company to Cambridge, MA. A 2019 Boston Consulting Group (BCG) report, Stars Aligned, showed late-stage VC funding in southern California trailed the Bay Area by over 90%. I guess my question is, as a new biotech entrepreneur, I’d like to tick that box – but are we there yet?

**Seidenberg:** There is a distinction at work here. An early-stage investor will want to be involved in the details of building the enterprise from the ground up, vetting and monitoring your business plan to make the right decisions on physical plant and talent recruitment. There is an incentive to stay local. At the later stage, VC money can enter from anywhere because the basics of the business and its value proposition are already in place and it’s easier to insist on a translocation contingency as part of the deal. That’s just the reality. Our mission at Westlake Village BioPartners is to get actively involved and build the start-ups we invest in right here in Los Angeles. And we also want to bring in late-stage money, as we have done for Atara Biotherapeutics and as Arie Belldegrun did for Kite Pharma. Getting that funding is not going to be an issue if the fundamentals are right.

**Jung:** Lab space is a pressing issue. I can see from my perspective that space is really hard to come by off campus. I understand that Alexandria Real Estate Equities has bought land in Culver City and is going to build there. We aren’t going to fulfill our potential in cell and gene therapy unless we add to our lab infrastructure in Los Angeles.

**Seidenberg:** Having to wait in line for lab space is a key concern for start-ups. Any downtime that affects your development cost money. The clock is always ticking on the intellectual property.

**Schultz:** At more than 4,000 square miles, Los Angeles county is bigger than Rhode Island and Delaware combined. We have no center of gravity in terms of real estate; instead we have clusters of lab and incubator facilities in Pasadena and adjacent to Amgen in Thousand Oaks. Rather than a singular geographic blob, the biotech industry here will look more like scattered droplets where scientists and teams can work closely to one another.

**Seidenberg:** It’s not going to be possible for Los Angeles to look like Kendall Square in Cambridge. We are likely to grow out to resemble the Bay Area, with many pockets or clusters of activity and a big divide between the peninsula and East Bay where you have people who just won’t shuttle back and forth on the bridges. It hasn’t hurt Silicon Valley too much – the big problems up there are housing costs, regulation and the war for talent leading to a challenge in recruiting and retaining top-quality researchers and experienced staff.

**What about enlightened public policies focused on zoning and tax breaks for incubators and a better overall approach to land use, including incentives for affordable housing? Does government actually work in California?**

**Seidenberg:** Where I am based, in the Thousand Oaks area, the response of city councils and other local government has been tremendous. Restrictive zoning there is not an issue. There has actually been a shift in emphasis over the past few years from attracting investment in warehousing, retail and manufacturing to biotech and other high-tech sectors that leave a small footprint on the land and offer high-paying jobs. Jobs data assembled by the industry have had a big impact in showing that life sciences generates more tax revenue than most other sectors and has a big spillover impact on retail and other businesses that depend on high-income workers.

**Moglia:** One of the big challenges in Los Angeles is zoning laws. There is very little land that is authorized for R&D activities; if you read the zoning code it is hard to determine whether or not a wet lab is even allowed here. We’ve discussed this with the city and it is looking at clarifying the legal situation. More flexibility on zoning and land use is definitely a plus given the demand for space to conduct research.

We should conclude with a consensus on the next steps necessary for Los Angeles to realize its potential in assembling the science, capital and talent to deliver tomorrow’s medical breakthroughs. As key players representing a cross-section of the city’s current biopharma infrastructure, how can you leverage this geography of opportunity to become top finisher in the global race for the knowledge assets that treat and cure disease?

**Seidenberg:** On the practical side, the biggest thing that must be fixed is the real estate. We need more lab space and a strategy on where to place it to achieve the greatest synergies between industry, services and adjacent businesses, academia and the big teaching hospitals. We’re solving the funding issue. With the opening of the Vida Ventures office, you are seeing other VCs following the same geo-centric path as Sean Harper and I have done. As far as late-stage money is concerned, that will come once we build more quality companies here with reputations following the same geo-centric path as Sean Harper and I have started at Amgen 20 years ago, we were just ourselves; there was no team. But that proved to be an advantage. David Reese joined us from UCLA because, as he said, it was an opportunity to build something. The same bootstraps mentality also appealed to Kite’s eventual co-founder, David Chang, when we first reached out to him.

There are so many other examples of successful people who wanted to be part of this culture of individual initiative and trying things differently than what was commonplace back east. We must put out the message that Los Angeles is small and big at the same time, with strengths and gaps that make it a wonderful place to reinvent yourself – and to keep doing it. I’d also mention that Los Angeles has an abundance of research talent in other technology sectors. This will be increasingly important as medicine becomes more personalized, using platforms that deliver treatment in ways no longer reliant on the small-molecule pill. We also shouldn’t forget those service functions like legal, accounting and finance that every new start-up needs to grow.

Does the city have an intellectual property infrastructure that every new start-up needs to grow?
as an enterprise. These are all here at scale.

Schultz: I agree that we have a lot of R&D talent. What are not so prevalent are people with general management expertise along with practitioners in specialty functions like CMC (chemistry, manufacturing and controls) and regulatory. We also need to seed that class of entrepreneurs who have built companies and closed them down – numerous times. This is an important and hard-won source of wisdom about how biotech really works.

Naiberg: UCLA is committed to establishing a closer connection between academia and industry. We feel it has to be integral to any growth agenda for biopharma in Los Angeles because the architecture is so rich in potential. Our Technology Development Group relies heavily on mentoring work. For example, we work with many of you here in this room as external experts to judge and support projects initiated by our faculty that can lead to successful commercialization.

The degree of commitment and involvement by industry colleagues has gotten deeper with time. They are mentoring our teams every step of the way, creating those milestones that keep everyone focused on realizing an investment return from all the new science our faculty creates in the lab. What we’ve achieved together in the two and a half years since I arrived at UCLA is gratifying. The model deserves to be replicated throughout the region as a priority for the entire research community.

Beldegrun: My wife sits on the board of directors at Cal Tech. I understand an investment fund is being created to support more foundational work there on biotechnology. The point is Cal Tech wants to increase its footprint in the new science.

Rosen: I share Amir’s perspective. City of Hope is an engine of productivity when it comes to developing new therapeutics. Of late, we’ve had two projects licensed out that amount to a vote of confidence in the several hundred million dollars we spend annually on research. Since I arrived five years ago, we’ve recruited about 70 new lab investigators; more than half of them came from tenured faculty positions. Also, City of Hope does not offer tenure. It’s a major vote of confidence in our ability to make new discoveries and bring them to start-up. Our board of directors has endorsed us setting up a separate biotech business development office. As a result, I expect the breadth and quality of these relationships to increase.

Beldegrun: Another area we can agree on is tax policy and incentives. Many parts of the country now offer tax breaks in return for investing in a state or community. When Massachusetts started doing this, you began to see more companies opening facilities in the state. The latest is France’s second-largest drugmaker, Servier Group, which opened a new US HQ in Boston earlier this month.

California is a state that has never, to my knowledge, offered tax breaks to biopharma in return for investments or jobs. It may be appropriate to discuss with the city and county how they intend to keep us as a leader in biopharma innovation. Mark Ridley-Thomas is the county supervisor who represents the area around UCLA. His record in support of the biotech sector has been unswerving. What’s unclear is the position of the city council and the Los Angeles delegation in the state legislature.

In the end, we know that if Los Angeles is able to attract another big pharma to locate here, in addition to Amgen and Gilead, it would be a game changer – further entrenched us on the map in ways that could attract more mid-size or smaller biotechs to invest and add to our base in human capital. I’d also like to ask my friends at Amgen if or how it plans to spend the $30bn in cash it reported having on hand at the JP Morgan investor conference in January. My hope is that a good portion of it will be put into projects here.

A ‘BIG BANG’ – AND THE OLYMPICS WILD CARD

Schultz: What we’re talking about is a “big bang” event – bigger than the $12bn Gilead Sciences paid for local innovator Kite Pharma two years ago.

Beldegrun: That’s why it’s doubly important to engage Amgen CEO Bob Bradway and new Gilead Sciences CEO Daniel O’Day as ambassadors to the rest of the big pharma community in making the case for high-level investments, as they have done in Los Angeles.

UCLA’s Technology Development Group will be holding its third Biosciences Innovation Day a year from now, at the start of a new decade. Do you have a sense of what the theme will be? What next are you excited about?

Naiberg: Next year, we will focus on the who, why, when and how of partnering. This year, this activity was a sidebar. The sentiment among attendees I spoke to is partnering has to be front and center. That includes active participation not just by the UCLA community but by other institutions in Los Angeles county – anyone who wants to join us. Our goal is to make the annual Biosciences Innovation Day a one-stop shop for showcasing biopharma innovation to highlight and advance best practices. And of course we are looking to increase turnout, which this year vastly exceeded our expectations.

Finally, Los Angeles has received the nod to host the summer Olympics in 2028. Among other things, preparations for this global, high-profile event usually entail significant local investment in infrastructure as well as a “rebranding” of the host city’s image. Is there an opportunity to include biotech and the life sciences in these initiatives?

Reese: All big companies and employers in the region are likely to benefit from the media spotlight that will be placed on Los Angeles and its incredible diversity of people and talent. If it leads to the build-out of a public transit infrastructure, that will help expand the cluster-based work and lifestyle approaches that many young scientists seem to prefer these days. We need to maintain our focus in being attractive to this employment demographic.

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Hippocrates (460-370BC) believed that all diseases begin in the gut. He was closer to the truth than he has been given credit for. It is reasonable to assume that gastrointestinal disorders or metabolic diseases may start in the gut. But research over the last 15 years into the nature and role of the gut microbiome — the trillions of microorganisms that reside in our intestine — has uncovered its far wider influence, including across many autoimmune conditions, cardiovascular disease and even cancer.

Even then, few would have linked gut health to Parkinson’s, autism or Alzheimer’s. Yet gut and brain health are far more intimately and intricately linked than previously imagined. The “gut-brain axis” is the focus of growing numbers of researchers, biotech companies and investors. They are uncovering multiple two-way communication pathways between belly and brain, spanning neural, hormonal and immune-system signalling. New research into the “brain-immune-gut-axis” also challenges prior assumptions of how isolated the brain is from the rest of the body and, in particular, from the immune system.

This gut-mediated back-door route to the brain offers several potential advantages for drug developers.

Scientists now understand that there are multiple, bi-directional links between gut and brain. They are using this knowledge to develop new treatments for some of the most challenging chronic conditions, including Alzheimer’s disease, Parkinson’s disease and obesity.

BY MELANIE SENIOR

The “gut-brain axis” is the focus of growing numbers of researchers, biotech companies and investors. They are uncovering multiple two-way communication pathways between belly and brain, spanning neural, hormonal and immune-system signalling.

Axial Biotherapeutics Inc.’s lead program involves mopping up a microbial metabolite which may be implicated in autism spectrum disorder. The gut is also an important modulator of various hormones used to signal satiety — telling us to stop eating. Companies like New York-based Kallyope Inc. and France’s TargEDys are

Could The Gut Cure Brain Disease?
using that information to develop new kinds of obesity treatments, tackling the behavioural aspect of the disease. “We now have very provocative evidence that we can influence various central nervous system disorders through the gut-brain axis,” summed up Nancy Thornberry, Kallyope’s CEO.

Related work into the “brain-immune-gut” axis also challenges prior assumptions of how isolated the brain is from the rest of the body and, in particular, from the immune system (much of which resides in the gut). This is uncovering further potential therapeutic avenues for brain diseases, and is the focus of discovery work at Boston-based PureTech Health PLC and California-based Alector Inc. Meantime, the gut microbiome’s effect on cancer – mediated by the immune system – is another booming R&D sub-sector. “The gut-brain axis and oncology are the hottest areas, with the biggest market potential, in the [gut] microbiome space,” opined Isabelle de Cremoux, managing director at investment firm Seventure Partners, whose Health for Life Capital II is the company’s second gut microbiome-focused fund, on its way to raising €200m.

More, Safer Routes To The Brain?
This gut-mediated “back-door” route to the brain offers several potential advantages for drug developers. The first is that therapies do not have to cross the blood-brain-barrier (BBB). The BBB is a tightly-built wall that prevents the majority of pathogens (as well as large immune-system molecules like antibodies) from crossing into the brain from the systemic circulation. The BBB has a vital protective role. But it is also one reason many CNS drug candidates have failed: they cannot get to where they are needed.

The second advantage of the gut-mediated route to the brain is safety: therapies whose actions are restricted to the gut – or which are based on naturally-occurring, human commensal microbes – are less likely to trigger unwanted or dangerous side-effects than systemically-delivered drugs. That will matter to regulators, particularly in the context of highly prevalent conditions like obesity and neuro-degenerative diseases.

Finally, scientists’ greater understand-
Scientists have known for some years that as many as half of children with autism spectrum disorder also suffer from gastro-intestinal upset. GI symptoms such as constipation are observed in many Parkinson’s patients over a decade before cognitive and motor problems show up. Until recently, no-one understood whether or how the GI issues linked to the conditions’ better-recognized behavioral and cognitive symptoms.

Axial’s scientific co-founder Sarkis Mazmanian, professor of microbiology at the California Institute of Technology (Caltech), and his team used these observations to design mouse models of both diseases. These have generated compelling preclinical evidence of a gut-brain link in these conditions. Mice bred to display the behavioral features of autism generated offspring that also displayed GI symptoms; specifically, ‘leaky gut’, in which the intestinal barrier (or gut wall – a crucial barrier protecting us from outside world) becomes more porous than usual. Significantly, treating those mice with *Bacteroides fragilis*, a human commensal bacterium, repaired the gut wall as well as correcting some behavioral abnormalities. Treating mice with microbiomes from autistic children induced similar behaviors in the mice.

Axial’s team has used metabolite profiling and other tools to investigate more deeply the molecular mechanisms behind these findings. It discovered that autistic mice had particularly high levels of a microbial metabolite, 4-ethylphenylsulfate (4-EPS), and that reducing 4-EPS levels improves behavior. It also found that feeding animals this metabolite led to behaviour abnormalities. That amounts not to definitive evidence of causality, but something close. “We think we’ve found something that is much stronger than correlation,” said David Donabedian, Axial co-founder and CEO.

So the company’s polymer chemists designed a small, non-biotherapeutic molecule, AB-2004, which mops up that metabolite before passing out of the body in the feces. Axial published preclinical data in May 2019 showing that AB-2004 restored GI integrity and reduced 4-EPS levels in mouse models of ASD. It also has early evidence of a link, in humans, between 4-EPS and two measures of social function. A study of 130 autistic children and 101 children from the general population found statistically signif cant differences in the mean levels of the metabolite between the groups. Starting levels of 4-EPS varied very widely among the subjects, however, making it tricky to establish a baseline.

“That’s early days, and ‘normal’ levels of 4-EPS in the general population aren’t well understood,” conceded Donabedian. But 4-EPS was clearly elevated in a large subset of autistic patients, and “these elevated levels appear to be correlating with certain aspects of the ASD profile,” he said. It may be that the pathological threshold for particular microbial metabolites is lower in some autistic patients, as a function of both genetic predisposition and underlying metabolite profile.

Axial is currently screening adolescent patients with autism and GI symptoms for inclusion in a Phase Ib/IIa clinical study that will further elucidate the roles and relevance of these metabolites. The company’s work may also help to more accurately, and helpfully, classify a very heterogenous condition.

Mazmanian and colleagues’ work with mouse models of Parkinson’s is also uncovering potentially causal mechanisms within the gut. Transplanting fecal samples from human Parkinson’s patients into germ-free mice led to parkinsonian...
behaviour in the mice, while healthy samples did not. Mice designed to express alpha-synuclein, a protein that mis-folds in Parkinson’s patients to form damaging clumps in parts of the brain, did not show symptoms so long as they lacked gut microbes. Motor deficits and alpha-synuclein aggregation in the brain both appeared in such mice, though, if fed with short-chain-fatty acids – an important category of microbial metabolites.

Axial hopes eventual treatments that emerge from these insights may improve both the behavioral and GI symptoms of Parkinson’s and autism.

**PureTech: Draining The Brain To Cure Diseases Of Aging**

PureTech Health is also going after new ways to treat brain diseases. One of its scientific collaborators in 2015 published a paper in *Nature* describing an entirely new component of the brain-immune-gut axis. Jonathan Kipnis, professor and chair of neuroscience and director of the Center for Brain Immunology and Glia at the University of Virginia School of Medicine and his team had uncovered a network of lymphatic vessels within the meninges – the multi-layered membrane covering the brain and spinal cord (see *Exhibit 2*).

The brain was previously believed to be insulated from the body’s lymphatic and immune systems by the BBB. (The brain itself does not contain lymphatic vessels.) Yet the lymph vasculature serves two very important roles for the rest of the body: removing unwanted fluid and protein, and immune surveillance – picking up warning signals from tissues that are used to mobilize an immune response. The healthy brain needs both those services too. Kipnis’ work helped elucidate precisely how they are delivered. (It also complemented the discovery, by Maiken Nedergaard at the University of Rochester Medical Center, of another part of the brain’s waste-disposal system. The so-called ‘glymphatic system’ flushes unwanted molecules out of the fluid in between brain cells far more efficiently than previously thought, by way of the CSF and blood vasculature.)

Importantly, Kipnis’ work also found “that the performance of the meningeal lymphatic system declines significantly with age,” said Joe Bolen, PureTech’s chief scientific officer. Bolen likened this decline to a “blocked drain,” causing protein waste and other materials to accumulate and cause damage.

Kipnis showed that blocking meningeal lymphatics in mice models of Alzheimer’s accelerated disease progression. Other researchers have since highlighted the system’s role in clearing disease-associated proteins including tau and alpha-synuclein from the brain. Together, these findings have opened up promising avenues for drug discovery, most obviously in neuro-degenerative disorders associated with aging.

PureTech, with Kipnis’ team (and technology licenses from the University of Virginia), is avidly combing those avenues for new medicines that can help clear potentially pathogenic macromolecules from the CNS. Encouragingly, Kipnis’ 2015 paper suggested that age-related functional deterioration of lymphatic system could be reversed by supplying vascular endothelial growth factor C (VEGFC), which affects the health and permeability of the lymphatic endothelium. “It was a great experiment. Jonathan [Kipnis] injected a VEGFC-expressing virus into the cerebrospinal fluid of old animals, and after a couple of weeks, the lymphatic vessels opened and started draining macro-molecules,” recounted Bolen.

The work is still at a very early stage: much remains to be uncovered about the detailed architecture of meningeal lymphatics and its regulatory pathways. But Bolen was excited: “We’ve isolated lymphatic endothelial cells from mice, sequenced them, and are starting to understand their biology,” he said – a feat that would have been impossible without today’s tools and knowledge. PureTech is also working on delivery technologies that leverage its growing knowledge of lymphatics – including delivering small molecule pro-drugs to mesenteric lymph nodes to modulate the immune system.

PureTech’s most advanced internal drug candidate is an immune-modulating anti-galectin-9 antibody, expected to reach IND stage in 2020. The company also invests in others working along various parts of the brain-gut-immune axis. Among its external affiliates is Vedanta Biosciences, whose therapeutic candidates are carefully chosen gut microbiome-derived live bacteria. With what it described as one of the largest collections of commensal gut bacteria in the world, Vedanta has identified strains whose gut-protective and immune-modulatory properties provide potential applications across infectious and auto-immune diseases, allergy and immune-oncology. The company raised an $18.5m extension to its series C financing in May 2019. Outside of the PureTech community, recently listed Alector is focusing on genetic mutations that disrupt the brain’s immune system. It believes these disruptions may be behind neuro-degenerative diseases including Alzheimer’s. Lead antibody candidates targeting those mutations are in early clinical trials.

**Kallyope: Telling The Brain You Are Full**

Kallyope is harnessing the gut-brain axis to tackle another chronic disease that remains under-served: obesity.

Among the company’s lead programs is a gut-restricted small molecule that stimulates multiple satiety hormones. Some of these hormones are well-known, explained CEO Thornberry. But Kallyope’s scientists have found new, better-defined routes through which to modulate their release.

Thanks to extensive mapping of the brain-gut circuitry using imaging and sequencing technologies, including tracking cell-specific proteins using light (optogenetics) or small molecules (chemogenetics), Kallyope has found ways to “elicit hormone release in a very rational way.” It has also come across cell types and hormones not previously identified in the gut, according to Thornberry.

Tackling obesity through behavior-change, rather than by restricting food intake or blocking fat absorption, is not a new idea. But past attempts to do so with drugs that interfered with neurotransmitters in the brain’s pleasure centers mostly failed. Sanofi’s Acomplia (rimonabant), which blocks cannabinoid receptors to dull appetite, was rejected by FDA in 2007 due to neurologic and psychiatric side effects. Where the drug is available, it carries cardiovascular risk warnings.Abbott Laboratories Inc.’s Meridia (sibutramine), a serotonin, dopamine and noradrenaline re-uptake inhibitor, was withdrawn from
the US and European markets in 2010.

The idea is that a gut-mediated passage to the brain’s behavior and appetite-regulation centers will prove safer and more effective. Thornberry hopes that Kallyope’s multi-faceted gut-hormone approach will lead to weight loss “substantially greater” than the single-digit percentage levels achieved, often only temporarily, by existing pharmaceuticals.

Novo Nordisk AS, which sells a leading share of insulins and GLP-1 agonists for diabetes and metabolic disease, signed a research agreement with Kallyope in 2018. The partners will identify peptide-based candidates using Kallyope’s platform; if successful, Novo will carry out further preclinical and clinical development.

**You Are Not Hungry, Your Gut Bacteria Are**

TargEdys also believes that gut-mediated behaviour change is key to tackling obesity. Its scientific co-founders believe that appetite regulation may involve not only host gut-to-brain signalling (including hormonal signalling), but also the energy status and feeding behaviour of the gut bacteria community itself. In obese people, they speculate, bacterial-derived hunger signals may compete with – and ultimately dominate – those from other hormones like satiety-inducing leptin, for example.

There is already plenty of evidence supporting the microbiome’s role in energy balance. Giving obese mice pre-biotics (to feed their gut microbes) increases leptin sensitivity. On the other hand, kwashiorkor, a severe form of malnutrition, can be transferred from people to mice by fecal transplantation. Studies have shown that both anorexia and obese people have an imbalance in their gut microbiota. These observations, coupled with more recent data around the dynamics of bacterial growth, may support “a theory of genetic competition between the host and its microbiota for food sources,” wrote Serguei Fetissov, professor of physiology at the University of Rouen, France, in a 2017 article in *Nature Reviews Endocrinology*. Fetissov and Pierre Déchelotte, also a professor at the University of Rouen, are TargEdys’ scientific co-founders.

Bacterial proteins and metabolites (such as short-chain-fatty acids) involved in breaking down our food act on specialist cells in the gut called enterendocrine cells, which in turn trigger the release of appetite-regulating hormones like PYY (pancreatic peptide YY), ghrelin or leptin. But what if other kinds of bacterial proteins, more closely linked to the bacteria’s own feeding pattern, could mimic these hormones? TargEdys’ scientists believe that a bacterial protein called caseinolytic peptidase B protein homolog (ClpB) may do just that, copying the actions of a satiety hormone called alpha-melanocyte-stimulating hormone (α-MSH). (In the context of broader work on the brain-immune system-gut axis, Fetissov also speculated that the immune system may be involved in long-term appetite regulation by gut bacteria. Antibodies, released in response to changes in diet or gut microbiota, may cross-react with appetite hormones like alpha-MSH.)

People with anorexia and related eating disorders are found to have higher than normal levels of ClpB, while the reverse is true for many obese or overweight patients. So TargEdys has developed a pro-biotic designed to restore ClpB levels in individuals who are overweight or obese. EnteroSatys, a food supplement available in France, contains a bacterial strain called *Hafnia alvei* 4597, originally isolated from raw milk cheese, along with bacterial-derived protein. “In our opinion, the problem [of excess weight and obesity] is eating behavior,” said TargEdys CEO Grégory Lambert. EnteroSatys works by “re-educating people on their choice of food and life-style,” and “helping them learn new behaviors.” It does not suppress appetite, Lambert emphasizes; instead it “normalizes it, restoring the natural [ClpB-mediated] mechanism” of appetite regulation.

TargEdys cannot make any health claims about EnteroSatys; no pro-biotic has been approved to do so in Europe (See Box: Pro-biotics, Food or Drug?). But TargEdys can show doctors and nutritionists preclinical, clinical and consumer data supporting the product. A “big” clinical trial is ongoing, according to Lambert, with results expected early in 2020. Preclinical work suggests that the bacteria does reduce food intake and weight, though not as much as Roche’s fat-blocking drug Xenical (orlistat). A consumer study of 45 people showed that 70% felt fuller after taking EnteroSatys, and felt that they had better control over their eating.

There is more to do to prove the product works: scientists do not yet understand precisely how important ClpB is in host appetite control, nor do they have conclusive evidence of causality between changes in microbiota composition and host feeding behavior. If such evidence accumulates, TargEdys may find the partners it needs to distribute its product beyond France; Lambert added that the company might also consider developing the protein as an active pharmaceutical ingredient, or as a live bio-therapeutic. “We’re waiting for the regulation to be a bit clearer” around live-bugs-as-drugs, he said.

**Using The Gut To Enhance Immuno-Attacks On Cancer**

Several companies are using gut-derived microbes and metabolites to re-direct the immune-system to fight cancer – potentially enhancing the actions of existing checkpoint inhibitors and other marketed immune-oncology drugs. Definitive evidence of such enhancement would take microbiome-derived drugs into the big league.

Such evidence is not yet available. Clinical trials have begun, though, of various microbial mixtures chosen for their immuno-genic actions. Evelo Biosciences, based in Cambridge, MA, has selected single microbe strains that are thought to modulate various immune pathways on their passage through the gut. Its orally-delivered, cancer-focused “monoclonal microbial,” EDP1503, in December 2018 began a Phase I/II trial in combination with Merck & Co. Inc.’s market-leading checkpoint inhibitor Keytruda (pembrolizumab). The trial will span several cancer types, including colorectal, triple-negative breast cancer. Evelo has other programs in inflammatory diseases.

Seres Therapeutics Inc.’s SER-401 is a mix of donor-derived commensal microbial strains chosen to improve patients’ response to checkpoint inhibitor treatment. It contains a bacterial signature found in melanoma patients that respond well to immunotherapy; the idea is to transfer that gut microbiome advantage
to others. The candidate is in a Phase Ib trial in metastatic melanoma, in combination with Bristol-Myers Squibb Co.’s Opdivo (nivolumab); preliminary read-out is expected in 2020. AstraZeneca PLC’s MedImmune signed a research agreement with Seres in March 2019, hoping to glean more about the mechanics of microbiome-enhanced cancer immunotherapy. The big pharma will pay $20m in fees and gets an option to negotiate rights to SER-401 and other candidates.

Meanwhile, BMS itself signed up in December 2018 to collaborate on a clinical trial of Vedanta Biosciences Inc.’s bacteria-based mixture VE800, combined with Opdivo, in advanced and metastatic cancers. The study is planned for 2019. VE800 contains 11 clonal strains of human commensal bacteria selected, like Seres’, to amplify the effects of checkpoint inhibitors. BMS is testing its drug with multiple different therapy-partners that might enhance Opdivo’s effectiveness, and thus its competitive standing, in the red-hot immune-oncology field.

Paris, France-headquartered Enterome Bioscience SA has made its drug candidates out of gut microbe metabolites, chosen for their high degree of similarity to various solid tumor antigens. EO2401 contains three such “onco-mimics,” matched to tumor antigens that are highly expressed in some kinds of brain tumor.

Also, investors see potential for Axial Biotherapeutics’ gut-selective technology in oncology: Taiho Ventures’ $10m contribution to the company’s B round in June 2019 is earmarked for that purpose. “There’s lots of enthusiasm around the [gut] microbiome and its effect on cancer,” remarked Domain’s Jim Blair. “It may be that elements of the microbiome can trigger some of the epigenetic processes” now known to be involved in cancer, he said.

A Neuro-Immune Super System?

Scientists now understand far more about the gut microbiome and its links to the brain than even just five years ago. But we are still at the early stages of mapping out the multiple mechanisms by which our resident bacterial communities influence our mental and physical health. For now, “there’s a lot of cataloguing going on,” said PureTech’s Bolen.

Increasing numbers of companies outside the regulated pharmaceuticals industry are capitalizing on scientists’ growing understanding of the gut microbiome’s role in health and disease. They are variously developing and marketing pre- and probiotics, food supplements and indeed food products, all of which offer lower-cost routes to market than conventional drugs, but which are limited in the health claims they can make. Several are working at the boundaries of probiotics and pharmaceuticals, for instance seeking to engineer live micro-organisms specifically to alleviate particular CNS symptoms. Emergent categories include “psychobiotics” – probiotics used to treat psychiatric disorders.

As the boundaries blur between drugs and foods, the need for clearer definitions and regulations is increasing. In Europe and the US, food or food ingredients cannot be associated with the treatment of a disease, only with maintenance of normal physiological functions. But are probiotics food? The European Food Safety Authority shies away from such questions, pointing instead to the European Commission and member states.

The US FDA might categorize probiotics as dietary supplement, food ingredient, medical food or drug, depending on the intended use. But even then, neither the category limits nor the precise evidence requirements are entirely clear. Makers of medical foods, for instance, can communicate benefits in the “dietary management of a disease,” but only if said disease has “distinctive nutritional requirements,” as established by “medical evaluation.” (In Canada, regulators in 2016 authorized a probiotic claiming to moderate anxiety and promote a healthy mood balance – a product to enhance the brain-gut-axis.)

As for bugs-as-drugs (carefully-selected strains of bacteria packaged up as prescription biopharmaceuticals), the FDA has not yet approved such a therapy, though several live gut microbiome-based products are in late-stage clinical trials. There is no firm regulatory framework, but draft guidance exists, and FDA is engaged in discussions with industry on how to treat this emerging category.

Researchers have found compelling correlations between levels of specific gut metabolites and certain disease phenotypes, but only rarely has a causal link been established. There is also more to learn about redundancies – what kinds of back-up mechanisms may come into play when a given pathway is interfered with? There remain knowledge gaps around the gut microbiome itself: scientists still do not know the function of many of the genes within gut microbial genomes, even among well-studied species. And the parameters of a “normal” gut microbiome remain to be determined: we understand that species diversity is important, but details of what comprises a “healthy” or “disease” state for a given individual are elusive.

Yet even as the contours of the gut-brain-immune axis are being uncovered, its relevance to disease is unquestioned. The top dozen or more chronic illnesses can be divided into either diseases of the immune system or of the nervous system, said Bolen. In the face of changing diet, life-styles and environmental stressors, these are “the only two adaptive systems” individuals have. Given the cross-talk between them, “they might more realistically be thought of as one super-system.”

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Comments:
Email the editor: Lucie.Ellis@Informa.com
In the EU, shortages are defined differently depending on the member state concerned. Reporting requirements vary widely, as do methods of measuring and addressing shortages, and it has become increasingly clear that taking a common European approach is the only way forward.

Efforts to do so have, until now, had limited success. But in early July, after three years of work, the European Medicines Agency published new guidance intended to help stakeholders deal with drug shortages. The guidance includes a common definition that regulators hope will help to kick off the next stage in the drive to tackle this knotty problem.

Drug shortages are not a recent phenomenon. Pharmacists in Europe have faced supply disruptions on a regular basis for many years, particularly in the hospital sector. Still, a survey by the European Association of Hospital Pharmacists (EAHP), published in November 2018, found not only that shortages were still occurring despite the best efforts of supply chain actors, but that the situation had worsened since its previous survey four years earlier.

“In a number of ways, these issues have become more problematic since the 2014 survey,” the EAHP said. Hospital pharmacists were spending more and more time trying to obtain information about shortages, and often they did not have enough – or any – advance warning to allow them to order substitute products where available. Around 90% of respondents across Europe said shortages were a recurrent problem, with many experiencing issues on a weekly or daily basis.

Antimicrobial agents were the type of medicine most frequently reported as having shortage problems, followed by vaccines and oncology drugs. The non-availability of medicines can be more serious for certain diseases such as epilepsy, where the use of...
alternative drugs is not always possible.

The European wholesaler association GIRP agreed that the problem had grown in recent years. It complained that full-service distributors regularly encounter difficulties in supplying a full range of medicines.

On the regulatory side, the European Medicines Agency pointed out that in such cases patients might have to be given less effective alternative medicines, or products that might increase the risk of medication errors or lead to adverse events.

The European Society for Medical Oncology (ESMO), which held an awareness-raising event at the European Parliament in April 2019, went as far as to speak of a “public health emergency,” pointing out that, particularly in the cancer area, there may be no alternatives to medicines whose supply is interrupted.

One thing all parties agree on is that the problem urgently needs to be addressed, and that this cannot be done by any single country alone.

The Reasons

The causes of supply problems are well known, ranging from raw material manufacturing problems and a decline in the number of suppliers, to safety concerns, drug pricing and procurement policies, as well as the failure of companies to place or maintain products on the market. Concentration and globalization in the manufacturing segment are key issues. GIRP noted that the “complexity and globalization of production, where active pharmaceutical ingredients [APIs] are sourced in one country, products are produced in another one and packaged in a third country leads to a high sensitivity for the slightest failure, which then can create a general shortage across Europe.”

Medicines for Europe, the association representing manufacturers of generic and biosimilar medicines, agreed: “The evidence is now compelling that many national markets across Europe are relying on too few suppliers for essential life-saving medicines in both the hospital and ambulatory sectors.”

The problem was highlighted in a French Senate report in 2018 that mentioned the “recurrent non-availability” of certain medicines such as anticancers and vaccines. The report also noted that 35% of the raw materials used in manufacturing medicines in France came from just three countries: China, India and the US. (Also see “Make Them In Europe: The French Solution To Drug Shortages” - Pink Sheet, 30 Oct, 2018.)

ESMO said that countries with small markets and relatively low drug prices were especially vulnerable because of the lack of incentives for manufacturers to keep supplying the market. It also suggested that parallel trade was “an important cause of medicines shortages” in certain countries, although GIRP disputed such a link. GIRP said “our initial reflection has not uncovered any real-world evidence to support this, and it is notable that many academic studies on this subject recycle stakeholder claims rather than give concrete facts and figures.”

Change In The Air?

European regulators have highlighted that the lack of a clear definition has meant that efforts to detect and coordinate the management of shortages in the EU have been inconsistent, while differences in reporting requirements have made it impossible to make comparisons of the situation in different countries. However, things could be about to improve after a task force set up by the EMA and Europe’s Heads of Medicines Agencies produced the first fruits of its labors in July 2019, in the form of two new guidance documents that included an EU-wide definition of a shortage and recommendations on the kind of shortages that need to be reported.

The task force, which was set up in 2016, is co-chaired by Kristen Raudsepp, head of the Estonian drugs regulator Ravimiamet, and Noël Wathion, deputy executive director of the EMA. Raudsepp told In Vivo that shortages and availability problems were complex and their causes “multifactorial with no quick solutions.” She said that drug regulatory authorities were just one of the many actors involved in availability issues, but that they played “an important role in their prevention and management. By bringing together experts on shortages from every EU member state the work of the taskforce lays the foundations for an improved and harmonized EU approach in addressing the problems of medicines availability issues.”

She added that the new definition agreed by the task force and stakeholders would guarantee the early notification of shortages, complement national definitions and allow national competent authorities to decide on the “criticality” of the medicine and the availability of any alternatives. It was also, she said, “simple, short and concise.”

The first iteration of the definition produced by the task force in December 2017 was anything but: “A drug shortage occurs when there are changes to either demand or supply of a drug, and demand can no

Exhibit 1

How Often Does Your Hospital Pharmacy Experience Medicine Shortages?

Note: EAHP survey results include 1,666 responses from 38 countries
longer be met. A drug shortage causes unexpected and unplanned temporary unavailability. The total stock across all levels of the national supply chain, across all geographical regions, cannot meet demand during a drug shortage.”

The definition subsequently underwent a number of iterations, and a much slimmed down version was presented in November last year at an EMA workshop held to gather the views of all interested parties. This stated simply: “A shortage of a medicinal product for human and veterinary use occurs when supply cannot meet demand at a national level.”

Following a targeted consultation with industry, the definition was later slightly reworded to read “does not” instead of “cannot.” It has now been formalized in a new guidance document that was published by the EMA on July 4, entitled Guidance On Detection And Notification Of Shortages Of Medicinal Products For Marketing Authorisation Holders (MAHs) In The Union (EEA).

The definition “clarifies regulators’ expectations with respect to minimum obligations of supply chain actors to ensure continuity of supply of medicines while paving the way for harmonized reporting of shortages across the EU/EEA,” Raudsepp said.

The EMA guidance also explains which issues should be reported: i.e. all shortages that are currently affecting one or more EU member state, and all impending/anticipated shortages that are expected to affect one or more EU member state. This includes all shortages that have occurred or will occur because of regulatory issues, quality defects or any other causes, such as good manufacturing and distribution practice issues, batch failures and medicine product recalls. It says that marketing authorization holders are in the best position to provide relevant supply information “as they have visibility of their stock, both national and global, taking into account foreseen shipments from their manufacturers.” A template for notifying shortages accompanies the guidance.

The information provided will be used by the relevant authority to assess the situation. It should therefore be “as accurate and up-to-date as possible, while being comprehensive and concise at the same time,” according to the guidance.

EU legislation requires the notification to be made no less than two months before the supply interruption, but the new guidance says MAHs should notify the authorities as early as possible, as soon as the shortage is confirmed. There may also be national reporting timeframes that should be taken into account.

Public Communications

A key question when dealing with a shortage situation is how best to communicate relevant information to the public, including health care professionals. As the EAHP said in an updated position paper in June this year, “only a comprehensive communication strategy on shortages targeting all European states will ensure that all supply chain actors, including hospital pharmacists, receive adequate information on the shortage of medicines in their countries.”

The task force has been working on this too, and on July 4 the EMA published a second guidance document explaining the key principles and examples of good practice for communication to the public on shortages as well as availability issues relating to the revocation or cessation of marketing authorizations. The document includes “key principles and examples of good practice,” although the EMA stressed that it was intended “for guidance only.” It said that implementation of communications practices “should be a matter for EMA and EU national competent authorities taking into account available resources and the communication needs within their territory.” It recommends that the EMA and national authorities use systematic listing – usually in the form of a catalogue – to communicate information about shortages. In the case of “high-impact” shortages, consideration should also be given to using high-profile communication tools such as press releases.

Collection And Evaluation Network

Aside from its work on the two guidance documents, the task force has been looking at how to address disparities in the way that EU member states collect and evaluate information on drug shortages, how that information is shared among regulators, and how it is communicated to others such as health care professionals and the public.
Raudsepp said a key objective of the task force was to set up a virtual network of experts from human and veterinary agencies across the EU to share information on availability issues and to provide a discussion forum for collaboration. “This network was set up in 2018 and its operation is currently being piloted to fine-tune operational aspects,” she said. “The key role of the network is to share information in relation to shortages and availability issues of authorized medicines in Europe, irrespective of the licensing route of these medicines in accordance with agreed criteria.”

The operation of the network will be described in a best practice guidance for regulators on sharing information within the EU regulatory network that will be submitted for adoption in December 2019, after which the pilot phase will be completed.

Two other items are scheduled for adoption in December: a set of recommendations on how to measure drug shortages, and an “EU Regulator’s Manual,” a compilation of existing tools for notification, coordination, assessment, communication and reporting of drug availability issues.

**Language Issues**

Another issue that can exacerbate the impact of a shortage is the language barrier. Medicinal products in the EU are labeled in the local language, which can make it difficult for a country experiencing a shortage to source a product from another country. Multilingual packages would allow industry to use the same labeling in a number of EU countries and were an important measure to mitigate imminent medicine shortages, Raudsepp observed.

She said the taskforce had “further simplified and minimized labeling requirements” and that these measures would be reflected in a revised Quality Review of Documents (QRD) template and in guidance on exemptions to the labeling and package leaflet obligations in the centralized procedure.

**ESMO Initiatives**

Meanwhile, ESMO has been working on its own activities to raise awareness of the causes and effects of drug shortages in the anticancer area. The society was one of the participants at the November workshop, where it spoke about the issues that particularly affected oncology drugs.

More recently, in April this year ESMO organized an event at the European Parliament where it declared shortages to be a “public health emergency.” Josep Tabernero, president of ESMO, said that the situation was particularly acute in the oncology area, pointing out that both new compounds and “old, inexpensive essential medicines” were affected, but that shortages of the latter “tend to be overlooked.”

“In oncology, shortages of generic, off-patent medicines are more pronounced because most often the medicines cannot be substituted. The patient’s treatment is halted until the medicine becomes available,” Tabernero told In Vivo.

ESMO said the April event was important because “it brought together all key stakeholders, policymakers, the European Commission and patients to hear their concerns and to convey the seriousness of this issue at the EU level.” The event also marked the launch of a “call to action” signed by 20 members of the European Parliament and 16 stakeholder groups to highlight ways of tackling this issue, as well as a number of concrete actions to be taken. They include developing an EU-wide study on the issue of medicines shortages and their overarching impact on the EU through independent advisory bodies on social and economic affairs, and “positioning inexpensive, essential medicines shortages as a key political priority for the EU 2019-2024 legislature.”

Tabernero, who also heads the Medical Oncology Department at the Vall d’Hebron Barcelona Hospital in Spain, said that stakeholders at the event “unanimously agreed” there was a need for a supranational solution, and that they supported ESMO’s call to action. It was agreed that a coordinated strategy was needed, with dialogue among the various stakeholders and partners, and not only at the EU level. One MEP at the meeting, Lieve Wierinck, said it was important to tackle medicines shortages “from a collaborative and international perspective.”

Wierinck said that “as a pan-European issue,” the EU needed to tackle the issue centrally and to convince its citizens that medicines shortages are “not a political issue but rather a fundamental human rights issue that everyone should tackle.”

Another MEP, Soledad Cabezón Ruiz, picked out three key challenges:

- industry and manufacturers should have the obligation to supply, and this supply must be assured and backed up by sanctions;
- parallel trade must be controlled;
- and a database should be developed to see which factors contribute to exacerbating this issue.

It was also noted at the meeting, Tabernero said, that the Dutch government has been addressing the shortages question for a number of years, and has formed a medicine shortages working group that meets twice a year with stakeholders, together with a shortage reporting center. “The Minister for Health in the Netherlands has asked for an investigation of vulnerabilities in the supply chain of medicines at EU level and called for further collaboration at the European level,” he declared.

Stakeholders at the event agreed that an EU-level study was needed, and that two workstreams should be pursued: addressing the root causes of shortages, and increasing collaboration and information sharing. ESMO would like the study to be conducted by an independent advisory EU body such as the European Economic and Social Committee.

Tabernero said ESMO would be conducting its own new survey to “assess the situation on the ground,” and would continue to collaborate with policymakers, the new European Commission and the EMA, among others, “to work towards finding a solution to mitigate this issue, which should not exist in the EU, or globally.”

He also highlighted that certain procurement practices for generic medicines could result in medicine shortages. “The choice of procurement method and type of award should be based on a comprehensive analysis of the market conditions, for example, the number of suppliers in the market, the market capacity, demand for the product, its cost, plans for future use, etc.” he said.

“When risks to supply security are identified in this analysis, the tender criteria and agreements should be adjusted to mitigate this risk. For example, extended contract periods could be used, or agree-
ments that ensure supply guarantee.”

Tabernero also recommended identifying good procurement practices that “address predictability and profitability for medicines manufacturers.” These could include using tender criteria that include price as well as other factors, such as the manufacturer’s quality track record, the harmonization of tender cycles within and across countries, as well as national procurement for medicines experiencing shortages.

**Brexit**

As in most things, of course, Brexit casts yet more uncertainty over the future supply of medicines, particularly if the UK leaves the EU without a withdrawal deal or a transitional period. There have been some anecdotal reports of medicine shortages in the UK being attributed to the lack of clarity over the UK’s future ties to the EU, but there does not seem to be much concrete evidence of a direct correlation.

Noting that shortages have complex and multifactorial causes, Tabernero said it was “hard to determine whether the recent increase is due to Brexit or to other reasons. However, it could also be that Brexit is [indirectly] contributing to the recent increase in shortages, through the contingency planning, including for example, the stockpiling of medicines.”

But the possibility of shortages in a no-deal Brexit scenario is a real worry, and the UK government has produced a number of documents advising pharmaceutical companies on what to do to mitigate the risk, including building up an additional six weeks of stock over and above normal levels.

In its latest advice, published in June, the government said that “significant disruption” to supplies could be expected in a no-deal scenario. It proposed a number of further actions including “express freight contingency arrangements” and re-routing deliveries away from the channel ports. (See also “UK Pharma Decries Govt’s Latest No-Deal Brexit Planning” - Pink Sheet, 27 Jun, 2019.)

Then, in July, new no-deal Brexit legislation on serious shortage protocols (SSP) took effect, under which pharmacists will be allowed to dispense alternative products, including generics and drugs with different active substances, in the case of “extreme” shortage scenarios. Under the new rules, the Secretary of State for Health and Social Care could issue an SSP in cases of serious shortages of medicine, after consultation with medical experts.

The SSP would specify an alternative product or quantity other than that on the prescription that could be supplied by a community pharmacist. This could be an alternative strength or formulation, a generic or therapeutic alternative, or a reduced quantity of the product. (See also “‘No-Deal Brexit’ Pharmacy Substitution Rules Take Effect In UK” - Pink Sheet, 2 Jul, 2019.)

Action is also being taken at EU level. Raudsepp noted that since May 2017 European regulators had been issuing guidance and urging companies to make the necessary changes, such as transferring marketing authorizations, rapporteurships and batch testing from the UK to the EU to minimize the risk of supply chain disruptions in the event of a no-deal exit. She said the EMA and the EU regulatory authorities were “continuing to monitor the situation and advising companies on the necessary steps to take and urging them to make these changes on time in order to allow continued availability of medicines once the UK has withdrawn from the EU.”

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Had there been a table in front of him, ResMed CEO Mick Farrell would have leant forward and banged it hard with his fist. Twenty minutes into a one-hour session at the 2019 MedTech Forum on burning issues for global medtech CEOs, and we were talking – still – about the current and potential effects on business and patient care of the EU Medical Device Regulation; “we” being the Peters Surgical (Bobigny, France) and Werfen (Barcelona, Spain) CEOs Thierry Herbreteau and Carlos Pascual, along with Farrell.

Granted, it is the biggest short- and medium-term issue occupying the minds of those medtechs who want to continue serving the EU market, post-MDR. Is this level of attention a surprise, given the traditionally “technical management” status of regulatory themes? Well, yes. And there are other issues of a traditionally strategic nature to tackle: value-based health care, digital, the new generation of medtech thinkers and new ways of addressing clinical needs against rising demand.

But there’s no hiding the truly pressing themes from CEOs, some of whom are now regarding the EU Medical Device Regulation (MDR) as a major and unnecessary threat, while others are seeing it – and maybe regulation in general – as a potential strategic tool. For the latter – to borrow a favorite phrase of the Association of British HealthTech Industries’ (ABHI) Phil Brown – regulatory is no longer just an internal corporate mechanism championed by the group’s “sales prevention team.”

So what? Future medtech CEOs will have different values, digital nativity and the ability to think agile and find creative solutions to issues.
on apparently less high-profile – but no less vital – themes within their groups, for these will also dictate how well they fare commercially in the future.

They had just heard Rob ten Hoedt, addressing the MTF audience at the Paris Cité des Sciences et de l’Industrie building, voice the view that the MDR is necessary, must be adapted to, and will not bring the unremitting gloom that many of its critics fear. Not all the panel agreed with the detail of the Medtech Europe president as he gave his open support for the MDR; but none denied the soundness of the principle. Nevertheless, the three offered their own slants on how best to introduce radical new regulation.

**MDR – Too Much, Too Soon**

Farrell would not say that the MDR was wrong or unnecessary, precisely, and qualified his criticism of the current rush to install the regulation by saying that it could be an error to “do the right thing too early.” This is another way of saying it could be the wrong thing right now, and could do harm in terms of access to patient care. The European Commission, for its part, is not ready to embark on contingencies. This position was aired publicly by commission head of unit Salvatore D’Acunto in an MDR panel session at the MTF moderated by this author.

So, no contingences, a view backed up by French notified body G-Med’s president, Lionel Dreux, to me in conversation at the MTF. But the most obvious hurdle in the whole MDR exercise is indeed notified body preparedness: there are now just two notified bodies accredited to do work under the MDR. As a reminder, there are still 58 notified bodies operating under the (three) directives.

“We may have five notified bodies within the next 12 months. But all the inputs, i.e. products, might get stuck in bottlenecks, and so we don’t get the outputs – i.e. products on the market,” said Farrell. “There is no question that improvements needed to be made to the CE mark, and the MDR is the right direction, but I think the implementation is too fast and it needs to be phased in a much more longitudinal way.” The EU should be looking at a five- to 10-year plan, instead of 12 just months, he said. In fact, there are less than 12 months remaining to transition before the MDR is implemented on May 26, 2020.

Farrell is not “massively concerned” for his own business under the change from Directives to MDR, but he fears that some orthopedic products (Farrell is on the board of directors of Zimmer Biomet) might not be able to get through the “funnel.” These are “great technologies,” he said. Maybe that’s the case for many companies and their innovations, hence Farrell’s view that the MDR is the right thing, but is coming too quickly.

Herbreteau is, if anything, even more concerned about the topic. “First of all, we need to adapt. But as an EU company, I am really concerned” about the effects of the MDR and IVDR. Peters Surgical’s business is in surgical products sterilizing and single-use products, with a strong international focus. The CEO’s ambition is to double growth, which would need quick and efficient access to country markets.

“In Europe, it has always been so that we could get in there with innovation first – but that’s no longer the case. It’s going to be more complicated and more bureaucratic.” It is now easier now to go to the US than to Europe, where there is now a level of unpredictability, “Companies will go where they know, and the US has done a lot to speed up its processes.” Europe seems to be losing the battle there, he said.

Many cannot help seeing the MDR as another barrier to market. “The big groups, and those in the middle, can adapt. But for start-ups, it’s a disaster.” Europe already has a lack of funding and now, with stricter access, what’s left? he asked. His frustration is evident, as he knows this money could be spent better.

“I would prefer to invest in R&D or in contact with customers. We need to invest in people. And no one has proven that...
European patients are less well treated than US patients. I still don’t get it!”

**Quality Will Not Be Enhanced Under IVDR**

The IVDR may be two years further away, but Werfen CEO Pascual is as concerned about it as his medical device counterparts are with the MDR. With over 30 years in the industry, especially in IVDs, he now sees a major challenge in adapting and providing more value over the next ten years – a time when there is expected to be a significant increase in health care demand. But there is a challenge in how to pay for it, as the way it has been funded – especially in Europe – over the last 30 years is not sustainable.

The IVDR will not help this drive to provide enhanced value. Pascual said the industry was focused on that as part of its current remit. The frustration for IVD players that have become accustomed to the existing IVD Directive is palpable. “It is difficult to imagine that in the next two years we will be able to go through new regulatory process with all products still on the market,” he said in a generic reference to IVD industry players. “We are not just talking about new products, but all those tests that have been on the market for the past 30 years that now have to go through this new regulatory process.”

Adapt and get on with it is the stock CEO view how to broach such problems. But there is almost a feeling of a sense vacuum. “For us as company, we are working on it, but the new regulation will do nothing to increase the levels of quality that we provide,” Pascual reiterated. “We will continue to work in the same way; we see this as a regulatory issue and as a very important challenge for the industry and citizens of Europe two years from now.”

There will likely be an impact on Werfen’s business, and yet Pascual is adamant that the quality of his company’s products will not improve simply by the new IVDR being brought into place. “So, we have to adapt, increase our costs, invest less in other areas to compensate for things that do not bring any value. When you have tests that have been working well for 20 years with no patient issues at all, demonstrating value all the while, why do we now have to do clinical trials to demon-
patients, said Farrell. “We take ethics and privacy by design incredibly seriously, particularly in the digital health space.”

Trust is hard won, and easily lost, or, as Farrell put it, “Trust is something that runs away on a horse and comes back on foot.”

**New Generation Of Leaders**

Concerns have been aired in the past about the attractiveness of the medtech industry for new entrants, and about who will lead the industry once the current vintage of CEOs decides to make way for the next candidates. But any worries are no longer justified, if they ever were, especially now medtech is on the cusp of a digital future. To put it in context, “The generation before us was also worried about us,” Farrell observed, and yet the current crop has done passably well. He added, “I think we’re going to be just fine.” And, of ResMed, he said the new crop of managers would revolutionize the company better than the current management.. “They’ll take it to the next level.”

Many staff are now wanting to join Peters Surgical, said Herbreteau, and one of the first questions they ask is about the company’s corporate social responsibility (CSR) policy. They want to know, beyond making products and profits, for instance, about energy saving, about manufacturing sites around the globe, and about whether the company is a good employer.

Ethics is not just by design, the Frenchman opined, but also “by culture.” In fact, it is a matter of culture and values. “If we’re still in the belief that it’s not attractive, one way to make it more so is to play on the ethics and the CSR side, and care more about patients.”

Werfen looks for values and “good people” that will represent the company. “We look for people with values over and above their qualifications.” Leadership people almost self-select. “If you want to be a manager in the medtech industry, the first thing you have to do is look to lead people properly and enjoy doing that. This is a challenge, and the most difficult position in a company,” the Spaniard said.

A company might have the best vision or strategy, but it cannot succeed without bright managers that understand they are there to serve the rest of the organization. “They are managers because the rest of the organization needs developing and coaching, and it needs help to perform properly.”

Honesty, integrity and trust are at the top of Farrell’s list of candidate’s assets. But also, “are they passionate about what we want to do at ResMed?” Specific talents and skills are needed, people who understand deep neural networks, advanced analytics, can think agile in terms of profitability versus waterfall, and can use different creative approaches to problems. “They are the thinkers who can reinvent our industry. We’re looking now at the talent we need for 2025, specifically those who can focus on the patient and create the industry we want.”

The CEOs agreed that the industry needs people who are ready and capable of making changes, taking risks, and those who have extraordinary skills and who know that it is acceptable to challenge, disrupt and push boundaries. “Young people now want to understand more and more the reasons behind what we do. The next generation is very idealistic, and, more than any other watching what you do, not what you say,” said Farrell. They also want to see the CEO walking the walk, spending time out in the community and giving back to the community.

The new generation relies on communities and their own connections. They are also ready to be more mobile, prepared to have a career spanning 10 jobs, where, in the past, two was more the norm.

**The Value-Based Setting**

Value-based health care (VBHC) has been slow to arrive, but its advantages are compelling: in France for instance, there has been a lot of change around VBHC over the past year. “There’s differentiation between cloud-connected reimbursed sleep apnea therapy and non-connected therapy,” said Farrell. “It’s revolutionized this country’s care, and over time has ensured that patients have higher compliance and stay out of hospital.”

And it will work, because governments are looking at the long-term return on their health care investments. It is taking time because it needs to be pragmatic. The VBHC approach has been changing outcomes in the past few years. All products now tend to take into consideration their effect on patient outcomes, the patient experience and how to control health care expenses. Ten years ago, the industry was thinking safety and intended use. Now it is more of a long-term vision and a joint challenge with governance, not just an industry challenge.

**Leadership Styles**

CEOs are many things to many people, but should they be ready to take a public view on societal issues? For Farrell, it should never be about politics, but policy and value. For Pascual, the public face should not go much further than CSR issues. But CEOs must be ready to react to politically inspired changes, such as Brexit. For Herbreteau, it is a case needing to be prepared, not over-preparing for the unknown, and ensuring whatever the change, that it will be acceptable for patients.
BY WILLIAM LOONEY

The Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) agreed in December last year between the UK government and the Association of the British Pharmaceutical Industry (ABPI), representing private-sector makers of branded medicines, is the latest in a series of five-year pacts on pricing that date back to 1957.

Its noticeable achievement is a government commitment to boost patient access to new innovative medicines, addressing the most distinctive feature of the UK drugs market: slow uptake of the latest therapies, at five years on average compared with other industrialized countries, especially the US.

So what? A predictable, rules-based VPAS in place for the next five years may help mitigate some of the domestic industry uncertainty associated with Brexit.

RICHARD TORBETT

Richard Torbett, the ABPI’s executive director for UK and international commercial policy, handled day-to-day representation with a small group of company managers during the year-long negotiation, which benefited from the initiative of both sides to bring a greater diversity of players to the table, including the powerful England wing of the National Health Service (NHS).

In Vivo: On the premise that the past is prologue, what was different about the new Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) that entered into force in January, compared with the 2014 negotiations? What does this say about the overall state of the relationship between the branded biopharma industry and the government?

Torbett: A distinguishing feature of the UK biopharma landscape is the desirability of maintaining a structured and predictable approach to managing the cost of medicines. There has been a voluntary arrangement to secure this objective since 1957, renewable every five years. The original premise was to cap branded industry profits, based on the idea that individual companies could offset their investments in the UK against the liabilities incurred by the cap. However, as globalization of supply chains and trade liberalization took hold, such an explicit connection between pricing and profits became harder to implement.

The result has been a subtle shift in emphasis by the government away from a straightforward profit cap to a conversation with the industry about structuring expenditures on branded medicines, as well as how to manage the price setting process for new products. Up until the 2009 Pharmaceutical Price Regulation Scheme (PPRS), we had list price reductions across the portfolio of branded medicines available through the National Health Service (NHS). The way it worked is that once these reductions were agreed, companies could “modulate” or apportion the cuts across their full product portfolio. The 2014 scheme was agreed at an unusual period of economic austerity in

In Vivo speaks to the UK branded industry’s negotiator for the latest five-year joint pricing pact with the government, Richard Torbett, who outlines, among other topics, five widely applicable precedents from the talks that can work in “getting to yes” – despite the fractious budgetary climate for health care evident in all major country markets.
the UK, which led to a move away from list price reductions to a cap in the growth of branded medicine sales.

The 2018 negotiations, which set the rules for branded medicines in the NHS to 2023, was distinctive from these earlier pacts, in several ways. First, the circle of players was larger this time. In the past, our sole negotiating partner was the UK government in Westminster. Although the health department’s role was critical in securing the financial provisions of the former PPRS, from a practical sense it has for some time been the NHS in England, Wales, Scotland and Northern Ireland that determine the actual conditions by which medicines are reimbursed on the market. It was a breakthrough in the latest round to have NHS England fully engaged alongside the Department of Health and Social Care in Westminster, with officials from these devolved parts of the UK providing input at key points in the negotiations. It was a first that what we now call the Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) has a separate chapter covering implementation of the scheme in England, the largest market for medicines in the UK, drafted in collaboration with the NHS.

Second, the negotiations accomplished a central goal of industry in putting the larger question of market access on the table, for the first time. Access joins pricing in the title of the new agreement. Reflecting this, industry was able to initiate a dialogue on conditions at ground level, especially regarding the experience of providers and patients in obtaining medicines for the right condition, at the right time. We were able to establish a consensus in identifying solutions to barriers to market access and to prioritize the role that medicines play in securing better health outcomes in the NHS. This includes a review of ways to make decisions taken by the public cost-effectiveness arbiter, the National Institute for Health and Care Excellence (NICE), more timely and transparent.

How was industry organized for representation during the VPAS negotiations?

The Association of the British Pharmaceutical Industry (ABPI), where I serve as executive director for commercial policy for the UK and international, has a membership of 70 companies active in the R&D space who supply more than 80% of the value of medicines used by the NHS. The ABPI has a special designation under the Health and Social Care Act to represent all companies that sell branded medicines in any statutory-based consultation with the government. What this means in practice is the ABPI devotes an enormous amount of time on industry-wide representation to the government – if we are not actually at the negotiating table, we are preparing for it in one way or another. On the positive side, it allows us to engage in the life sciences space on multiple fronts, from the small biotech to the global big pharma companies based in the US, Europe and Japan; each has diverse product portfolios at different stages of R&D. It’s a thriving community, one that we survey constantly to test ideas and priorities that should be topmost in the continuing dialogue with government. A tactic we pursued with some success during the VPAS negotiations was to convene regular “town hall” meetings that mixed ABPI members with other companies outside our circle. It was a way for us to interact with them and to give and receive feedback. This put me and my team in a better position to negotiate on their behalf with the government.

Can you provide some detail on the scope and pace of the 2018 negotiations?

The formal negotiation took up nearly the entire year. We spent the first quarter in a number of preparatory workshops, which can best be described as negotiating about negotiating – testing our preferences, drawing boundaries and setting objectives. After that, we were in line-by-line negotiations right up to December. Both sides worked to keep the actual negotiating team small. For the ABPI it was myself, and a few general managers from the member companies selected for a mix of company size, product portfolios and geography as well as individual expertise and experience. Our lead was Louise Houson, managing director of Merck Sharp & Dohme (MSD) UK. The government team consisted of a lead from the Department of Health and Social Care as well as representatives of NHS England.

As the talks progressed, we brought in civil servants representing the different nations of the UK as well as industry people, all with specific expertise relevant to issues being debated. This is the venue where most of the details in the agreement were hammered out, with the lead negotiating team providing strategic guidance and resolving problems as they arose. Both parties benefited from choosing a more diverse group of negotiators than in the past, while keeping it small enough to be decisive when needed.

Were patients or other external stakeholders outside government and industry engaged in the negotiations?

The patient perspective on VPAS was very important to both industry and the government. We both had a good dialogue at key points in the negotiations with patient organizations through the Patient Organization Forum, which comprises around 40 UK patient advocacy groups. The success of this scheme will ultimately be judged on whether we do a better job over the next five years of ensuring patients get access to the medicines they need.

Working on international advocacy for the R&D-based industry is part of your remit at ABPI. When you face audiences outside the UK, how do you describe the UK industry’s place in the global biopharma ecosystem? Does the market stand out as a source of best practices or is it better seen as a lesson in avoidance?

The UK presents a mixed picture for the industry. Compared with other developed economies, the UK simply doesn’t invest as much in health care – we rank sixth among the G-7 largest advanced economies, just above Italy. Of the 34 rich country members of the Organization for Economic Cooperation and Development (OECD), the UK spends a little more than 9% of its national health care budget on medicines, well below the 11% average for similarly sized countries in the group. The UK is also noted for its therapeutic conservatism, resulting in a slower than normal uptake of novel innovative medicines compared with the US, even after cases where NICE has evidenced these as cost-effective.

It’s particularly slow in the early years after launch. In fact, the UK government’s Office for Life Sciences publishes something called the Competitiveness Indicators, which compares the UK uptake rate against a basket of other countries like the US, Japan...
and the other major European markets. What we find is that in the UK it takes about five years for UK patients to receive new cost-effective medicines at the same rates as in other countries; overall, for every 100 patients who gain access to a new drug in the other markets in the first year after launch, only 21 receive it in the UK. This “innovation gap” in access at launch is a serious festering issue for the UK industry. It makes securing new investments by foreign drugmakers here quite problematic.

Along with therapeutic conservatism, the UK has a perspective different from the US and many other markets in accepting that rationing of care is sometimes necessary to preserve the principle of equity of access overall. Doesn’t that create problems in justifying the drugs bill when so many other aspects of care delivery are vying for the same limited resources in a single-payer system?

I think access is now firmly on the agenda of health policy in the UK, which is a trend that is advantageous to the innovative drug industry. There is growing awareness that medicines can drive efficiency improvements by keeping patients with chronic conditions outside hospitals and emergency rooms. I see a willingness to change the old way of thinking of budgets as a zero-sum game. The National Institute for Care and Health Excellence (NICE) is still very much part of the landscape. There is a constant need to evolve NICE’s methods and processes, particularly to cope with rare diseases and new advanced therapies. But at the end of the day setting clear common standards for cost-effectiveness is seen as important for industry – especially within a budget-capped market – as it is for the government. NHS England is now a key player too and will increasingly take a central role in negotiating commercial arrangements with drug companies.

All of this is reinforced by the VPAS emphasis on incorporating market access as a priority equal to pricing.

Underlying and not often noticed is a series of initiatives to define a coherent national industrial policy for the life sciences, one where biopharmaceutical competitiveness becomes integral to the UK’s economic future. Ironically, Brexit is helping drive the effort because it necessitates reinforcing that the UK remains one of the world’s leading locations for drug R&D. We still have more R&D taking place here in Britain than in the other 27 members of the EU.

The UK is also mobilizing government as funder of “mission oriented” research, through broad public interest projects that try to stimulate thinking on how technology can solve health challenges of the future. The inspiration is around precedents in the US, like the Department of Defense Advanced Research Projects Agency (DARPA), which, among other things, supports the life sciences industry through cutting-edge technologies designed to address latent threats like drug-resistant pandemics. In the UK, work is progressing to see how industry, academia and government can coalesce around big topics like aging or digital transformation in health services.

I think there is a real opportunity here, particularly given the NHS has access to enormous quantities of patient data and is committed to making better use of it to manage costs, enhance the patient experience with care and improve outcomes. If we can join the dots and create data sets that link genomic information to EHR records, and combine that with the aggregating power of a single-payer system, then you have the knowledge and scale to highlight the cost-effectiveness of different interventions like drugs – and increase access to health overall. To me, this kind of creativity and innovation offers a brighter future for the UK market than our current challenges might suggest.

What specific aspects of the VPAS best positions the industry to secure this brighter future?

If you consider the iterations of these voluntary schemes over the years, we have gone from a rigid cap on the profits the industry derives from the demands of providers and patients for our products to the current situation where we have an allowable growth rate on total sales of branded medicines across the UK. It’s a more flexible arrangement for individual companies. The agreed growth rate of 2% each year for the next five years on net sales is actually double the rate allowed under the 2014 scheme. While the government expects the VPAS to yield approximately £1bn in savings on the drugs bill over five years, overall we think it’s a positive by giving more room for the innovative market to grow while also ensuring predictability as to what this country will spend on branded medicines going forward. This is in marked contrast to the frequent surprises the industry experiences elsewhere in Europe when it is targeted for cuts or “give backs” during the annual factional struggles over health spending.

There are many other provisions that the ABPI considers as markers of progress for the UK branded industry. One is the joint commitment of both parties – government and industry – to support “best” innovation in therapeutic classes and to aid the growth of small biotech. One practical step to accomplish this is an exemption for new active substances from payment to the NHS during the first 36 months after receiving licensing approval.
effect, this is an incentive for branded companies to focus on introducing new products to meet unmet medical needs. A concession to small companies is elimination of the growth-limiting £5 million annual ceiling on sales revenues, below which a company remains exempt from the voluntary agreement’s payment mechanism – simply put, it meant that any company that sold even a penny more than £5 million was in for the fix for the full 100% of its sales. That’s now replaced with a generous tapering mechanism giving more wriggle room for growing companies to manage their exposure to VPAS pricing provisions.

The other aspect is non-financial and entails a set of commitments to improve collaboration between industry and government on issues like providing more clarity on the interactions between NICE, NHS England and other government entities that often complicate the terms of commercial access for the industry in launching new products. And there is a return to joint activity with the government on “horizon scanning” to identify emerging technologies that might impact the NHS drugs bill in the future.

In essence, what we’ve been promised through VPAS is a clearer path to commercial access – to have an easier, sensible conversation with decision-makers so that the right deal can be secured for the best product and under the right circumstances for the patient and the health budget. NICE, as the guardian on access, and NHS England, as the payer, are now under watch to replace the interminable back and forth that has slowed commercial access with a more flexible approach to structuring deals that meet these criteria. One aspect related to the VPAS negotiations is an upcoming review of NICE methodologies to ensure maximum transparency and more clarity in how it measures cost-effectiveness. The VPAS document endorses the review as a confidence-building priority for the UK industry. We look forward to that.

**How do you think foreign-based big pharma and biotech should evaluate the VPAS? As a major breakthrough or half of a loaf?**

ABPI members include all the major big pharma firms as well as leading biotechs based in the US. Our new president is from Novartis AG and our vice president represents Sanofi. There is a consensus among the foreign-based and domestic companies that VPAS will finally address the longstanding lag in uptake of new medicines in the early years after launch. Everyone agrees this is distinctive about the UK commercial environment and stands out as a major disincentive to innovation.

To make this commitment tangible, there is a provision in the VPAS requiring the government to identify the five classes of drugs that are likely to drive the most health gain to patients and to ensure the uptake of those products reaches the “upper quartile” of comparable countries. Discussions on these priorities are underway and the ABPI will do its best to hold the government to account for results. In addition, our foreign-based members continue to have problems in figuring out how to navigate those opaque and complex ties between the NHS, NICE, the Department of Health and Social Care and local authorities. The fact that NHS England, in a separate chapter of the VPAS, pledges to work with the ABPI to improve the decision-making process is seen by all as meaningful and most likely to yield results.

**Building on that, what lessons from your leadership on the industry side of the VPAS negotiations can you point to as precedent in negotiating with government and regulators to achieve change?**

Following on what I just said, I’d cite five points on the cultural determinants of successful negotiating. First, success is set even before you enter the room – it all depends on how well you prepare in advance. It’s about investing in the right analytical tools, including forecasting based on input from a diverse range of human sources. It’s spending time on formulating policy to drive consensus, choosing aptly among a small set of goals that are realistic for the target audience and can foster alignment going forward. This means in turn that a negotiator must be good at identifying common ground, as quickly as possible.

Second, I remind people that negotiation with powerful governments is not like buying or selling a car – the relationship, like it or not, is long term – you might call it permanent – and for that reason there is a premium on making both parties feel they are consistently obtaining value from the process. The real danger lies in failing to read the audience, pushing hard for too much too soon, and ending up in an adversarial dead end too early in the negotiations. If that happens there is no winner; everyone fails.

Third, the best counter to this outcome is to be highly disciplined in deciding at the beginning what the group needs to achieve – integrating the perspectives of both government and industry. Objectives have to be clear. Red lines have to be explained, leaving room for context. In addition, as a negotiating partner, you need a few early “wins,” again from both sides, which can maintain confidence further down the line in negotiations, when silo-thinking recurs and difficult trade-offs have to be made.

Next, you need clarity and candor about how...
the group will handle the tensions that inevitably occur over something as large as regulating an entire industry. It is critical to be set up to avoid a situation where the negotiations start being conducted in the newspaper – or on social media. It follows that the parties must decide what the process should be if negotiations stall or reach a stalemate. Is there a trigger to escalate the resolution of disagreements to decision-makers further up the food chain – if so, how should that be managed? Accounting for such a prospect in advance creates a “safe space” that either side can use when talks get out of hand. But that option should be used sparingly because if it becomes the norm it’s that much harder to go back to the table. You’ve lost trust. Disagreements get personal and from there relationships will founder.

Finally, while inclusion and engagement are prerequisites for an effective negotiating process, at the end of the day you have to empower your negotiating team with the authority to initiate and decide. The fact is it’s unproductive – virtually impossible – to go back to as many as 130 different life sciences companies in the UK and obtain their permission to pursue a specific course of action. The teams have to be given the leeway to act.

How were these strategy lessons reflected in the VPAS negotiation?

We spent a good deal of time at the beginning coming up with a straightforwardly simple statement of purpose, where we achieved an optimal balance around three things. First, everyone at the table agreed that maximizing patient outcomes and patient access to the best medicines would help the government control its budgetary exposure and raise industry incentives to innovate – a “win-win” proposition. The second common thread was to keep the UK innovating as a global center for biopharmaceutical investment in treatments for unmet medical needs, with government and industry contributing their fair share in making that happen. The third was to reiterate that pursuit of the other two goals should be consistent with a realistic view of the financial constraints on the NHS.

The focus on ensuring a sustainable industry was evident in addressing the problems of smaller companies in striving to innovate while confronting regulations that inhibit their growth. All of us agreed that this was something that required resolution through the VPAS – and we brought forward some special pro-growth provisions that ended up in the final text. But the debate within the industry got more challenging when the discussion moved on to the overall state of competition in the UK drugs market, and whether it made sense to introduce exemptions to the VPAS payment mechanism, such as when branded products are subject to very aggressive local tendering and procurement rules.

Now, some of our members thought this was a strong argument. The challenge was that, with so much of the branded market now being subject to a high degree of competition, if those parts had been excluded, the only segment left would have been the very medicines the industry agreed to protect the most – innovation! VPAS had to be inclusive in referencing innovation and to work for every one of our members – if it was to work at all. The ability to coalesce around this principle kept us on course toward an agreement whose simple takeaway message is to prioritize drug innovation in the health system. The lesson is you don’t succeed as a negotiating team unless your principles and your objectives are seamlessly aligned.

How important was evidence backed by data in bringing the talks to a successful conclusion? Or did the negotiations continue to be largely driven by politics?

Evidence counts today, perhaps more than it ever has. No evidence means some conversations with potential partners never even start. It was certainly a critical factor in the VPAS. The industry put a big effort in creating a drug forecast tool for the medicines budget through the next five years at the level of net spend. The government also had its own forecast, so debate about the relative merits of each other’s analytics proved a critical part of the negotiations. Beyond forecasting, I personally believe the industry is not investing enough in the generation of evidence that proves medicines create value at every stage of the patient journey. Of course, there is no doubt the industry is exposed to politics and often has to play with a weak hand. Not all conversations with stakeholders can be won with compelling charts or a detailed regression analysis. But it certainly helps.

It would be remiss to end without mentioning Brexit. Perhaps the best way to frame the question is: does VPAS carry the legal weight to remain in force through what appears to be an indefinite period of instability in British politics and institutions?

I cannot offer guidance on what Brexit will look like for UK biopharma, assuming it happens. Per your question, VPAS is a voluntary agreement, not a contract. Looking back 60 years, these five-year agreements were signed and implemented by Labor and Conservative governments – regardless of party, the provisions have stayed in place. Thus, it would be seen as a serious breach if a new Labor government renounced or revised the agreement negotiated by the current Conservative regime.

In my view, Brexit might actually reinforce the importance of VPAS in offering stability on pricing, better access and a visible public commitment to making Britain’s life sciences sector globally competitive. However, it is equally true that under VPAS companies are required to make a major financial contribution to defray the national drugs bill, at a time when Brexit is adding to the risk of making local investments that, even in the best circumstances, take years to play out. In the end, I believe VPAS will be viewed as one measure that provides a little certainty against the roiling populism that affects all the major markets today. It would be truly extraordinary if VPAS was scrapped.
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## On the Move

Recent executive appointments in the life sciences industry

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<tr>
<td>Joseph Farmer</td>
<td>Akrevia Inc</td>
<td>Chief Operating Officer</td>
<td>Tesaro Inc</td>
<td>Senior Vice President, General Counsel, and Corporate Secretary</td>
<td>12-Jun-19</td>
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<tr>
<td>Wayne Gombotz</td>
<td>Alpine Immune Sciences</td>
<td>Chief Technology Officer</td>
<td>Immune Design</td>
<td>Chief Development Officer</td>
<td>3-Jun-19</td>
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<td>Jotin Marango</td>
<td>Aptose Biosciences Inc</td>
<td>Chief Business Officer and Senior Vice President</td>
<td>Samuel Waxman Cancer Research Foundation</td>
<td>Chief Operating Officer</td>
<td>3-Jun-19</td>
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<tr>
<td>William H. Collier</td>
<td>Arbutus Biopharma Corp</td>
<td>Chief Executive Officer, President and Director</td>
<td>ViiV Healthcare</td>
<td>President and General Manager, North America</td>
<td>24-Jun-19</td>
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<td>Robert Petit</td>
<td>Carisma Therapeutics Inc</td>
<td>Chief Science Officer</td>
<td>Advaxis Inc</td>
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<tr>
<td>Mary Spellman</td>
<td>Castle Creek Pharmaceuticals llc</td>
<td>Chief Medical Officer and Senior Vice President, Research and Development</td>
<td>Menlo Therapeutics</td>
<td>Chief Medical Officer</td>
<td>3-Jun-19</td>
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<tr>
<td>Tariq Kassum</td>
<td>Celsius Therapeutics</td>
<td>Chief Executive Officer and President</td>
<td>Obsidian Therapeutics</td>
<td>Co-Founder, Chief Operating Officer and Head, Corporate Development</td>
<td>11-Jun-19</td>
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<tr>
<td>Raj Kannan</td>
<td>Chiasma Inc</td>
<td>Chief Executive Officer and Director</td>
<td>Kiniksa Pharmaceuticals</td>
<td>Chief Commercial Officer</td>
<td>17-Jun-19</td>
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<td>Andrew Knudten</td>
<td>Cirius Therapeutics</td>
<td>Chief Technical Officer</td>
<td>AveXis Inc</td>
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<td>Rick Epstein</td>
<td>Conventus Orthopaedics</td>
<td>Chief Executive Officer and President</td>
<td>OMNI Life Sciences</td>
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<td>5-Jun-19</td>
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## COMPANY CHANGES

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<tr>
<td>Rob Ciappennelli</td>
<td>Dicerna Pharmaceuticals Inc</td>
<td>Chief Commercial Officer</td>
<td>Momenta Pharmaceuticals</td>
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<td>4-Jun-19</td>
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<tr>
<td>Thomas Langenickel</td>
<td>Ethris GmbH</td>
<td>Chief Medical Officer</td>
<td>Novartis AG</td>
<td>Executive Director and Head, Respiratory</td>
<td>3-Jun-19</td>
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<tr>
<td>Said Saim</td>
<td>EyePoint Pharmaceuticals Inc</td>
<td>Chief Technology Officer</td>
<td>Collegium Pharmaceutical</td>
<td>Vice President, Pharmaceutical Development</td>
<td>10-Jun-19</td>
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<tr>
<td>Toni Hanninen</td>
<td>Faron Pharmaceuticals</td>
<td>Chief Financial Officer</td>
<td>Danaher Group</td>
<td>Chief Financial Officer, EMEA, X-Rite</td>
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<tr>
<td>Tracey Lodie</td>
<td>Gamida Cell Ltd</td>
<td>Chief Scientific Officer</td>
<td>BlueRock Therapeutics</td>
<td>Senior Vice President, Translational Immunology</td>
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<tr>
<td>Johanna Mercier</td>
<td>Gilead Sciences Inc</td>
<td>Chief Commercial Officer</td>
<td>Bristol-Myers Squibb</td>
<td>President and Head, Large Markets</td>
<td>1-Jul-19</td>
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<tr>
<td>Shaojing Tong</td>
<td>InnoCare</td>
<td>Chief Financial Officer</td>
<td>UBS China</td>
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<td>Christoph Bronnimann</td>
<td>Medartis AG</td>
<td>Chief Executive Officer</td>
<td>Johnson &amp; Johnson ONE Medical Device Unit</td>
<td>Head</td>
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<tr>
<td>Chris Wardhaugh</td>
<td>MGB Biopharma</td>
<td>Chief Business Officer</td>
<td>Nanogenics</td>
<td>Senior Executive Advisor</td>
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<tr>
<td>Edwina Baskin-Bey</td>
<td>Nanobiotix</td>
<td>Chief Medical Officer</td>
<td>Innocrin Pharmaceuticals</td>
<td>Chief Medical Officer</td>
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<tr>
<td>Samuel Zhang</td>
<td>NeoImmuneTech</td>
<td>Chief Business Officer</td>
<td>Merus</td>
<td>Vice President, Product and Portfolio Strategy</td>
<td>3-Jun-19</td>
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## COMPANY CHANGES

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<tr>
<td>Marie-France Tschudin</td>
<td>Novartis AG</td>
<td>President</td>
<td>Advanced Accelerator Applications</td>
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<td>David Appell</td>
<td>Parallax Health Sciences Inc</td>
<td>Chief Operating Officer</td>
<td>Carbon Capital Corp.</td>
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<td>Eric d’Esparbes</td>
<td>Progenity Inc</td>
<td>Chief Financial Officer and Senior Vice President</td>
<td>Innoviva Inc</td>
<td>Chief Financial Officer and Interim Principal Executive Officer</td>
<td>5-Jun-19</td>
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<tr>
<td>Laxman Narasimhan</td>
<td>Reckitt Benckiser plc</td>
<td>Chief Executive Officer</td>
<td>PepsiCo</td>
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<tr>
<td>Sharath Hegde</td>
<td>Recursion Pharmaceuticals LLC</td>
<td>Chief Scientific Officer</td>
<td>Theravance Biopharma</td>
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<td>Alex C. Sapir</td>
<td>ReViral Ltd</td>
<td>Chief Executive Officer and Director</td>
<td>Dova Pharmaceuticals</td>
<td>President and CEO</td>
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<tr>
<td>Barbara Schadler</td>
<td>Roche</td>
<td>Head, Group Communications</td>
<td>E.ON SE</td>
<td>Head, Communications and Public Affairs</td>
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<td>Glenn Reicin</td>
<td>Sigilon Therapeutics Inc</td>
<td>Chief Financial Officer</td>
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<td>JehanZeb Noor</td>
<td>Smiths Medical</td>
<td>Chief Executive Officer</td>
<td>Amcor Flexibles Inc</td>
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<td>Andrew Hindman</td>
<td>Theravance Biopharma US Inc</td>
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<td>Valeria Fantin</td>
<td>Zai Laboratory Inc</td>
<td>Chief Scientific Officer</td>
<td>ORIC Pharmaceuticals</td>
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## PROMOTIONS

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<tr>
<td>Will Brown</td>
<td>Altimmune Inc</td>
<td>Chief Financial Officer</td>
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<tr>
<td>Gregory J. Divis</td>
<td>Avadel Pharmaceuticals Plc</td>
<td>Chief Executive Officer and Director</td>
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<td>3-Jun-19</td>
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<td>Gerald R. Cysewski</td>
<td>Cyanotech Corp</td>
<td>Chief Executive Officer</td>
<td>President and Chief Scientific Officer</td>
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<tr>
<td>Hans Bishop</td>
<td>Grail Inc</td>
<td>Chief Executive Officer and Director</td>
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<tr>
<td>Rami Epstein</td>
<td>Kadimastem Ltd</td>
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<td>Neil Owens</td>
<td>Medicure Inc</td>
<td>President and Chief Operating Officer</td>
<td>Director, Scientific Affairs</td>
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<td>Barbara Weiland</td>
<td>Merck KGaA</td>
<td>Chief Compliance Officer</td>
<td>Head, Internal Auditing</td>
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<td>Daniel Steiner</td>
<td>Molecular Partners AG</td>
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<td>Emily Hill</td>
<td>PTC Therapeutics Inc</td>
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<td>Thomas Schinecker</td>
<td>Roche</td>
<td>Chief Executive Officer, Roche Diagnostics</td>
<td>Head, Centralized and Point of Care Solutions</td>
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<td>Scott Wilhoit</td>
<td>Strongbridge Biopharma plc</td>
<td>Chief Commercial Officer</td>
<td>Senior Vice President, Global Market Access and Patient Services</td>
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<td>Jessica Sachs</td>
<td>Unum Therapeutics Inc</td>
<td>Chief Medical Officer</td>
<td>Vice President, Clinical Sciences</td>
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<td>Michael Stein</td>
<td>Valo Therapeutics</td>
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<td>Robert E. Gagnon</td>
<td>Verastem Inc</td>
<td>Chief Financial Officer and Chief Business Officer</td>
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<td>Michael Halpin</td>
<td>Vericel Corp</td>
<td>Chief Operating Officer</td>
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## DIRECTORS

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<td>Susan Windham-Bannister</td>
<td>Aridis Pharmaceuticals Inc</td>
<td>Director</td>
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<tr>
<td>Wade Rosen</td>
<td>Collagen Solutions plc</td>
<td>Non-Executive Director</td>
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<td>Sylvie Ryckebusch</td>
<td>Domain Therapeutics</td>
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<td>Suzanne Blaug</td>
<td>FibroGen Inc</td>
<td>Independent Director</td>
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<td>Maykin Ho</td>
<td>Grail Inc</td>
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<td>Jovance Biotherapeutics Inc</td>
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<td>Melissa Rewolinski</td>
<td>Lannett Co Inc</td>
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<tr>
<td>Richard Murray</td>
<td>Platelet BioGenesis</td>
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<td>Jill Beraud</td>
<td>Revance</td>
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<td>Peter Hongaard Andersen</td>
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<td>Susan Mahony</td>
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<td>Troy Cox</td>
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## ADVISORS

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<td>Sulma Mohammed</td>
<td>Cannabis Science Inc</td>
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<td>James Summers</td>
<td>Cerevance Inc</td>
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<td>Daniel Bloomfield</td>
<td>Cirius Therapeutics</td>
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<td>Stephanie Martin</td>
<td>Clinical Computer Systems Inc</td>
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<td>David Bowers</td>
<td>Recce Ltd</td>
<td>Chairman, Clinical Advisory Committee</td>
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<td>Joseph C. Kvedar</td>
<td>ResApp Health Ltd</td>
<td>Industry Advisory Board Member</td>
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<td>Naomi Fried</td>
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Deal-Making
Covering deals made July 2019

IN VITRO DIAGNOSTICS
FINANCINGS
Initial public offering nets $144mm for Personalis

MEDICAL DEVICES
MERGERS & ACQUISITIONS
Zoll buys Cardiac Science
Gliakos acquires Dose Medical
Hologic to acquire SuperSonic Imagine
Merit Medical acquires BrightWater Medical for up to $50mm
Varian pays $185mm to buy interventional oncology companies Endocare and Alicon

ALLIANCES
Terumo gets exclusive rights to Orchestra BioMed’s Virtue SEB

PHARMACEUTICALS
MERGERS & ACQUISITIONS
AbbVie pays $63bn in cash and stock for Allergan
Brickell, Vical reverse merge to create company focused on Brickell’s dermatology pipeline
Merck buys Tilos for up to $773mm
Pfizer buys Array BioPharma in $11.4bn deal
Sobi pays CHF515mm to buy newco housing Gamifant from Novimmune
Vertex acquires Exonics for up to $1bn

ALLIANCES
Achaogen sells Zemdri rights to Cipla, Qilu
Artizan, Brii enter collaboration in China
Arvinas and Bayer to use PROTAC technology in cardiology, gynecology, and oncology
Astellas, Vect-Horus team up in CNS diseases
Starpharma and AZ pen second DEP cancer agreement
Lilly pens AI-focused drug discovery agreement with Atomwise
Eton gains US rights to Acta’s lamotrigine seizure compound
Everest gains rights to IgA nephropathy therapy from Calliditas
Gilead partners with Carma for next-gen cancer immunotherapies
Deciphera grants Zai exclusive ripretinib rights in Greater China
Denovo licenses worldwide rights to Orion’s ORM12741 CNS candidate
Upsher-Smith licenses US rights to two Promius sumatriptan migraine products
Eddingpharm licenses thrombocytopenia drug Mupleta from Shionogi
EffRx to sell Pharmaxis’ cystic fibrosis drug in Switzerland
Terns licenses exclusive elafibranor rights from Genfit
Genmab, Janssen team up once again
Nurix pens $2.3bn collaboration with Gilead
Grupo Ferrer gets rights to sell Shionogi’s Rizmoic in Spain
Siga grants Meridian Medical rights to promote TPOXX
Theramex gains ex-US rights to TherapeuticsMD’s Invexxy and Bijuva HRTs

FINANCINGS
AcelRx secures $25mm debt facility from Oxford Finance
Akero Therapeutics nets $98.4mm through IPO
ArQule nets $97.5mm via follow-on offering
Biohaven nets $282mm through IPO
Brickell enters $25mm financing agreement with NovaQuest
BridgeBio goes public netting $324mm
Calithera nets $54mm through public offering
Catalent closes $500mm senior note sale
ContraVir nets $14.5mm through public sale of common and preferred shares
Public offering nets $34.5mm for Genocea
Global Blood nets $193mm in public offering
Inhibrix attempts initial public offering
Karuna nets $83mm in up-sized IPO
Latest public offering nets $108.4mm for Kura Oncology
Mirati nets $191.5mm through latest public offering
Morphic nets $83.7mm via IPO
Public offering nets $117.3mm for Odonate
Preval Therapeutics nets $116.3mm in IPO
Resverlogix nets $Cdn14mm through public offering
Public offering nets $16.4mm for Rockwell
Scholar Rock FOPO nets $42.3mm
Sellas nets $13.5mm via FOPO
Seres nets $56.4mm via follow-on
Sesen Bio nets $28.2mm through public offering
Sorrento Therapeutics nets $23.5mm through public offering
Stoke Therapeutics nets $132mm in Nasdaq IPO
The Medicines Co. nets $141.4mm via FOPO
ZymeWorks goes public netting $189mm via public offering

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES
FINANCINGS
Adaptive Bio goes public netting $279mm

Derived from Strategic Transactions, Informa’s premium source for tracking life sciences deal activity, the Deal-Making column is a survey of recent health care transactions listed by relevant industry segment – In Vitro Diagnostics, Medical Devices, Pharmaceuticals, and Research, Analytical Equipment and Supplies – and then categorized by type – Acquisition, Alliance, or Financing.

Strategic Transactions is updated daily with in-depth deal analysis, structural and financial terms, and links to SEC-filed contracts.

For information about access please contact Customer Care at 888-670-8900 or PharmaNewsSales@informa.com
**IN VITRO DIAGNOSTICS**

**FINANCINGS**

**PERSONALIS INC.**

Personalis Inc. (oncology diagnostics and genomic analysis) netted $144m through its initial public offering. The company sold 9.1 million common shares (including the overallotment) at $17, higher than its intended range of $14-16 for 6.67 million shares. (Jun.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Cowen & Co. LLC; Morgan Stanley & Co.; Oppenheimer & Co. Inc.

**MERGERS & ACQUISITIONS**

**ASAHI KASEI CORP.**

Zoll Medical Corp.

**OPTO CIRCUITS (INDIA) LTD.**

Cardiac Science Corp.

Asahi Kasei's Zoll Medical Corp. is acquiring fellow private device firm Cardiac Science Corp., for an undisclosed sum. (Jun.) Cardiac Science provides Powerheart automated external defibrillators (AEDs) and Rescue Ready services and accessories. The firm also has a pipeline of innovative products that are expected to launch this year. Zoll offers the PlusTrac web-based system that ensures the ongoing compliance of AEDs. (All 50 US states require routine maintenance of AED devices.) Zoll's AED Link connects first responders with the closest available AED, thus getting help more quickly to patients in cardiac arrest. In addition to gaining Cardiac Science's portfolio, Zoll also gets facilities in the US and Europe. Over the years Zoll has been actively buying device firms, its most recent acquisitions being Kyma Medical and Advanced Circulatory Systems.

**GLAUKOS CORP.**

DOSE MEDICAL CORP.

Glaukos Corp. is acquiring fellow ophthalmic-focused firm Dose Medical Corp. for $2.5m in cash, plus earn-outs based on regulatory approvals and commercial achievements. (Jun.)

The earn-out payments are as follows: $5m-$22.5m if certain Dose products receive FDA approval within ten years following the closing of the merger; $1.25m-$2.5m should certain products received approval from the EMA within ten years after the deal closes; and $7.5m-$20m based on sales milestones. Glaukos will also shell out 5% in royalty payments for ten years. Upon FDA approval of certain Dose products, Glaukos can choose to buyout the additional earn-out and royalty payments by paying Dose shareholders $10m-$55m depending on whether the products involved are protein- or steroid-based. Dose will become a wholly owned Glaukos subsidiary. The two firms are already familiar with each other. Dose spun off from Glaukos in 2010. In April 2017 they entered into a partnership in which Glaukos acquired Dose's intraocular pressure (IOP) sensor system and related assets for $5.5m in cash, plus up to $5.5m tied to development and regulatory milestones. The system is complementary to Glaukos’ own iStent implant that allows glaucoma patients to manage their IOP. Dose is developing micro-invasive, biodegradable, sustained-release drug delivery systems. (Jun.)

**HOLOGIC INC.**

**SUPERSONIC IMAGINE SA**

Hologic Inc. made a binding offer to acquire French ultrasound imaging firm Supersonic Imagine SA for up to $85m and has entered into exclusive negotiations with the company. The price includes the purchase of all Supersonic outstanding shares at €1.50 apiece ($1.68, a 41% premium) for $39m ($42m including warrants and options), plus funds to repay up to $43m in net debt. (Jun.)

Supersonic was formed in 2005 and markets the Aixplorer ultrasound system which utilizes both ultrasound waves and shear waves to improve the detection and characterization of cancers including tumors in the breast, liver, thyroid, abdomen, and prostate. Hologic has been marketing Aixplorer for breast indications under a deal signed in 2010. It now gains full control of the product through the acquisition, noting that Aixplorer complements the Viera wireless handheld ultrasound scanner Hologic markets through an agreement with Clarius. Hologic’s other breast imaging products include the 3Dimensions mammography system, ATEC guidance and ultrasound system for breast biopsy, and the Faxitron radiography system (which the company gained through its 2018 acquisition of Faxitron Biopics). In 2018, Hologic brought in $29m in sales; the company has about 180 employees.

**MERIT MEDICAL SYSTEMS INC.**

**BRIGHTWATER MEDICAL INC.**

Merit Medical Systems Inc. acquired private non-invasive surgical device maker BrightWater Medical Inc. (convertible nephroureteral (NU) and biliary stent systems). (Jun.)

Merit will pay $35m in cash up front and could provide up to $55m more in earn-outs based on CE mark approval and achievement of future sales targets. BrightWater’s ConvertX stent system—which treats ureteral obstructions due to kidney stones, tumors, enlarged prostate, or scarring from previous surgeries to prevent urine in the kidneys from draining to the bladder—was approved in 2016. The system is designed to be implanted by an interventional radiologist once and converted from an NU catheter to an NU stent, eliminating the need for a second invasive surgery. Earlier this year, BrightWater’s ConvertX biliary stent system received FDA clearance. Similar in concept to the NU system, the ConvertX biliary system is also one-procedure treatment for biliary obstructions--blockages of the ducts that carry bile from the liver and gallbladder to the small intestine—caused by tumors, gallstones, enlarged lymph nodes, cysts, or strictures. Merit Medical plans to retain Brightwater’s current production facility while duplicating its capabilities in its own catheter facility before transferring the ConvertX manufacturing operations to its Utah headquarters. The deal enables Merit to expand its offerings into urology; most of its devices for interventional and diagnostic procedures are currently centered around cardiovascular and general surgeries.
FINANCINGS

ICAD INC.
Digital imaging firm iCAD Inc. netted $8.5m through the public sale of 1.6 million common shares at $5.50. The company’s offerings include computer-aided detection systems for diagnosis, and radiation therapy solutions for breast, prostate, and colorectal cancers. (Jun.)

Investment Banks/Advisors: Craig-Hallum Inc.

MIMEDX GROUP INC.
Blue Torch Finance provided MiMedx Group Inc. (allotments) with a three-year $75m term loan facility which was fully funded immediately. MiMedx will use some of the proceeds for growth objectives including its BLA pipeline. (Jun.)

Investment Banks/Advisors: PJT Partners

SIENTRA INC.
Sientra Inc. (medical aesthetic devices) netted $94m through the public offering of 17.4 million shares at $5.75. The company will use the proceeds to carry out sales and marketing initiatives, expand commercially in the US and globally, and fund R&D. Potentially, some of the funds may also support future acquisitions or investments in complementary businesses, products, or technologies. Sientra offers both a portfolio of breast products (including implants, tissue expanders, and scar management products sold to plastic surgeons) as well as the miraDry system (for reduction of underarm sweat, odor, and hair), with a 2019 sales outlook of $44.4m and $35.3m for the segments, respectively. (Jun.)

Investment Banks/Advisors: SVB Leerink; Stifel Nicolaus & Co. Inc.; William Blair & Co.

PHARMACEUTICALS

MERGERS & ACQUISITIONS

ABBVIE INC.

ALLERGAN PLC
AbbVie Inc. is buying Allergan PLC for an equity value of $63bn in cash and stock. Allergan shareholders will receive $188.24 per share ($120.30 in cash and 0.8660 AbbVie shares (worth $67.94)). (Jun.)

Post-transaction, AbbVie and Allergan shareholders will hold an 83%/17% stake of the combined company, respectively. The deal provides AbbVie with sufficient revenue as the firm prepares for the loss of patent protection for Humira (adalimumab), which is the world’s top-selling drug and accounted for 58% of AbbVie’s sales last year ($9.1bn). The therapy is approved for various autoimmune diseases including rheumatoid arthritis. Through settlement agreements, AbbVie has delayed biosimilar competition for Humira in the US until 2023, although biosimilars are available across Europe and other key international markets. The company’s next two leading drugs are Imbruvica (brutinib) for blood cancer (partnered with Johnson & Johnson and Mavryte (glecaprevir/pibrentasvir) for hepatitis C. They generated a combined $7bn last year. AbbVie’s portfolio also includes risankizumab (an anti-IL-23 antibody) and the JAK1 inhibitor upadacitinib for multiple immunology indications. These drugs are slated to replace Humira as the best-in-class therapeutics. Both therapies have been submitted for initial regulatory review in the US—upadacitinib in rheumatoid arthritis and risankizumab in psoriasis—with further clinical trial data generated across a wide range of indications including psoriatic arthritis, atopic dermatitis, Crohn’s and ulcerative colitis. Allergan’s lead revenue generator is Botox, which is part of its medical aesthetics (MA) business. Products within the MA segment represent 43% of international revenues. The AbbVie/Allergan combination is expected to generate $48bn in 2019 revenue. Allergan will benefit from AbbVie’s R&D capabilities, an area where investors have become concerned about productivity. The acquisition provides immediate scale and profitability to AbbVie’s growth platform, enhances long-term R&D funding capacity, and increases global commercial scale to further maximize the value of Allergan’s portfolio. Prior to the deal, rumors had been circulating that Allergan was getting ready to split and analysts say the sale represents a welcome exit for investors. Investment Banks/Advisors: JP Morgan & Co. (Allergan PLC); Morgan Stanley & Co.; PJT Partners (AbbVie Inc.).
ing BBI3000, a Phase I oral reninoid for cutaneous T-cell lymphoma (POC study expected to start in late 2020); preclinical BBI6000, a topical RORγ inhibitor (with a POC study in psoriasis expected to start in early 2021) in-licensed from Orca in 2015; as well as several programs in other skin disease indications. R&D funding for Phase III trials will be provided by NovaQuest Capital Management through a concurrent $25m financing commitment as well as Vical’s $35m in cash, expected to last through Q4 2020. In the third quarter of 2018, Vical announced plans to reviewing multiple strategic alternatives and discontinued its Phase II antifungal VL2397 in February 2019 to conserve cash; the company believes the reverse merger transaction will provide the best return for its shareholders. Vical’s core technology involves the insertion of DNA into plasmids designed to deliver the genes of interest into specific cells. It’s unclear if this technology will be used or Vical’s pipeline of mostly preclinical vaccines for infectious diseases and oncology will be assumed by the combined entity.

Investment Banks/Advisors: MTS Health Partners (Vical Inc.); BMO Financial Group (Brickell Biotech Inc.)

**MERCK & CO. INC. TILOS THERAPEUTICS INC.**

Merck & Co. Inc. agreed to acquire privately held Tilos Therapeutics Inc. (developing therapies targeting TGF beta complex) for up to $773m. The price includes an up-front payment and earn-outs. (Jun.)

Tilos—formed in 2016 based on research from Dr. Howard Weiner of Brigham and Women’s Hospital and Harvard Medical School—works on anti-LAP (latency-associated peptide) antibodies that inhibit the effects of cytokine TGF beta LAP. TGF beta is involved in the development and progression of cancer and fibrotic diseases. LAP forms a cage around TGF beta, holding it in an inactive state until it is deployed, but anti-LAP antibodies, such as those Tilos is working on, target cells in the tumor microenvironment for depletion and inhibit the release of TGF beta from the LAP complex, thereby fighting cancerous cells more effectively than existing TGF beta therapies. Tilos’s antibodies have applications in a variety of solid tumors including head and neck, ovarian, colorectal, gastric, and non-small cell lung cancers, as well as in fibrosis and autoimmune diseases. According to SEC filings, the company has raised about $4m since inception. Investors include Boehringer Ingelheim Venture Fund, Partners Innovation Fund, and ShangPharma Innovation Fund.

**PFIZER INC. ARRAY BIOPHARMA INC.**

In an effort to expand its cancer offerings with targeted therapies, Pfizer Inc. is paying $11.4bn in cash ($4.8 per share; a 66% premium) to acquire Array BioPharma Inc. (Jun.) Pfizer gains Array’s FDA-approved combination therapy of Brafvoti (encoralenib) and Mekktovi (binimetinib) for the treatment of BRAFV600E or BRAFV600K mutant unresectable or metastatic melanoma. The drugs are also in Phase III for BRAF-mutant metastatic colorectal cancer and, according to Biomedtracker, Brafvoti and Mekktovi have a 43% (8% above average) and 41% (6% above average) likelihood of approval, respectively. They are also in various other clinical trials for multiple solid tumors including non-small cell lung cancer. The drugs generated a combined $35m in sales for Q1 2019. Brafvoti and Mekktovi face competition from Merck’s Keytruda (pembrolizumab) and Bristol-Myers Squibb’s Opdivo (nivolumab) in the melanoma indication, but the Brafvoti/Mekktovi combo therapy could potentially be a leading player in BRAF-mutated colorectal cancer based on exceptional clinical data. The majority of Array’s portfolio consists of out-licensed cancer therapies. Partners include One, Pierre Fabre, Bayer, Roche, and several others. Pfizer will benefit from royalties of those partnered programs over time. Array also has several undisclosed preclinical programs in cancer and rare diseases and says it plans to bring one new cancer drug into the clinic each year. At the end of March 2019, Array had $96.6m in cash. Pfizer says the acquisition supports its long-term growth strategy and has the potential to create an industry-leading franchise for colorectal cancer alongside the Big Pharma’s own expertise in breast and prostate cancer. Investment Banks/Advisors: Guggenheim Partners LLC; Morgan Stanley & Co. (Pfizer Inc.); Centerview Partners LLC (Array BioPharma Inc.)

**SWEDISH ORPHAN BIOVITRUM AB NOVIMMUNE SA**

One year after granting Swedish Orphan Biovitrum AB (Sobi) exclusive global rights to the interferon gamma antagonist emapalumab (which has since been approved as Gamifant), Novimmune SA has now created a new entity which holds the compound and all related assets, and is selling that newco to Sobi for CHF515m ($519.4m). (Jun.)

Gamifant was approved by the FDA in November 2018 to treat pediatric and adult patients with primary haemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent, or progressive disease or intolerance to conventional HLH therapy. HLH is a rare disease of extreme immune activation that causes histiocytes and lymphocytes (types of white blood cells) to attack other blood cells. The abnormal cells collect in the liver and spleen, causing enlargement and other symptoms including swollen lymph nodes, jaundice, lung and digestive issues, and neurological problems. Under terms of their original deal, Sobi paid CHF50m up front for rights, and committed to up to CHF400m in additional payments. The new entity now created by Novimmune contains all assets related to emapalumab (intellectual property, patent rights, data, and know-how); Sobi takes on all staff involved in the development of the drug as well. Also, as part of the acquisition, Sobi gains a Priority Review Voucher that it can use or sell, and options to share financial rights to two immuno-oncology assets--N1701 (Phase I anti-CD19/anti-CD47 bispecific antibody for blood cancers) and N1801 (preclinical anti-CD47/mesothelin bispecific antibody for solid tumors). On the same day as Sobi announced the deal with Novimmune, it also revealed a planned reorganization intended to further steer the company’s focus towards two core therapy areas, hematology and immunology. As a result, the workforce will be cut by 30% and candidates falling outside of the new core areas will be divested (including the Phase I Sanfilippo syndrome project SOB1003 and preclinical autoimmuno/inflammatory disease candidate SOB1006).

**VERTEX PHARMACEUTICALS INC. EXONICS THERAPEUTICS INC.**

Vertex Pharmaceuticals Inc. acquired privately held Exonics Therapeutics Inc. (gene editing therapies for Duchenne muscular dystrophy (DMD)) for up to $1bn. (Jun.) Vertex will provide $245m at closing, another $74m in additional payments at a later date, plus up to $728m in potential earn-outs related to the achievement of clinical and regulatory milestones associated with the R&D and commercialization of DMD and myotonic dystrophy type 1 (DM1) programs. Launched in 2017 with a $5m seed round from CureDuchenne Ventures, Exonics has raised $45m to date. Its SingleCut CRISPR gene editing technology, intended to permanently repair errors in the DNA sequence that cause disease, is licensed from the University of Texas Southwestern Medical Center, where it was discovered by a team led by Eric Olson, PhD, Exonics’ co-founder and chief scientific adviser. Directed by highly specific single guide-strand RNA, the SingleCut platform uses an adeno-associated virus (AAV) to deliver the gene-editing enzymes CRISPR/Cas9 by cutting the DNA of chromosomes at selected sites in the DNA sequence to remove or insert segments. Exonics’ initial focus is repairing mutations in dystrophin (exon 51), a key protein that stabilizes and protects muscle fibers, but is lacking in DMD patients. Its lead program has demonstrated in preclinical mouse models that a one-time administration of the SingleCut technology delivered through AAV is sufficient...
to restore the production of dystrophin and improve the structure and function of both skeletal muscles and the heart of mice with these mutations. The company believes the technology will also have applications in a range of other genetic neuromuscular diseases. In addition to gaining Exonics’ platform, Vertex concurrently expanded its 2015 agreement for sickle cell disease and beta thalassemia with CRISPR Therapeutics into DMD and DM1, agreeing to pay CRISPR $1bn for its programs in these disease areas and exclusive worldwide rights to CRISPR’s CRISPR/Cas9 technology.

**ALLIANCES**

**ACHAOGEN INC.**

Cipla Ltd.
Cipla USA Inc.

QILU ANTIBIOTICS PHARMACEUTICAL CO. LTD.

Achaogen Inc. is selling off global rights to Zemdri (plazomicin). (Jun.)

Achaogen filed the voluntary Chapter 11 petition in April. The company is granting Cipla USA Inc. worldwide rights (excluding China, Hong Kong, Macao, and Taiwan) to Zemdri and related assets. Qilu Antibiotics Pharmaceutical Co. Ltd. is getting exclusive royalty-free rights to the drug in Greater China. Zemdri received FDA approval in mid-2018 for treating adults with complicated urinary tract infections (cUTIs). Separately, Heritage Global Partners is buying Achaogen’s lab equipment. The firm is also auctioning off its C-Scape cUTI assets. Earlier this year Achaogen netted $14.1m through a follow-on offering.

**ARTIZAN BIOSCIENCES INC.**

**BRII BIOSCIENCES**

Concurrent with raising $12m in its series A round, Artizan Biosciences Inc. is teaming up with BRII Biosciences on up to three Artizan programs. (Jun.)

The firms will collaborate on up to three Artizan programs. Once Artizan demonstrates proof-of-concept (expected in the next two years), BRII gets rights to develop and commercialize the compounds in China. Specific terms of the deal were undisclosed however it does include money up front, milestones, and royalties, and BRII participated in Artizan’s series A financing. Artizan’s programs are based on its IgA-SEQ platform created with IP originating at Yale University. The technology can identify disease-causing bacteria--by scanning for the immunoglobulin A antibody coating--and can distinguish it from intestinal microbiota. Artizan’s compounds are designed to neutralize pathogens.

**ARVINAS INC.**

**BAYER AG**

Arvinas Inc. and Bayer AG agreed to use the former’s PROTAC technology to develop drug candidates for cardiovascular and gynecological diseases, and cancer. Separately, the companies established a 50/50 joint venture that will use PROTAC in the agricultural industry. (Jun.)

Bayer pays $17.5m up front in cash plus $32.5m through the purchase of 1.4 million Arvinas shares--representing about a 4% equity stake--at $24.14 (an 11% premium). Bayer is also responsible for $12m in research funding payments (consisting of $3m per year during the first four years), $197.5m in development milestones, $490m in sales milestones, and sales royalties in the mid-single to low-double digits. The Big Pharma will select targets and have rights to novel lead structures. PROTAC, which stands for proteolysis-targeting chimera, are molecules that use the cell’s ubiquitin/proteasome system to degrade disease-causing proteins. Arvinas believes PROTACs have advantages over traditional small-molecule protein inhibitors, including avoiding side effects and drug resistance. Thus far, Arvinas has focused its work on PROTAC candidates in prostate and breast cancers, as well as CNS diseases, and so the current deal will test the utility of the technology in new areas such as cardiovascular and gynecological diseases. In the past, Arvinas has worked with Pfizer, Genentech, and Merck & Co., all in undisclosed therapy areas. The agricultural portion of the current agreement is worth $55m, representing funding from Bayer. The investment in the JV falls in line with Bayer’s crop sciences business, a diversified operation (built up even more though the acquisition of Monsanto in 2018) that the Big Pharma is still investing in as opposed to animal health, a unit that Bayer is planning to divest as it puts more efforts into life sciences.

**ASTELLAS PHARMA INC.**

**VECT-HORUS**

Vect-Horus and Astellas Pharma Inc. are collaborating in the development of therapies for CNS diseases. (Jun.)

Vect-Horus’ VECTrans technology uses a screening platform of peptide and VHH (single-domain) antibody libraries to identify and optimize vectors that specifically target endogenous receptors to facilitate the transport of agents across natural biological barriers such as the blood-brain barrier. Vect-Horus will conjugate Astellas’ antibody with its vectors and handle conjugate design, initial production, and validation. Vect-Horus will use VECTrans to transport the antibody to the brain for treating CNS diseases. Vect-Horus is eligible for money up front, development and commercial milestones, and sales royalties. Earlier this year, Vect-Horus signed a similar agreement with Ono Pharmaceutical involving the development of neurodegenerative disease therapeutics using the VECTrans technology.

**ASTRAZENECA PLC**

**STARPHARMA HOLDINGS LTD.**

AstraZeneca PLC and Starpharma Holdings Ltd. signed a second agreement involving Starpharma’s DEP dendrimer drug delivery technology, this time for the development of an undisclosed marketed AZ cancer product. (Jun.)

The DEP (Dendrimer Enhanced Product) platform joins an active drug to a dendrimer construct and provides for increased solubility, extended duration of action, improved efficacy, and a reduction in toxic side effects. Starpharma will conduct preclinical studies on a DEP version of AZ’s drug, after which point AZ has an option to license the candidate. If the option is exercised, Starpharma gets a $5m fee in addition to “industry standard” development and commercialization milestone, plus escalating sales royalties. If AZ doesn’t take rights, Starpharma could license the drug for development and commercialization either on its own or through a sublicense, in which case AZ would be eligible for milestones and royalties. The companies partnered in 2015 in a deal through which AZ licensed rights to use DEP in the development of multiple products (in contrast to the current agreement that calls for Starpharma to conduct studies on one specific AZ drug). Terms of the initial deal included a $2m up-front payment to Starpharma and up to $124m in milestones.

**ATOMWISE INC.**

**ELI LILLY & CO.**

Eli Lilly & Co. penned a deal with AI drug discovery firm Atomwise Inc. to support Lilly’s preclinical discovery efforts. (Jun.)

Atomwise, founded in 2012, created the first deep learning AI technology for structure-based small molecule drug discovery. The company’s AtomNet platform uses a statistical approach incorporating deep learning algorithms and supercomputers to extract insights from millions of experimental affinity measurements and thousands of protein structures to predict how small molecules will bind to proteins. This allows for analysis of millions of potential molecules to provide toxicity, side effects, mechanism of action, and efficacy of a drug, much earlier than typical in a drug pipeline. Lilly will pay Atomwise $1m per target (for up to ten targets) in discovery milestones to apply the technology to the Big Pharma’s drug discovery projects. Atomwise could also get up to $550m in development and commercialization milestones (for all targets), and retains an option to develop any compounds from
the partnership that Lilly decides not to further pursue. The application of artificial intelligence and machine learning to drug discovery efforts has been a hot topic of late. Strategic Transactions has covered about ten deals between biopharma and AI firms in just the last year, most notably a tie-up between bluebird bio and Gritstone (POC $1.2bn) through which Gritstone is using its EDGE AI platform and biopsy sequencing data to provide ten tumor-specific targets for bluebird’s use in its cell therapy program.

**AUCLIA PHARMACEUTICALS INC.** **ETON PHARMACEUTICALS INC.**

Eton Pharmaceuticals Inc. licensed US marketing rights to Aucta Pharmaceuticals Inc.’s oral liquid formulation of lamotrigine, which Eton will call E105. (Jun.) Aucta submitted an NDA for lamotrigine for pediatric epilepsy in May 2019. Contingent upon the FDA’s acceptance of Aucta’s NDA, Eton will pay up to $2m up-front, $2m upon FDA approval and product launch, and $1m upon the issuance of an Orange Book-listed patent. In addition, Aucta gets a low-double-digit royalty on net sales, plus sales milestones up to $18m ($1m when net sales exceed $10m; $2m when that threshold exceeds $20m; $5m when sales exceed $50m; and $10m when sales exceed $100m). Eton plans to establish a neurological-focused sales force to support commercialization efforts for E105—which it expects to launch in the US during the H1 2020— and its other CNS candidates. So far lamotrigine is only approved in tablet form, but Eton believes Aucta’s oral liquid version will offer a preferred route of administration as well as a lower dosing option as an ad- junct therapy for partial seizures, primary generalized tonic-clonic seizures, and generalized seizures of Lennox-Gastaut syndrome in patients two years of age and older. Aucta’s expertise lies in creating new dosage forms, dosing regimens, and indications for proven molecules using the 505(b)(2) expedited regulatory pathway. The addition of E105 complements Eton’s existing pipeline of oral liquid reformulations of approved solid dosage forms for undisclosed CNS diseases, which are also expected to advance through the 505(b) (2) process.

**CALLIDITAS THERAPEUTICS AB** **EVEREST MEDICINES LTD.**

Calliditas Therapeutics AB (formerly Pharmalink) granted Everest Medicines Ltd. exclusive rights to develop and sell the IgA nephropathy candidate Nefecon (enteric budesonide) in China, Hong Kong, Macau, Taiwan, and Singapore. (Jun.) Everest pays $15m up front; development, regulatory, and commercialization milestones of up to $106m (including $20m if Nefecon is developed in other indica- tions); and royalties. IgA nephropathy, also known as Berger’s disease, is a condition where IgA deposits build up in the kidneys and cause damaging inflammation. Nefecon, a corticosteroid, was developing using Archimedes TARGIT drug delivery technology, enabling the drug to be delivered locally to the lower small intestine and other colonic areas. Calliditas currently has the candidate in Phase III trials. The partners note that while IgA nephropathy is an orphan disease in the US and Europe, the condition is much more prevalent in Everest’s territory of China. The deal is the third for Everest since the beginning of 2019. In July/August, it licensed rights to antibiotics from Spero ($1m up front), and in April, it paid $65m up front for rights to Immunomedics’ solid tumor candidate sacituzumab.

**CARNA BIOSCIENCES INC.** **GILEAD SCIENCES INC.**

Gilead Sciences Inc. and Carna Biosciences Inc. penned a collaboration for the development and commercialization of next-generation small-molecule cancer immunotherapies. (Jun.) The deal will utilize Carna’s proprietary lipid kinase drug discovery program, to which Gilead gains exclusive access. Gilead also gets global rights to develop and sell inhibitors against an undisclosed I/O target. The company paid $20m up front and could hand over another $450m in milestones, plus royalties. Carna’s discovery platforms provide for the identification of a variety of kinase inhibitors, and has been used in the development of treatments for cancer, autoimmune conditions, and neurological diseases. In addition to Gilead, the firm’s list of partners includes Sierra Oncology, Sumitomo Dainippon, National Cancer Center Japan, Hiroshima University, and Kitasato University.

**DECIPHERA PHARMACEUTICALS INC.** **ZAI LAB LTD.**

Deciphera Pharmaceuticals Inc. granted Zai Lab Ltd. exclusive development and commercialization rights for its gastrointestinal stromal tumor (GIST) therapy ripretinib in China, Hong Kong, Macau, and Taiwan. (Jun.) Ripretinib is a KIT and PDGFRa kinase switch control inhibitor in Phase III trials for GIST, a type of benign or malignant tumor that is believed to grow from interstitial cells of Cajal in the wall of the GI tract. It is also being studied for other solid tumors driven by KIT or PDGFRa including systemic mastocytosis and glioblastoma multiforme. Zai pays $20m up front for the rights, plus development milestones of up to $50m, sales milestones that could hit $135m, and royalties ranging from the low- to high-teens. The company has a strong oncology pipeline that includes two products already on the market (Ze- jula (niraparib) for ovarian cancer and the Optune Tumor Treating Fields device for brain cancer), plus additional candidates in mid- and late-stage development for a variety of other solid tumors.

**DENovo BIOPHARma LLC** **ORION CORP.**

Denovo Biopharma LLC licensed exclusive worldwide development, manufacturing, and commercialization rights to Orion Corp.’s ORM12741, an alpha 2-adrenoreceptor antagonist for Alzheimer’s disease (AD). (Jun.) Under a 2013 deal, J&J’s Janssen had worldwide rights (except in Europe) to ORM12741, but discontinued development in April 2018 following a Phase IIa trial study on agitation/aggression symptoms in AD that did not meet projected efficacy objectives. ORM12741, which Denovo will rename DB105, was also previously in clinical trials by Orion for Raynaud’s phenomenon (reached Phase II until dis- continued in 2012) and schizophrenia (through Phase I in 2011, after which it was no longer noted in the company’s pipeline). Denovo plans to apply its bio- marker approach—enabling the design of new clinical trials in smaller and targeted patient populations than the previously failed studies—to develop DB105 as a personalized medicine. Based on prior clinical trials, Denovo is hoping DB105 may be useful for AD, schizophrenia, and other neuropsychiatric indications, including depression. DB105 complements Denovo’s existing in-licensed CNS pipeline, which includes Phase II-ready candidates DB103 (pomaglumetad) for schizophrenia and DB104 (liafensine) for treatment-resistant depression. Denovo also has an oncology candidate (licensed from Lilly) in development.

**DR. REDDY’S LABORATORIES LTD.** **Promius Pharma LLC** **SAWAI PHARMACEUTICAL CO. LTD.** **Upsher-Smith Laboratories LLC**

Upsher-Smith Laboratories LLC gained US marketing rights to Tosymra (sumatriptan) nasal spray 10 mg and Zembrace/Sym- Touch (sumatriptan succinate) injection 3 mg from Dr. Reddy’s Laboratories Ltd.’s Promius Pharma LLC subsidiary. (Jun.) Upsher-Smith pays $70m up front; up to $40.5m in near-term milestones and additional financial considerations, including existing contractual obligation and inventory; and sales-based royalties on a quarterly basis. Formulated with an excipi- dent that helps achieve blood levels similar to a subcutaneous injection, Tosymra was FDA approved earlier this year and is expected to launch soon. Dr. Reddy’s gained exclusive worldwide marketing rights to Tosymra under a 2010 deal with the drug’s originator, Aegis Therapeutics. Zembrace/ SymTouch is a drug-device combo that...
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FOR SPONSORSHIP OPPORTUNITIES CONTACT:
Rob Coulson
E: rob.coulson@informa.com
T: +44 (0) 7825 845 666

FOR ALL OTHER ENQUIRIES:
Natalie Cornwell
E: natalie.cornwell@informa.com
T: +44 (0) 7827 993 776
uses a pre-filled, single-dose, disposable autoinjector to subcutaneously dispense sumatriptan, a selective 5-hydroxytryptamine (5-HT) 1B/1D receptor agonist, for acute migraine. Zembrace/SymTouch was FDA approved in 2016 and launched in the US that same year. The addition of Promius’ approved migraine treatments complement Upsher-Smith’s existing CNS portfolio, which includes Qudexy XR (topiramate) extended-release capsules, cleared in the US for migraine in 2017 and also indicated for certain types of seizures.

EDDINGPHARM INTERNATIONAL HOLDINGS LTD. SHIONOGI & CO. LTD. Shionogi & Co. Ltd. granted Eddingpharm International Holdings Ltd. exclusive rights to commercialize the thrombopietin receptor agonist Mulpleta (lusprometin) in Mainland China, Hong Kong, and Macau. (Jun.)

Shionogi, which will supply the product to Eddingpharm, gets an undisclosed up-front payment and sales milestones. Mulpleta is indicated for severe thrombocytopenia in patients with chronic liver disease. It was approved for sale in Japan in 2015, the US in July of 2018, and in Europe earlier this year. The deal is the third out-licensing for Shionogi in the last few months. In April, it licensed Sandoz rights to sell the opiate-induced constipation drug Rizmoic (nalmedine) in Germany, the UK, and the Netherlands, and about a week before announcing the Eddingpharm deal, it granted Grupo Ferrer Rizmoic rights in Spain.

EFFRX PHARMACEUTICALS SA PHARMAXIS LTD. Pharmaxis Ltd. licensed EffRx Pharmaceuticals SA exclusive rights to commercialize its cystic fibrosis drug Bronchitol (man-nitol) in Switzerland. (Jun.)

EffRx is responsible for registering, obtaining pricing and reimbursement, and commercializing Bronchitol. The drug is administered via a dry-powder inhaler twice a day and designed to rehydrate the airway/lung surface thus stimulating a productive cough and helping clear mucus and improve lung function. Bronchitol should be launched in Switzerland by 2021. Under a late 2014 deal, Chiesi Farmaceutici has exclusive rights to sell Bronchitol in the US. In mid-2017 the agreement was expanded to include rights in Italy.

GENFIT SA TURNS PHARMACEUTICALS INC. Genfit SA granted Terns Pharmaceuticals Inc. exclusive rights to develop, register, and sell elafibranor for nonalcoholic steatohepatitis (NASH) and primary biliary cholangitis (PBC) in China, Hong Kong, Macau, and Taiwan. (Jun.)

Under terms of the deal, Terns pays $35m up front; up to $193m in development, regulatory, and commercialization milestones; and mid-teens royalties (Strategic Transactions estimates) 14-16%. Elafibranor, a peroxisome proliferator-activated receptor alpha/delta agonist, is in Phase III trials (with Fast Track designation) for NASH, and Phase II (with Breakthrough Therapy designation) for PBC. In addition to Terns’ licenses, the partners will also work together on additional development projects including potential elafibranor combination therapies with Terns’ farnesoid X receptor (FXR) agonist TERN201 and semicarbazide-sensitive amine oxidase (SSAO) inhibitor TERN201 (both in-licensed from Lilly last year), and thyroid hormone receptor (THR) B-selective agonist and apoptosis signal-regulating kinase 1 (ASK1) inhibitor programs.

GENMAB AS JOHNSON & JOHNSON Janssen Biotech Inc. Genmab AS and Janssen Biotech penned an exclusive worldwide license and option agreement involving the development and commercialization of next-generation HexaBody-CD38. (Jun.)

Genmab will fund R&D activities of HexaBody-CD38 through completion of clinical proof-of-concept in multiple myeloma and diffuse large B-cell lymphoma. Janssen can then opt to license global rights to develop, manufacture, and commercialize the monoclonal antibody and would shell out a $150m option exercise fee. Genmab would also be eligible for up to $125m in development milestones in addition to 20% sales royalties on HexaBody-CD38 until a specified time in 2031, followed by 15-20% tiered royalties on sales thereafter. If Janssen chooses not to exercise its option, Genmab will continue to develop and commercialize HexaBody-CD38 for Darzalex-resistant patients, and in all other indications excluding multiple myeloma or amyloidosis indications where Darzalex is either approved or is being actively developed. HexaBody-CD38 has already demonstrated promising results in preclinical studies in multiple myeloma, lymphoma, and leukemia. Genmab and Janssen first began collaborating in 2012 when they signed two agreements in as many months. Genmab agreed to use its Duobody technology to create and develop bispecific antibodies for several disease targets (up to 10 programs) that Janssen selects. In the second deal, Janssen got exclusive global development and marketing rights to Darzalex and a back-up anti-CD38 compound. Both partnerships are continuing to progress well and have resulted in multiple milestone payments.

GILEAD SCIENCES INC. NURIX INC. Nurix Therapeutics Inc. gained another major partner through a new multi-year deal with Gilead Sciences Inc. in which the companies will focus on targeted protein degradation treatments for cancer and other serious diseases. (Jun.)

Working with the concept that dysregulated and mutated proteins are important to progression of many diseases, Nurix’s drug development efforts center around E3 ligases and manipulation of the ubiquitin system to control protein levels in cells. Under terms of the deal, the company will utilize its discovery platform to identify agents that use E3 ligases to induce targeted protein degradation of certain targets. Gilead has the option to license candidates aimed at up to five targets, while Nurix retains an option to co-develop and co-detail up to two in the US. Gilead pays $45m up front and could hand over up to $2.3bn in development, regulatory, and sales milestones, plus up to low-double digit royalties. If Nurix chooses to exercise its opt-in rights, the partners will split costs and profits/losses 50/50 in the US, with Nurix eligible for ex-US royalties and reduced milestone payments. The deal is the second big collaboration for Nurix since the company was formed in 2012. Celgene paid $150m up front in 2015 for options to small-molecule therapies targeting the ubiquitin proteasome system for cancer, inflammation, immunology, and immuno-oncology. Nurix could get up to $45m more in option exercise fees and milestones, plus royalties. Other companies working in the protein degradation space include Arvinas, Kymera Therapeutics, C4 Therapeutics.

GRUPO FERRER INTERNACIONAL SA SHIONOGI & CO. LTD. Shionogi & Co. Ltd. licensed Grupo Ferrer Internacional SA exclusive rights to promote its Rizmoic (nalmedine) in Spain. (Jun.)

Rizmoic is indicated for treating opioid-induced constipation (OIC) in adults previously treated with a laxative. The drug has been approved in the US since June 2017 and is sold there as Symproic. It received European approval in February 2019 and is expected to launch in Spain next year. Just two months ago Shionogi licensed BioDelivery Sciences exclusive rights to commercialize Symproic in the US and Puerto Rico, and granted Sandoz exclusive rights in Germany, the UK, and the Netherlands.

PFIZER INC. King Pharmaceuticals Inc. Meridian Medical Technologies Inc. SIGA TECHNOLOGIES INC. Sigma Technologies Inc. granted Meridian Medical Technologies Inc. exclusive global rights (excluding the US and South Korea) to promote oral TPOX (tecovirimat) for treating smallpox. (Jun.)

Specific terms of the agreement were not disclosed however up-front cash payments.
are not a part of the deal and both firms will fund their own activities. Meridian will receive a fee based on a percentage of net sales. **TPOX** is the first FDA-approved drug for treating smallpox in adults and children weighing at least 29 pounds. It is designed to inhibit viral maturation of variola virus and other poxviruses by preventing the formation of a secondary viral envelope. Siga chose Meridian as a partner because of its global network within the medical countermeasure industry.

**THERAMEX THERAPEUTICSMD INC.**

Theramex licensed exclusive commercialization rights outside the US to **THERAPEUTICSMD INC.**’s **Imvexxy** (estradiol; TX004HR) and **Bijuva** (estradiol/progesterone; TX003HR) prescription hormone replacement therapies (HRTs) for menopausal women. (Jun.)

The agreement excludes Canada and Israel, where **Knight Therapeutics** has exclusive commercialization rights from TherapeuticsMD through a 2018 alliance. Under the current deal, Theramex pays €1.2m ($15.8m) up front; €2.9m in milestones (an aggregate €2m upon regulatory approvals in certain specified markets and €27.5m [payable in escalating tranches] when certain net sales goals in the licensed territories ranging from €25-100m are met); plus, royalties on net sales. Both HRTs were already FDA approved last year, but Theramex is responsible for all additional regulatory and commercialization activities in the licensed territories. Administered as a vaginal suppository using the **VagiCap** softgel capsule, **Imvexxy** was launched in the US in September 2018 for dyspareunia (vaginal pain associated with sexual activity) due to menopause. Launched in the US in April 2019, **Bijuva** is an oral capsule for vasomotor symptoms (also known as hot flashes) of menopause. The deal broadens Theramex’s current portfolio of women’s health offerings in the areas of contraception, fertility, menopause, and osteoporosis.

**FINANCINGS**

**ACELRX PHARMACEUTICALS INC.**

Oxford Finance provided AcelRx Pharmaceuticals Inc. (sublingual delivery of pain medications) with a $25m senior secured debt facility, which was fully funded at closing. The term loan will mature on June 1, 2023 and bears interest at variable rate equal to the greater of 9.25% or the 30-day US LIBOR rate, with interest-only payments for the first 12 months. AcelRx will use the proceeds to further support the commercial launch of **Dsuvia** (sufentanil) sublingual tablets for pain (FDA approved in November 2018 and launched in February 2019) and repay its $9m balance on a previous credit facility. (Jun.)

**AKERO THERAPEUTICS INC.**

Akero Therapeutics Inc. (developing treatments for nonalcoholic steatohepatitis (NASH) and serious metabolic diseases) netted $98.4m through its initial public offering of 6.6 million common shares (including the overallotment) at $15.6. The company originally planned to sell 5 million shares at $14-16. (Jun.)

Investment Banks/Advisors: Evercore Partners; JP Morgan Chase & Co.; Jefferies & Co. Inc.; Roth Capital Partners

**ARQUE INC.**

ArQule Inc. (developing therapies for cancers and rare diseases) netted $97.5m through a follow-on public offering of 10.6 million common shares (including full exercise of the overallotment) at $9.75 each to fund ongoing development of its clinical candidates. (Jun.)

Investment Banks/Advisors: B. Riley FBR Inc.; Needham & Co. Inc.; Oppenheimer & Co. Inc.; RBC Capital Markets; Roth Capital Partners; SVB Leerink

**BIOHAVEN PHARMACEUTICAL HOLDING CO. LTD.**

Neuro-focused **Biohaven Pharmaceutical Holding Co. Ltd.** netted $282m in a public offering of 7 million shares at $43. The company will use the proceeds to support continued and expanded development of its three platforms: calcitonin gene-related peptide (CGRP) receptor antagonists; glutamate modulators; and myeloperoxidase (MPO) inhibitors. An NDA submission is expected in mid-2019 for its most advanced CGRP candidate rimegepant (in Phase III for migraine) using a priority review voucher (PRV) Biohaven bought earlier this year from **GW PHARMACEUTICALS**, allowing the former to designate a single NDA for priority status and providing an accelerated six-month review period. (Jun.)


**BRICKELL BIOTECH INC.**

NovaQuest Capital Management committed up to $25m in near-term research and development funding to **Brickell Biotech Inc.**, following the closing of Brickell’s concurrent reverse merger with **Vical Inc.**, which will hold a 40% stake in the combined company. (Jun.)

**BRIDGEBIO PHARMA INC.**

BridgeBio Pharma Inc. netted $324.1m in its oversubscribed initial public offering of 20.5 million common shares at $17 each on the Nasdaq. The company had planned to sell 15 million shares between $14 and $16. (Jun.)


**CALITHERA BIOSCIENCES INC.**

Calithera Biosciences Inc. netted $54.4m through the public sale of 14.4 million common shares (including the overallotment) at $4. The company is developing small-molecule drugs directed against tumor metabolism and tumor immunology targets, and will put the proceeds towards continued pipeline development, with projects including telaglenastat for renal cell carcinoma, CB158 for solid tumors, CB280 for cystic fibrosis, and immunology candidate CB708. (Jun.)

Investment Banks/Advisors: SVB Leerink; Wells Fargo Securities LLC; William Blair & Co.

**CATALENT INC.**

Catalent Inc. privately sold $50m in aggregate principal amount of 5% senior unsecured notes due 2027 priced at par. The company will use the proceeds to pay off outstanding borrowings and related fees under term loans from existing senior secured credit facilities. (Jun.)

**CONTRAVIR PHARMACEUTICALS INC.**

ContraVir Pharmaceuticals Inc. (treatments for nonalcoholic steatohepatitis and chronic hepatitis infections) netted $14.5m through a public offering of common and preferred shares. The company sold 936,333 Class A units at $6 (with each unit consisting of one common share and one five-year common share purchase warrant exercisable at $6), and also issued 10,570 Class B units at $1k apiece, with each holding one series E preferred share (convertible into 167 common) and 167 warrants. (Jun.)

Investment Banks/Advisors: Roth Capital Partners

**GENOCEA BIOSCIENCES INC.**

Genocea Biosciences Inc. (neoantigen immunotherapies) netted $34.5m through the public sale of 10.5 million common shares at $3.50. Proceeds will go towards continued development of personalized cancer vaccine GEN009 (Phase IIa trials for solid tumors including cutaneous melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck, urothelial carcinoma, and renal cell carcinoma); filing of an IND and initiating development of GEN011 (adoptive T-cell therapy); and preclinical studies with GEN010 (next-gen neoantigen vaccine). (Jun.)


**GLOBAL BLOOD THERAPEUTICS INC.**

Global Blood Therapeutics Inc. netted $193m through a public offering of 3.4 million common shares at $59.25. Proceeds...
will support continued development and future commercialization activities surrounding voxelotor for sickle cell disease, and will also go towards R&D of additional projects including inclacumab for vasculo-occlusive crisis. (Jun.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.

INHIBRX INC.

Inhibrx Inc. (biologics for cancer, infectious diseases, and orphan conditions) filed for its initial public offering. (Jun.)

Investment Banks/Advisors: Barclays Bank PLC; Evercore Partners; Nomura Securities International Inc.; Raymond James & Associates Inc.

KARUNA THERAPEUTICS INC.

Karuna Therapeutics Inc. (muscarnic receptor modulators for psychiatric and cognitive disorders) netted $83m in an initial public offering of 5.6 million shares at $16, the midpoint of its anticipated range. The company originally planned to sell 4.375 million shares. (Jun.)

Investment Banks/Advisors: Citigroup Inc.; Goldman Sachs & Co.; Wedbush PacGrow Life Sciences; Wells Fargo Securities LLC

KURA ONCOLOGY INC.

Precision cancer medicine company Kura Oncology Inc. netted $108.4m through a public offering of 6.8 million common shares (including the overallotment) at $17. Proceeds are earmarked for continued R&D including development of tipifarnib for solid and blood cancers; K0947 and K0539 for solid tumors and AML, respectively; and additional pipeline projects. (Jun.)

Investment Banks/Advisors: Cowen & Co. LLC; HC Wainwright & Co.; Oppenheimer & Co. Inc.; SVB Leerink; Wedbush PacGrow Life Sciences

MIRATI THERAPEUTICS INC.

Mirati Therapeutics Inc. (oncology) netted $91.5m through a public offering of 2.1 million common shares at $43. The company plans to use the funds for development of sitratavdin (NSCLC, melanoma, bladder cancer, and other solid tumors), MRTX849 (NSCLC and colorectal cancer (CRC)), and preclinical projects including a KRAS G12D inhibitor for NSCLC, colorectal, and pancreatic cancers. (Jun.)

Investment Banks/Advisors: Barclays Bank PLC; Cowen & Co. LLC; Credit Suisse Group; Guggenheim Partners LLC; HC Wainwright & Co.; Oppenheimer & Co. Inc.

MORPHIC THERAPEUTIC INC.

Morphic Therapeutic Inc. netted $83.7m through its initial public offering on the Nasdaq of 6 million common shares at $15 each. It had planned to sell 5 million shares between $14 and $16. (Jun.)

Investment Banks/Advisors: BMO Financial Group; Cowen & Co. LLC; Jefferies & Co. Inc.; Wells Fargo Securities LLC

ODONATE THERAPEUTICS LLC

Odonate Therapeutics Inc. (developing taxane therapies for cancer) netted $117.3m via a public offering of 4.75 million common shares at $26. Proceeds are earmarked for continued development of tesetaxel, which is in Phase II/III studies for metastatic breast cancer and metastatic triple-negative breast cancer. (Jun.)

Investment Banks/Advisors: Cowen & Co. LLC; Jefferies & Co. Inc.; LifeSci Capital LLC

PREVAIL THERAPEUTICS INC.

Neurodegenerative-focused Prevail Therapeutics Inc. (adeno-associated virus (AAV)-based vectors for gene therapies) netted $116.3m in its initial public offering of 7.4 million shares at $16, the midpoint of its anticipated range. (Jun.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Cowen & Co. LLC; Morgan Stanley & Co.; Wedbush PacGrow Life Sciences

RESVERLOGIX CORP.

Resverlogix Inc. (epigenetics-based drug development) netted $CDN14m ($10.5m) through a public offering of 3.8 million units at $CDN4. Each unit consisted of one common share and a four-year warrant to purchase a share at $4.60. HC Wainwright was the placement agent. Proceeds will fund ongoing R&D, including the BETonMACE Phase III trial with lead candidate apabetalone, which is evaluating if treatment with apabetalone compared to placebo increases the time to first occurrence of a major adverse cardiac event in high-risk cardiovascular disease patients with Type II diabetes and low levels of HDL. (Jun.)

Investment Banks/Advisors: Bloom Burton & Co.; HC Wainwright & Co.

ROCKWELL MEDICAL INC.

Rockwell Medical Inc. (treatments for end-stage renal disease and chronic kidney disease) sold 5.8 million common shares at $3 piece in a public offering that netted the company $16.4m. Funds will support commercialization of dialysate Triferic (ferri pyrophosphate citrate), and will also go towards commercialization of intravenous Triferic once it is approved. (Jun.)


SCHOLAR ROCK HOLDING CORP.

Scholar Rock Holding Corp. (therapeutic antibodies based on protein growth factor signaling modulation) netted $42.3m in a public offering of 3 million shares at $15. The company will use the proceeds to support ongoing development of lead antibody candidate SRK015 (in Phase II for spinal muscular atrophy); preclinical and initial Phase I proof-of-concept trial activities for SRK181 (a transforming growth factor beta 1 inhibitor for cancers resistant to checkpoint blockade therapies); and preclinical studies for other pipeline programs. (Jun.)

Investment Banks/Advisors: BMO Financial Group; Cowen & Co. LLC; Jefferies & Co. Inc.; Wedbush PacGrow Life Sciences

SELLAS LIFE SCIENCES GROUP INC.

SELLas Life Sciences Group Inc. netted $13.5m through a public offering in which the company sold 23.6 million common shares at $0.15 (plus five-year warrants to buy 23.36 million common at $0.50) and $73.6 million pre-funded warrants at $0.1499 (along with warrants to purchase 73.6 million common at $0.50). Most of the funds will help the company initiate a pivotal Phase III trial with lead project galinpepimut-S for acute myeloid leukemia and continue a Phase I/II trial of the candidate in combination with pembrolizumab for blood and solid cancers. (Jun.)

Investment Banks/Advisors: Maxim Group LLC

SERES THERAPEUTICS INC.

Microbiome therapeutics developer Seres Therapeutics Inc. netted $56.4m through a follow-on public offering of 26.67 million common shares at $2.25 each. (Jun.)

Investment Banks/Advisors: Cowen & Co. LLC; Goldman Sachs & Co.

SESEN BIO INC.

Sesen Bio Inc. (oncology) netted $28.2m through a public offering of 20.4 million common shares at $1.47. Investors also received one-year warrants to purchase 20.4 million more shares at the purchase price. Proceeds will support continued development, regulatory and manufacturing activities, and future commercialization of Vicinium (oportuzumab monatox) for non-muscle invasive bladder cancer (NIMBC). (Jun.)

Investment Banks/Advisors: Canaccord Genuity Inc.

SORRENTO THERAPEUTICS INC.

Sorrento Therapeutics Inc. (immuno-oncology and pain management) netted $23.5m through a public offering of 8.33 million common shares at $3. Each share was also sold with the following warrants: ten-year series A warrant to purchase a common share at $3.75; nine-month series B warrant for one common at $3; and a ten-year series C warrant, to be exercised at $3.75 if a corresponding series B warrant was exercised. Proceeds will support continued development of the company’s RTX (resiniferatoxin, for cancer pain), CEA
CAR-T (liver tumors), and CD38 CART (multiple myeloma) programs. (Jun.)
Investment Banks/Advisors: HC Wainwright & Co.; JMP Securities LLC

STOKE THERAPEUTICS INC.
Genetic disease-focused Stoke Therapeutics Inc. (antisense oligonucleotides to upregulate gene expression) netted $132m in its initial public offering of 7.9 million shares at $18. The company originally planned to sell 6.7 million shares at a $14-$16 range. (Jun.)
Investment Banks/Advisors: Canaccord Genuity Inc.; Cowen & Co. LLC; Credit Suisse Group; JP Morgan & Co.

THE MEDICINES CO.
The Medicines Co. (mostly focused in the cardiovascular disease space) netted $141.4m through the follow-on public sale of 4.55 million common shares at $33 each. The company will use the funds for ongoing development of its Phase III inclisiran for homozygous familial hypercholesterolemia. (Jun.)

ZYMEWORKS INC.
ZymeWorks Inc. (bspecific antibodies and ADCs for cancer) netted $189m through its latest public offering. The company sold 7 million common shares (including the overallotment) at $26, and to a certain extent 2.7 million pre-funded warrants at $17.999 apiece. ZymeWorks will use some of the proceeds to support continued development of the bspecific antibody ZW25 as a single and combination therapy for HER2-expressing solid tumors; ZW49, a bspecific antibody-conjugate also for HER2-expressing tumors; and other preclinical pipeline programs. (Jun.)

RESEARCH, ANALYTICAL
EQUIPMENT & SUPPLIES

ADAPTIVE BIOTECHNOLOGIES CORP.
Adaptive Biotechnologies Corp. (immuno-sequencing diagnostics) netted $279m in its oversubscribed initial public offering of 15 million common shares at $20 each on the Nasdaq. The company planned to sell 12.5 million shares between $15 and $17 each. (Jun.)
Investment Banks/Advisors: BTIG LLC; Bank of America Merrill Lynch; Cowen & Co. LLC; Goldman Sachs & Co.; Guggenheim Partners LLC; JP Morgan & Co.; William Blair & Co.