In Vivo
Informa Pharma Intelligence

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DEAL-MAKING

Acquisitions • Alliances • Financing

2020 Could Spell The End Of Mega-Mergers, For Now

The Only Way Is Nasdaq

Investors See Medtech Continuing To Ride Growth Wave Into 2020

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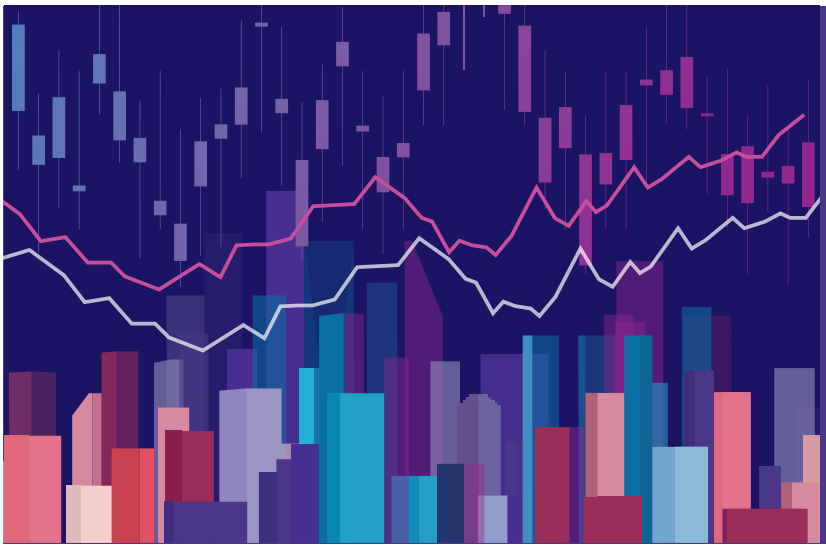
In Vivo

Informa Pharma Intelligence

February 2020



DEAL-MAKING

ACQUISITIONS

ALLIANCES

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In Vivo
Informa Pharma Intelligence

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DEPARTMENTS

AROUND THE INDUSTRY

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EXCLUSIVE ONLINE CONTENT

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From The Editor

LUCIE ELLIS

Welcome to *In Vivo*'s deal-making and partnering special issue.

This month we have analyzed 2019's deals to learn lessons for 2020. But we have also gone back even further, exploring two decades of mega-deals in an infographic (*see page 8*).

The biopharma sector is often accused of a being a slow-moving engine, but a look back over the past 20 years reveals that a lot has changed. Our infographic timeline explores the history of high-impact M&A transactions in the pharma industry between 1999 and 2019.

Also in this issue, Melanie Senior explores why the US Nasdaq exchange has become the only option for ambitious UK and European biotechs, looking into case studies such as Genmab's $582m IPO in 2019.

As for 2020, it seems a busy year of deal-making is on the cards. Still, biopharma might have seen the end of the "mega-merger" for now. Industry experts are predicting that 2020 will be a year in which mid-sized companies will drive most of the deal activity, either acquiring or being acquired. And as big pharma seeks bolt-on acquisitions to build out strategies, deals to acquire biotechs valued at between $5bn and $10bn will be the sweet spot for this activity.

Other important notices:

In Vivo has launched its refreshed Editorial Advisory Board for 2020. Please see the list of all EAB members in the back of this issue. The advisory board will be providing guidance and insight as we look to bring you the very best features and analysis.

We also want to hear from our readers. We are conducting a survey to better understand our subscribers' content and delivery needs. If there are any changes you'd like to see in the format of the content or the method in which you receive and access *In Vivo*, or if you love it how it is, now is the time to have your voice heard. Go online to take part: https://bit.ly/2Srv3Y8

Up-Front

SNAPSHOTS FROM FEBRUARY'S CONTENT

"The most important theme when we invest in companies is 'How can I help you translate this unique science into a drug that a physician will prescribe, and an insurance company will pay for?'"

PAGE 36

– Roel Bulthuis

"Care is going into the home, and hopefully that's where this industry is going," says OrbiMed Advisors' Anat Naschitz. Patient interaction with devices is a key factor, and devices offering this facility are setting the pace. PAGE 22

INFOGRAPHIC: PAGE 8

152

Total number of deals worth more than $2bn (1999-2019)

114

Total number of deals worth more than $2bn (2009-2019)

$1.3TN

Combined value of the last decade's mega deals (>$2bn; 2009-2019)

EY identified four factors fueling last year's record-breaking activity:

1. Readily available capital for deals, or "Firepower"
2. Slowing revenue growth at life sciences incumbents
3. A recalibration of the US and European public markets
4. A desire to deepen therapy area focus

PAGE 26

In 2019, there were 12 deals in the life sciences (including consumer health, medtech and animal health) valued at **$5bn** or more. Of those 12 deals, six involved the acquisition of a biotech.

PAGE 10

Around The Industry

Regular Acceptance Of Simulation Studies More Likely In 2020s

Lyon, France-based Novadiscovery is developing a user-facing technology to run *in silico* studies, a method it expects to cut development costs and improve trial success rates. But acceptance of "new" data types is often a concern for drug developers, despite world-leading regulatory bodies stating their desire for 21st century approaches.

In a recent interview, Novadiscovery CEO François-Henri Boissel outlined his company's ambition to utilize *in silico* or virtual clinical trials to give a much-needed efficiency boost to the biopharma industry. The company aims to use its unusual trial platform – Jinko – to allow customers to first model their drug candidate on a virtual human in a computer simulation before the drug is tested on humans.

"The objective of this platform is to help our customers to improve productivity of the R&D process, potentially reducing time to market, reducing the cost to those firms and in some instances reducing the size of the trial necessary to demonstrate efficacy; as well as hopefully improving the probability of success," Boissel told *In Vivo*.

On January 9, Novadiscovery announced that the Debiopharm Innovation Fund was investing €5m in its series A financing round. Tanja Dowe, CEO of the Debiopharm Innovation Fund, spoke of its strategy of investing in best-in-class companies seeking to disrupt the pharmaceutical industry, either in the way drugs are developed or how patients are treated. "The pharma industry needs faster ways to run clinical trials and smarter ways. Drug development cost has gotten out of hand. We have turned to personalized medicine, but we behave as if we are still developing these big blockbuster drugs of 'one-size-fits-all.' We definitely have to find better approaches," Dowe said.Boissel expects Novadiscovery to close the series A round in 2020, after reaching a target of €7m.

Boissel believes that *in silico* trials will become part and parcel of drug R&D, not with a view to fully replacing randomized clinical trials (RCTs) but rather informing the more conventional operations. "We aren't saying *in silico* trials will at any point in time become a full replacement to testing drugs on humans," Boissel noted. "What we're saying is that this technology will help us identify a drug candidate and certainly improve the matching between those drug candidates and the best responder profile, to make the whole process more efficient in more of an engineering mindset."

"The objective of this platform is to help our customers to improve productivity of the R&D process, potentially reducing time to market, reducing the cost to those firms and in some instances reducing the size of the trial necessary to demonstrate efficacy."

François-Henri Boissel

Dowe affirmed this with an analogy about the aerospace industry. "There is no way any new plane would fly without first simulating many times. Right now, in pharma, we're not simulating – we have the knowledge – but we're not simulating," she said. "We're putting drugs into humans after preclinical trials" and then into human studies. While virtual simulation studies would add another layer to the drug discovery process, Dowe argued that this method should make the entire process more efficient. Just as computers have done for many other industries.

THE JINKO PLATFORM

Novadiscovery, which has been around for almost a decade, is built upon the Jinko platform for *in silico* trials. While not the only company in this space, Novadiscovery is differentiated in that it not only makes use of quantum computing but also aims to use machine reading and machine learning to draw upon the vast scientific knowledge in literature. This allows the technology to absorb information in a diverse range of fields to better understand the various biological mechanisms of a disease. This can then be added into the modeling of the effects of a proposed drug candidate during the virtual trial.

"We're trying to amass all the biological entities that are known to be implicated in those various biological processes and the functional relationship between those

entities," Boissel said. Novadiscovery's technology will launch over the course of 2021. He explained that Nova will progressively expand on functionality. With one of the benefits of having a software-to-service platform being that you can plug in additional functionality and upgrades to the platform over time. The platform is already operational internally, but needs work to become a tool for external users. "Essentially there is a thick layer of user interface and user experience that we need to work on, among other things, to get us to a commercial product stage," said Boissel.

Debiopharm looked at a lot of companies that aim to improve drug development but the majority of these companies work in the discovery phase, Dowe noted. "They are looking at big data, using artificial intelligence, to discover new druggable targets or new leads. There are fewer companies that are using smart systems for predicting the efficacy of clinical trials," she said. This later development stage is a field that is "data poor," so typical AI companies cannot operate here. "You need drug development colleagues, you need medical understanding, biological understanding – combining these with simulation skills, and of course there is a little bit of AI involved as well. This is the reason we went for Novadiscovery," Dowe explained.

When it comes to limitations of *in silico* trials, Boissel pointed to two overlapping areas. The first hurdle is current understanding of a disease. Boissel described knowledge as the primary base material of these virtual trials, and if there is a lack of understanding around a disease then uncertainties can be introduced to the model. However, the CEO noted that the platform could also help researchers test assumptions on the understanding of a disease in a much more structured way.

The second issue is reliability. There is a risk related to the "strength of the evidence extracted from the scientific articles. This is something the platform addresses in a functional way," Boissel said.

REGULATORY OUTLOOK

A wider issue for the AI and virtual trials sector is acceptance by regulators of the data these studies generate. Boissel said the key issue was validation of the model. "Can we provide proof to the regulator that the model has been properly validated before we use simulations to help inform the design of an upcoming trial?" he asked. "The FDA is working on drafting those guidances for computational model validation. They launched, in 2018, a trial program called MIDD for modeling in drug development, which Novadiscovery has been a part of."

Essentially, the FDA is building a portfolio of new cases to inform a framework so that digital evidence becomes acceptable in the context of a drug's development. Boissel predicted that the FDA would formally issue guidelines in the next year or so.

In Europe, the Avicenna Alliance, or Association for Predictive Medicine, was established in 2015 and funded by the European Commission to create a "roadmap for *in silico* medicine." The Alliance's findings were published two years later and argued strongly for the European Commission and other international and national funding agencies to "include these research targets among their priorities, allocating significant resources to support approaches that could result in huge socioeconomic benefit."

The report also pointed to the aerospace industry – as well as other sectors such as nuclear power – as examples of sectors making extensive use of simulations, which could be emulated in pharmaceutical product development. The current approach creates the need for long and complex experiments *in vitro*, in animals and then in patients during clinical trials, which pushes development costs to the unsustainable levels we see today, while stifling innovation.

In its Regulatory Science Strategy for 2025, the European Medicines Agency noted that novel approaches, such as systems on a chip and *in silico* modeling, are the subject of much ongoing research and have the potential to benefit drug development and support early efficacy studies, as well as improve predictive ability.

The EMA is aware that there may, however, be hesitancy on the part of developers to use such new methods in marketing authorization applications because of concerns that these will not be accepted by regulators and may stall the approval process. To address this, the EMA has proposed promoting *in silico* methodology and novel *in vitro* assays to reduce animal use, particularly in toxicology/epidemiology and batch control.

The agency is also working on plans to drive adoption of novel practices that facilitate clinical trial authorization, such as the acceptance of digital endpoints. On modeling and simulation and extrapolation in clinical trials, the EMA had recently stated that these should incorporate real-world data, natural history and/or observational data. The agency is convinced that *in silico* clinical trials could help to reduce, refine and partially replace traditional clinical trials.

IV124437

WILLIAM MASTERS

Additional reporting by Vibha Sharma and Derrick Gingery.

New Business Models Are Needed To Support Innovative Payer Partnerships

Maximizing patient access to innovative and effective treatments will require increased transparency, improved outcomes data analyses, dynamic contract management and perhaps most importantly, good faith on both sides.

Innovation continues to reshape the life sciences industry, enabling the development of groundbreaking, life-enhancing therapies. Despite these positive advancements, payers are demanding greater transparency on costs and accountability for outcomes delivered to patients and the wider health care ecosystem. While this appears to be a daunting challenge, it also presents an opportunity for pharmaceutical and biotech companies to rethink their business models. Building stronger partnerships with payers can help to protect sustainable returns, while delivering the benefits of greater patient access to innovative products.

CHALLENGES TO CURRENT PHARMA-PAYER RELATIONSHIPS

Pharmaceutical organizations need to have an honest, transparent view of the benefits of innovative therapies and realistic profitability expectations. In a recent MIT survey, 91% of payers attributed their vast concern over emerging

high-cost therapies to the products' risk and unknown effectiveness. Organizations cannot afford to underestimate the importance of generating evidence that validates the relevant value for payers and patients during drug development. Similarly, payers will need to be willing to move beyond the constraints of short-term budget horizons, siloed finances (e.g., drug budget versus hospital or social care funding) or relying on expedient pricing mechanisms and rigid evaluation processes. For example, international reference pricing, which relies on pricing comparisons with selected, often lower-cost markets, remains a barrier to more flexible approaches to pricing and recognizing value.

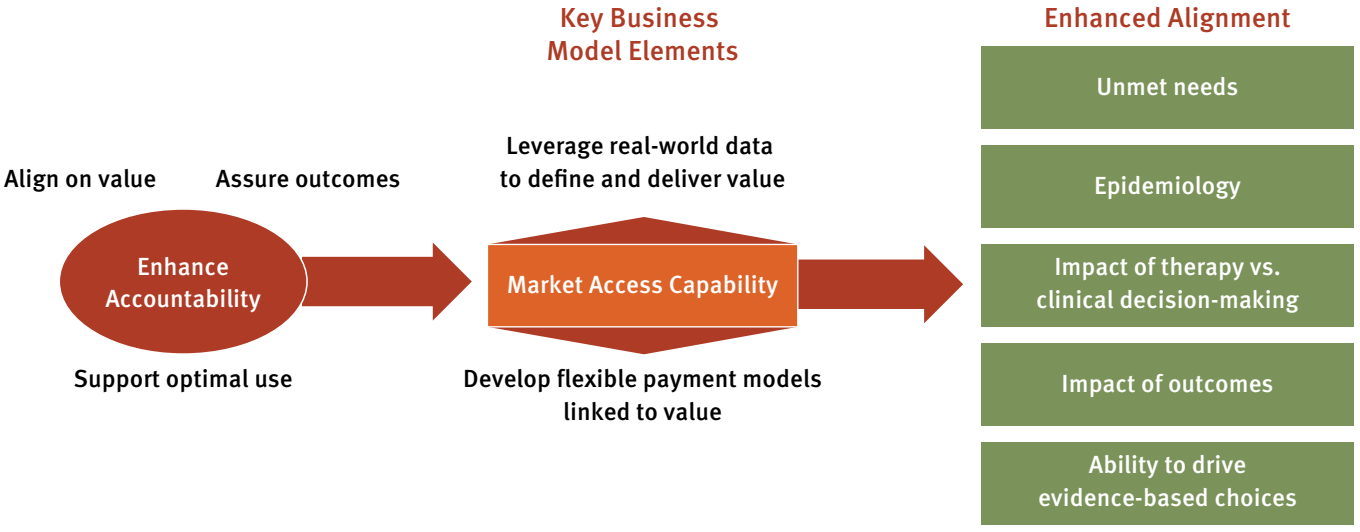
INTEGRATING KEY CAPABILITIES TO ENHANCE PAYER ACCOUNTABILITY

When designing new business models with a focus on enhanced accountability there are two key market access competencies that pharmaceutical organizations need to nurture. To start, businesses need the ability to use real-world data to better define patient needs, set value parameters and demonstrate the outcomes being delivered over time. Second, organizations need to develop flexible payment models linked to those outcomes. Integrating these elements into a new business model will help provide opportunities for greater alignment with payers, including enhanced alignment around unmet needs, patient profiling and the clinical and economic impact of optimizing therapy within the relevant health care system.

In the short to mid-term, the indus-

Exhibit 1

New Business Model Elements To Enhance Payer Partnerships



SOURCE: Huron

try is likely to be reliant on third-party partnerships in order to build real-world evidence capabilities and drive efficiency. Artificial Intelligence and data analytics are increasingly being sought to enhance the pharmaceutical industry's ability to obtain dynamic, real-time insights into drug and device utilization and outcomes. Even as organizations continue to develop their own in-house resources, there will remain an advantage to having external parties collate, process and report patient outcomes data given compliance considerations and the requirement for value-based contract payments to be arbitrated objectively.

The combination of value-based contracting and the demand for robust data is driving the need to strengthen several competencies and relationships within the pharmaceutical industry's global and affiliate organizations. At the global level, teams will need to develop a broad value-based contracting framework that defines feasible options – such as product-specific health outcomes metrics, cost savings, or both – to negotiate around the value and uncertainty of new technologies and products. These frameworks must balance the risk between the company and its payer partners. Additionally, these options need to be incorporated into commercial forecast models for organizations to accurately project the return on investment. Pricing governance models must also be calibrated to reflect the impact on net prices across all markets.

Furthermore, affiliates will need to deepen their ability to negotiate around value and effectively engage local stakeholders involved in data generation. This will help ensure that data collection methods are tailored to value metrics deemed relevant to local payer and health technology assessment (HTA) bodies.

EMBEDDING SUCCESS

A better partnership between pharmaceutical companies and payers cannot be achieved in a vacuum and needs to be built on a solid foundation. Companies already evolving their business models offer several lessons to follow, including:

- The importance of organizational design. The integration of real-world data and outcome-based contracting solutions require a deeper level of cross-functional skills and perspectives as well as a blurring of traditional roles within these functions; pricing and contracting acumen combined with deep product knowledge or outcomes data analysis, for example. Additionally, payer partners will need to be managed, not just engaged, with contract performance being continually reported and revisited based on emerging data and insights on a product's value proposition.
- Industry collaboration requires the right infrastructure. A closer working partnership between third parties and global and local teams should become the new normal for the industry. This increased visibility can enable organizations to better develop and apply value-based, real-time data driven models and tools to drive efficiency and validate patient outcomes, including dashboards to manage flexible contracting and filter performance or utilization feedback into drug positioning and value communications.
- Leaders need to commit to long-term thinking. Given the significant investment required for new capabilities and competencies, the success of creating pharmaceutical business models that support accountability – and ultimately value – are unlikely to be viable if approached as one-off product strategies. Any new business model needs to be aligned to how a company does business across its portfolio – even if it requires structural and organizational change to redefine roles and responsibilities.

Ultimately, these new business models must be built on a partnership mindset and culture that recognizes a mutual dependency between pharmaceutical companies and payers. These new partnerships, fueled by new analytical tools, processes and management structures can empower organizations to not only shape how companies demonstrate value, but also show the work supporting it. Proving product value to payers on relevant, measurable and transparent terms can help ensure that life-enhancing therapies get into the hands of the people that need them the most – patients.

IV124432

CHRIS EASLEY

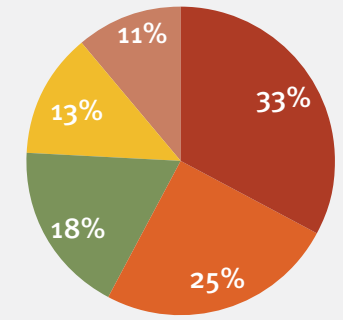
Chris Easley is a managing director in Huron's life sciences business.

DEALS OF THE YEAR

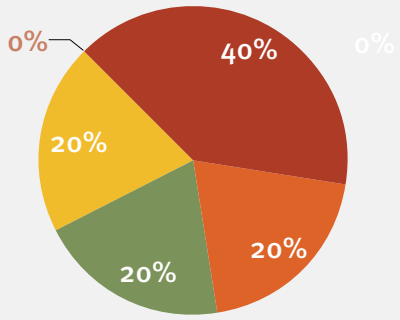
WINNERS ANNOUNCED

The results are in for *In Vivo*'s 12th annual Deals Of The Year contest. Chosen by our readers, the winners are...

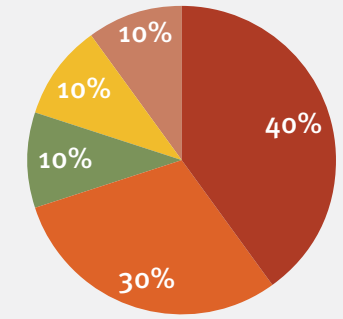
2019 TOP M&A



2019 TOP FINANCING



2019 TOP ALLIANCE



20 YEARS OF MEGA-DEALS

The biopharma sector is often accused of a being a slow-moving engine, but a look back over the last 20 years reveals that a lot has changed. *In Vivo* explores the history of high impact M&A Deals (2009-2019).

BIGGEST DEAL OF THE LAST DECADE

2019 saw the largest acquisition of the last decade when Bristol-Myers Squibb finally closed its deal to purchase Celgene for $74bn.

DEALS THAT FELL APART

In 2014, AbbVie terminated its proposed acquisition of Shire - valued at $54.7bn. Shire has since been bought by Takeda.

The biggest whirlwind story: Pfizer's merger with Allergan never made it to the finish line. The deal had been valued at $160bn.

CONCLUSION & EXPECTATIONS

152

Total number of deals worth more than $2bn (1999-2019)

114

Total number of deals worth more than $2bn in the last decade (2009-2019)

$1.3TN

Combined value of the last decade's mega deals (›$2bn; 2009-2019)

Sources: *In Vivo; Scrip*
Design: Gayle Rembold Furbert, Jean Marie Smith/Informa Pharma Intelligence Design Team

TOP 20 DEALS OF THE LAST 20 YEARS (1999-2019)

DEAL VALUE ($BN)

Deal Value ($bn)

1999

- APR 6 — ASTRA/ ZENECA — $37
- JUN 18 — PFIZER/ WARNER-LAMBERT — $90
- DEC 27 — GLAXO WELLCOME/ SMITHKLINE BEECHAM — $75.7
- APR 16 — PFIZER/ PHARMACIA — $60
- AUG 23 — SANOFI-SYNTHÉLABO/ AVENTIS — $63.2

1999 | 2000 | 2003 | 2004

- AUG 26 — NOVARTIS/ ALCON (52% stake) — $37
- OCT 15 — PFIZER/ WYETH — $68
- MAR 26 — ROCHE/ GENENTECH — $46.8
- MAR 11 — MERCK & CO/ SCHERING-PLOUGH — $41.1
- JUL 12 — BAYER/ SCHERING AG — $21.5

2010 | 2009 | 2006

- JAN 7 — ALLERGAN (formerly Actavis)/ FOREST LABORATORIES — $28
- MAR 17 — ACTAVIS (renamed Allergan)/ ALLERGAN — $70.5
- MAY 26 — ABBVIE/ PHARMACYCLICS — $21
- JUN 3 — SHIRE/ BAXALTA — $32
- AUG 2 — TEVA PHARMACEUTICAL INDUSTRIES/ ACTAVIS GENERICS — $38.8

2014 | 2015 | 2016

2019

- NOV 21 — BRISTOL-MYERS SQUIBB/ CELGENE — $74
- JUN 25 — ABBVIE/ ALLERGAN — $63
- JAN 8 — TAKEDA/ SHIRE — $62.3
- JUN 16 — JOHNSON & JOHNSON/ ACTELION — $30
- JAN 4 — ABBOTT LABORATORIES/ ST JUDE MEDICAL — $25

2019 | 2017

KEY

Date of Completion
ACQUIRER
TARGET
Deal Value

2020 Could Spell The End Of Mega-Mergers, For Now

Industry experts expect a continued uptick in deals valued between $2bn-$10bn this year as buyers look to add critical mass in areas like oncology, rare disease and cell and gene therapy. Divestitures to free up capital and narrow focus should continue too.

BY JOSEPH HAAS

Biopharmaceutical deal-making should coalesce mainly around mid-sized deals in 2020, analysts at PwC predict, as buyers seek bolt-on acquisitions that help them to become leaders in areas like oncology and cell and gene therapy.

Most industry watchers see a repeat of last year's two mega-mergers as unlikely – instead they expect companies valued at $2bn to $10 bn, even up to $15bn, to drive M&A.

Although aggregate deal value may be lower than in 2019, 2020 is expected to be an active year for M&A.

PwC's Pharma and Life Sciences group expects mid-sized biotechs developing life-saving drugs to be highly sought, while larger companies will continue divesting non-core assets to free up capital and narrow focus to core competencies and targeted growth areas.

PwC's *Global Pharma & Life Sciences Deals Insights Year-End 2019 & 2020 Outlook* report suggests that 2020 will be a year in which mid-sized companies will drive most of the deal activity, either acquiring or being acquired. And as big pharma seeks bolt-on acquisitions to build out strategies, deals to acquire biotechs valued at between $5bn and $10bn will be the sweet spot for this activity. A few deals valued between $20bn and $30bn also could occur to further sector leadership strategies.

Speaking on a deals panel at the BIO CEO & Investor conference in New York on February 10, financial advisor Eric Tokat of Centerview Partners, which advised Spark Therapeutics in its merger with Roche last year, also predicted more small or mid-size deals as big pharma settles down. "Historically, large pharma mergers were driven by efficiency, cost-cutting, cash flow, diversification. In this era, the drivers are a bit different than we have seen in the past," he said. The science-driven nature of deal-making today should continue the momentum behind smaller bolt-on deals in 2020, he predicted. "I do anticipate more of the $1bn-$5bn or $1bn-$10bn deals."

PwC's report also suggests that increased activity by private equity investors will drive business development this year.

The growing presence of private equity investors is also cited by Morrison & Foerster in its *Key M&A Trends For 2020* report, as a factor that will shape M&A activity this year in the life sciences and the larger economy. The Morrison & Foerster report, which looks at deal-making across all sectors of the economy, concludes that increased share-

holder activism and increased antitrust oversight of large mergers will influence the deal-making climate.

"The calls for more stringent standards and aggressive [antitrust] enforcement have focused particularly on 'big tech' and 'big pharma' companies, as well as firms in other industries, where patent-protected innovations, platform-based business models, and data-driven insights provide significant competitive advantages or may generate 'winner-take-all' network effects," M&F's report states.

The biopharma industry has braced for increased regulatory scrutiny, which was a factor in multiple large deals in 2019. The US Federal Trade Commission's review of Bristol-Myers Squibb Co. $74bn acquisition of Celgene Corp. meant that a deal announced in January did not close until November, and required the divestiture of Celgene's autoimmune blockbuster Otezla (apremilast) to Amgen Inc. for $14.3bn. FTC oversight also caused the $4.8bn Roche/Spark merger to need roughly 10 months to close as the FTC did an "exhaustive" review of the competitive dynamics in hemophilia A. *(Also see "Biopharma M&A: Lessons From 2019, Trends For 2020" in this issue .)*

Pharma deal value in 2019 was stable compared to 2018, even though volume was down, with the two mega-mergers combining BMS/Celgene and AbbVie Inc. and Allergan PLC keeping deal valuation up. PwC's US Pharma and Life Sciences deals leader Glenn Hunzinger thinks the industry's appetite for mega-mergers is satisfied for now, due to a variety of factors including the integration process following major deals of recent years and companies being more confident in their current strategies. This confidence, in turn, means they are more likely to look to smaller, targeted deals to build out on their strategies.

Why No More Mega-Mergers?

"Where we sit now – we kind of felt it at J.P. Morgan this year – was there was a little more calmness at the meeting, everybody was operating under a strategic agenda, they felt like they had a good plan, they were focused, they didn't necessarily need or feel the pressure to announce a few things at JPM," Hunzinger said in an interview.

"Companies spent an enormous amount of time in 2019 really pushing the envelope ... that's why I think in biotech, just given the nature of oncology and cell and gene therapy companies being a little more fragmented, I think we'll see a lot of what we call mid-sized deals in that $2bn-$10bn range," Hunzinger added. This activity will be driven by more targeted pursuits of "great science," he explained, such as companies looking "to fill gaps in specific oncology portfolios – if they have lung, they want to have ovarian, they want to do combinations."

The M&F report notes that health care M&A outpaced overall M&A deal-making last year, with aggregate value of health care M&A up 26% compared to 2018. Across all economic sectors, M&A litigation will hinder acquisition activity in 2020, the report predicts, but shareholder activism will remain a driver for both M&A and divestment transactions. An estimated 47% of activist investor campaigns focused on M&A in 2019, up from about 35% in previous years, M&F said.

Meanwhile, the need for large-scale acquisitions is less prevalent as new corporate strategies have had some time to take shape, Hunzinger said. "I think so much happened last year. When I look across the large pharma companies, they all have gone through some level of transformational event in some shape or form," he explained. "I combine that with the fact that across the industry, the organic growth has never been better in 10 years. People feel good about their portfolios, they feel good about their strategies and we've heard from a lot of different companies their views on building block-type acquisitions versus taking big bets. ... It's really a matter of incrementalism versus making a big mega-deal."

KPMG also sees more targeted activity in the coming year, with continued focus on next-generation therapies, such as cell and gene therapies, and personalized medicine that are driving forces in the current business development environment. In its 2020 *Opportunities and Challenges In An Evolving Market* report, KPMG says drug makers "are diversifying across multiple platform types and pursuing different strategies." The report notes that "some companies are investing in

PRIVATE EQUITY ON THE RISE

- PwC notes that private equity players have about $1.7tn to invest and are positioned to take advantage of divestment opportunities in the life sciences sector.

- Private equity investment is no longer reactive, awaiting auction opportunities, the *Year-End 2019 & 2020 Outlook* report says, but proactively looking for "take private" opportunities, corporate divestitures and partnerships with mid-market companies.

- A prime example of this in 2019 was a consortium led by EQT AB purchasing Nestle's Skin Health division for about $10.1bn and then rebranding it as Galderma.

- Hot spots for private equity investment include pharmatech companies, and PwC expects cell and gene therapy specialists and microbiome-focused companies to be of increasing interest.

- Morrison & Foerster's review of 2019 deal-making across all industries noted that private equity firms in 2020 will be "armed with a record level of cash," which it estimates at nearly $1.5tn.

- About $450bn in private equity deals were closed in 2019, M&F added, a modest decrease from 2018. But the firm noted a change in investment focus as PE buyers invested not only in public and more mature companies with established cash flows, but also "bought younger firms and engaged in growth equity, joint ventures and other majority or minority investments with greater frequency in 2019."

vertically integrated capabilities, which allow them to capture market segments before second-movers emerge and to position themselves as the best partners for emerging biotechs."

"Other companies are taking a more conservative approach by following large capital investments with multiple partnerships across different innovative platforms, which gives them time to determine which will eventually show the most potential," KPMG added.

But everyone focusing on the same area has an impact. Numerous players seeking oncology and cell and gene therapy acquisitions can lead to asset scarcity and make it challenging to remain within reasonable valuations, Hunzinger said.

"Last year, I think we saw a lot of that, where companies needed to make certain moves to at least start to add to their building blocks or their foundation in their therapeutic category," he said. "This is part of what the industry always has to address, how do you balance risk as well as staying disciplined. A lot of the corporate development people I've come across do a tremendous job trying to balance that risk. The risk is always there, the value discussion is always there, I see people excited about technology and about certain companies and drugs, but they just can't get there on the valuations. I think that while they know there's a scarcity factor, people know that they have to have discipline."

2019 DEAL-MAKING TRENDS

There were 12 deals in the life sciences (including consumer health, medtech and animal health) valued at $5bn or more.

Of those 12 deals, six involved the acquisition of a biotech. PwC expects biotech buyouts valued at $5bn or more to increase in 2020.

The big pharma sector, however, saw a decrease in deal volume to fewer than 100 transactions, while biotech, medtech and other sectors had increased deal volume.

Aggregate deal value in biotech nearly tripled from 2018 to 2019 to roughly $180bn, while deal volume rose as well.

Making Room For Bolt-On Deals

In tandem with continuing focus on with corporate strategies and a reduced appetite for larger M&A, Hunzinger expects a continuation of the divestment trend seen in the biopharma sector. In recent years, this has taken the form of sell-off of assets and business units, as well as spinouts and initial public offerings, he explained. He thinks companies will do more spinouts in 2020 both to divest non-core assets and to help pay down debt.

"You have companies with wide portfolios; what comes with wide portfolios is operational complexity, trying to be everything to everybody in terms of geography, therapeutic categories, manufacturing," Hunzinger said. "There are people looking at their business models and saying 'I need to figure out how to transform my business operationally, I want to be able to invest in the growth areas,' and they know in some of these therapeutic areas scale is super important. If they are not the category leader and do not have scale, then they know that maybe certain therapeutic areas or products are better off in someone else's hands."

Cell And Gene Spotlight

EY's business development group anticipates efforts by biopharma companies to optimize their portfolios could drive as much as $300bn in deal-making this year centered on five therapeutic areas: oncology; cardiovascular and metabolic disease; immunology, infectious disease; and central nervous system disorders.

EY also expects 2020 deal-making to be dominated by cell and gene therapy, as well as immuno-oncology, according to a report released in conjunction with the J.P. Morgan Healthcare Conference.

Gilead Sciences Inc. and Novo Nordisk AS are viewed as motivated buyers in the cell and gene space, but the early track record of some of the products that have reached market caused investor anxiety during the second half of 2019. While Novartis AG's gene therapy Zolgensma (onasemnogene abeparvovec-xioi) got off to a solid launch, Spark's Luxturna (voretigene neparvovec) yielded minimal initial sales. Meanwhile, the launch of bluebird bio Inc.'s Zynteglo (autologous CD34+ cells encoding βA-T87Q-globin gene) was hindered by manufacturing issues. *(Also see "Gene Therapy Manufacturing Hitch Solved, Bluebird Aims For European Debut In 2020" - Scrip, 24 Oct, 2019.)*

Hemophilia A and B and rare diseases such as Dravet syndrome, Pompe disease and beta thalassemia are expected to among the therapeutic areas driving interest in cell/gene therapy companies, along with Duchenne muscular dystrophy.

Roche's $4.3bn acquisition of Spark was just one of four noteworthy cell/

gene therapy M&A deals in 2019. Astellas Pharma Inc. bought Audentes and its rare neuromuscular disease candidate AT132 in December for $3bn. Below the billion-dollar threshold, 2019 also saw Biogen Inc.'s $867m acquisition of Nightstar Therapeutics PLC and Vertex Pharmaceuticals Inc.'s $245m purchase of gene-editing play Exonics.

Looking more broadly at the life sciences as a whole, KPMG anticipates deal-making to be driven by efforts to capture leadership positions in market segments, similar to PwC's expectations, but its survey of 66 companies indicates that uncertainty about the outcome of the 2020 US elections as well as pricing-related issues means volatility for how deal-making and other investment by the health care sector will proceed as the year goes on.

The uncertainty of the US political landscape was also discussed during the deals panel at the recent BIO CEO & Investor conference, where panelists agreed that the impact is not priced into current models. J.P. Morgan vice chair Philip Ross speculated that more uncertainty could come later in the year when the Democratic nominee is selected, and that uncertainty could also impact the financing and IPO environment. The consensus at the J.P. Morgan Healthcare Conference and Biotech Showcase meetings at the start of the year was that activity will slow in the second half due to the impending election.

In its report, KPMG notes that deal-making was robust in 2019, up 40% from 2018 as of the end of November. In its survey, 35% said overall health care investment is bolstered by strong underlying fundamentals, although only 28% say that of the life sciences sector.

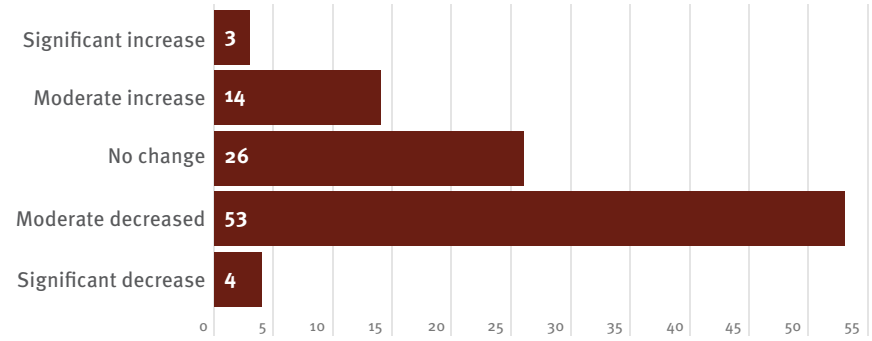
Innovation, particularly in the areas of rare diseases and cancer, is motivating deal-making, the KPMG report says, as 85% of its sample said a willingness to pay for innovation will drive transactions. It pointed to 58 deals last year in cell and gene therapy, including 17 full acquisitions, and predicted such deals will increase in 2020.

"In addition to small molecule drugs and antibodies, there are a number of new drug types for rare diseases," KPMG states, noting 34 of the 59 new molecular

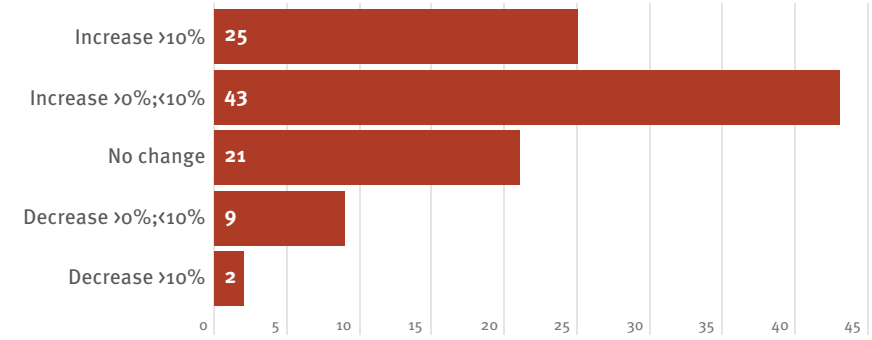
KPMG SURVEY FINDINGS

KPMG's 2020 "Opportunities And Challenges In An Evolving Market" report surveyed 66 respondents around the life sciences sector on how they assess the deal-making environment heading into 2020 and how various factors might affect the deal-making climate.

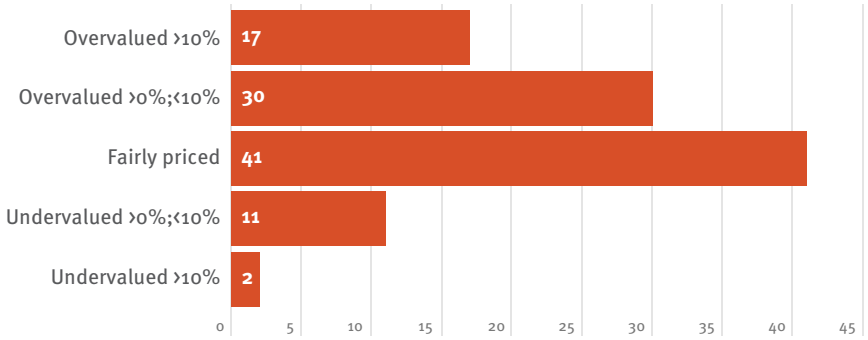
Effect Of Drug Pricing Controls On Deal-Making (%)



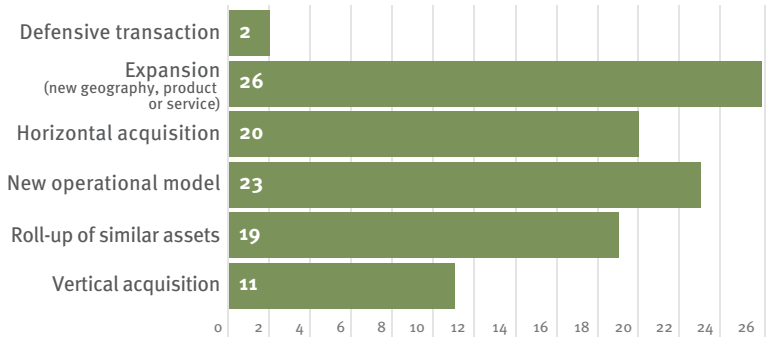
Deal Volume Expectations Compared To 2019 (%)



Asset Valuation (%)



What Will Be Primary Motivation For M&A?



SOURCE: KPMG

entities approved by the FDA in 2018 were to treat diseases with 200,000 patients or fewer in the US.

"Next-generation nucleic acid-based therapeutics target rare diseases at the genetic level and prevent the manifestation of disease-causing proteins," the report continues. "Viral vector-based therapies – modified viruses that can penetrate cells and tissues to cure disease – are emerging as treatments for cancer, infectious diseases and rare disease genetic disorders." KPMG estimates there are nearly 500 viral vector-based therapies in the global R&D pipeline.

Potential Impact Of External Factors On Deal-Making

KPMG queried its 66 respondents from the pharmaceutical and biotechnology product and services sector on how the possibility of drug pricing legislation or related policy changes could affect their investment activities, including deal-making, in 2020. Fifty-eight percent said that if drug pricing control legislation advances in the US, that could have a negative impact on investment. The respondents also are wary of the impact of the 2020 election, with nearly half saying it could cause decreased investment – 37% predicted some decrease, while 12% expect a significance decline in investment. *(Also see "US Drug Pricing Legislation Efforts Headed Toward Spring Renewal? A Look Ahead" - Pink Sheet, 2 Jan, 2020.)*

While the KPMG survey indicates apprehension about drug pricing legislation, however, it also shows a positive view toward other mechanisms to affect prices and patient access (*see Exhibit 1*). Fifty-six percent said "shift to value" mechanisms such as alternative payment mechanisms in which drug companies share risks with payers will increase investment. New ways to pay for innovation, such as the annuity model being used to spread out the cost of Novartis's gene therapy Zolgensma, are viewed positively, with 70% in the survey saying new payment methods might lead to increase investment.

"KPMG's survey found that expansion into new geographies or product/service areas is expected to be the main driver of M&A activity in 2020, followed by deals to shore up new operational models or deals to bolster existing business."

Early returns on Novartis's annuity model do not appear promising, however. At the J.P. Morgan Healthcare Conference in January, David Lennon, president of Novartis subsidiary AveXis, noted that no payer had signed on for the extended payment plan at that point.

KPMG's survey found that expansion into new geographies or product/service areas is expected to be the main driver of M&A activity in 2020, followed by deals to shore up new operational models or deals to bolster existing business.

The picture the survey paints is pretty good. More than half of the respondents said asset prices in their subsector are fair or undervalued, and 68% expected deal volume to rise in the coming year. But political risk remains the biggest concern: the only potential disruptor seen as having a negative impact is the US election, and 53% of the respondents cited ongoing efforts to control drug prices as a factor holding down deal-making.

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Comments:
Email the author: *Joseph.Haas@Informa.com*

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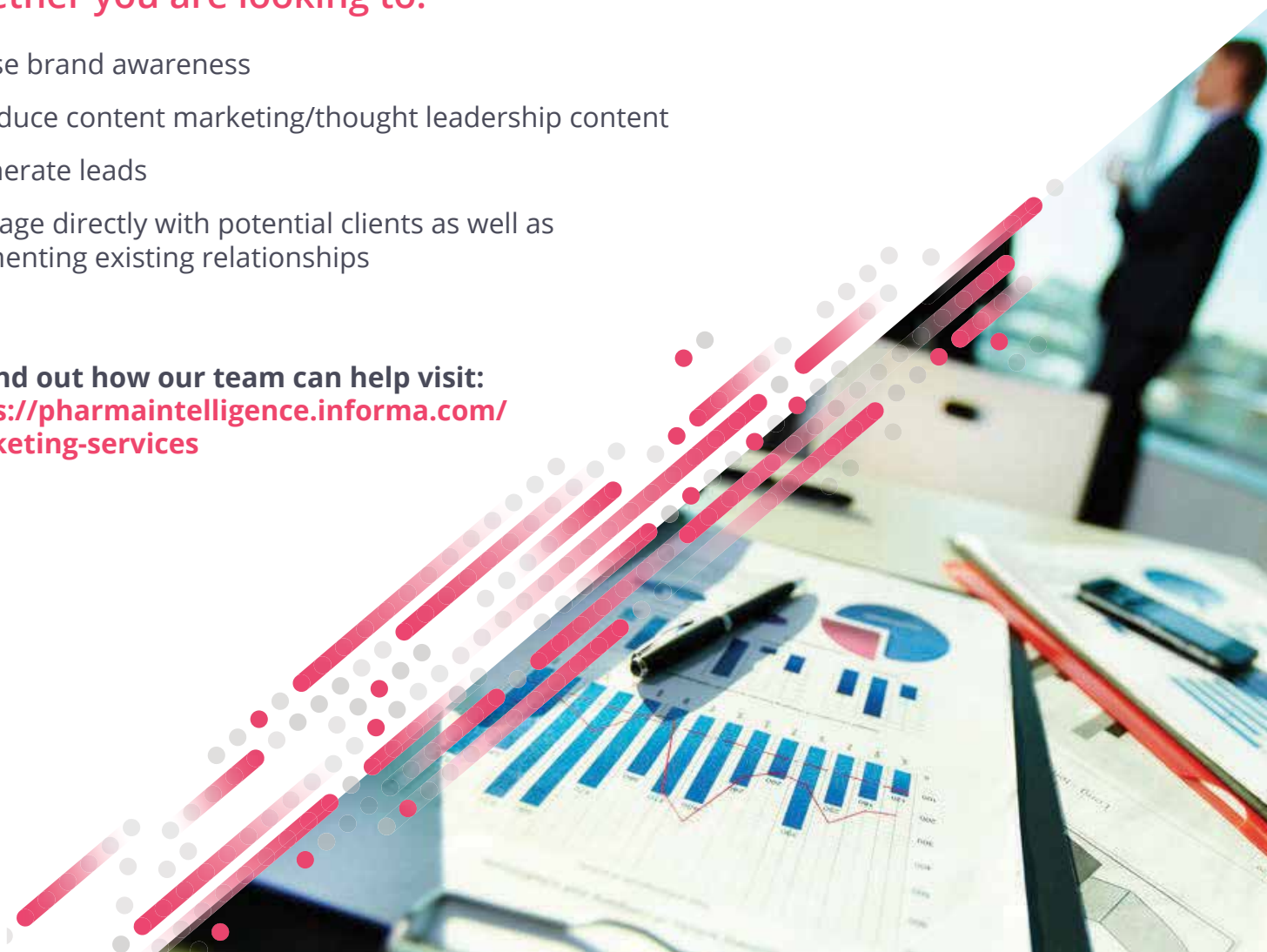

The Only Way Is Nasdaq

The US Nasdaq exchange has become the only option for ambitious UK and European biotechs.

BY MELANIE SENIOR

More capital, more expertise, more liquidity: those are the well-known advantages of the US Nasdaq exchange over its European counterparts.

Yet until recently, most European biotechs have sought a local listing before going to the US.

That is changing. Many of Europe's R&D focused players are now going direct-to-Nasdaq, viewing it as the only way to access the funding required to remain competitive.

Nasdaq punishes failure as fervently as it rewards success, however – and the 10-year bull market won't last.

So the ride will be bumpy. But Europe's biotechs need to be on board. Their own public markets, it seems, simply cannot compete.

Danish antibody company Genmab AS raised over half a billion dollars in its US Nasdaq IPO in July 2019 – the second-largest US biotech IPO ever. Genmab was one of a handful of European-headquartered biotechs to list in the US in 2019; its mighty haul pulled up the group's average IPO proceeds to almost $175m. That is not bad by US market biotech IPOs. By the standards of European IPOs, it is huge (*see Exhibit 1*). The average amount raised on London's Alternative Investment Market (AIM) is about £25m ($32.7m) – and there were not any biotech IPOs on AIM in 2019 at all. It was a dismal year for European listings.

Admittedly, 20-year old Genmab is not your standard biotech. It is profitable, with two approved drugs, Arzerra (ofatumumab) and Darzalex (daratumumab), marketed by big pharma partners. It has a $1.5bn cash pile, no debt. Genmab had listed on the Copenhagen Nasdaq Exchange in 2000, a year after its founding. Despite some set-backs along the way, at the time of its US IPO, it was already, at over $10bn, the largest European-headquartered biotech in market cap terms.

But Genmab's ambition went further. With over half-a-dozen proprietary clinical candidates, it wanted to be able to hang onto a greater share of those for itself. It was chasing the oft-cited dream of becoming the next Vertex Pharmaceuticals Inc./Gilead Sciences Inc./Amgen Inc. That meant accessing more money – much more than European investors could provide. "We needed a higher profile in the US, in order to get more analyst coverage and to gain the attention of large mutual and generalist funds that didn't know we existed," said CEO Jan van de Winkel during a *Yahoo Finance* interview in September 2019. It needed the firepower and financial flexibility to take the next step – from a $10bn company to a $40bn company. "Our US listing was long overdue," conceded van de Winkel.

Other European biotech veterans have taken a similar path. Germany's MorphoSys AG raised a cool $239m (gross) in its 2018 US listing, almost 20 years after the antibody company first listed in Frankfurt. Its shares have never been higher; the company's

Exhibit 1

European Pharma Nasdaq Appearances In 2019

COMPANY	US IPO SIZE	COUNTRY OF ORIGIN
Genmab AS	$582m	Denmark
BioNtech SE	$150m	Germany
Genfit SA	$135m	France
Innate Pharma	$68m*	France
Bicycle Therapeutics	$60m	UK
Centogene AG	$52m	Germany
Aprea Therapeutics Inc.	$98m	Sweden/US
Hookipa Pharma Inc.	$84m	Austria/US

*includes European private placement
SOURCE: Strategic Transactions

market cap is now over $4bn. In 2017, Belgium-based Ablynx NV (now part of Sanofi) raised $230m on Nasdaq – including $75m from a single investor, recalls then CEO Edwin Moses. Ablynx had for a decade prior been listed on the Brussels Euronext. "We wanted to give Europe a chance, to see if we could become properly valued," said Moses. But in the end, having watched compatriot Galapagos NV raise $275m in its US debut two years earlier, he realized that there was no choice but to do the same.

Not just for what is raised at IPO in the US, but, perhaps more importantly, for the funding that is accessible thereafter. Ten-year old Dutch antibody company Argenx SE (also listed in Brussels) pulled in over $100m in its 2017 US IPO – followed by a whopping $557m follow on public offering two years later. Cambridge, UK-headquartered GW Pharmaceuticals PLC has raised over $1.5bn since its 2013 Nasdaq IPO – though it was among the UK-based Nasdaq pioneers.

GW – which develops cannabinoid-based medicines – had spent 12 years languishing on AIM. When it turned to Nasdaq, "we felt we were blazing a trail," recalled CEO Justin Gover. (UK-rooted gene sequencing technology group Solexa had listed in 2006, a year before being acquired by Illumina Inc.) And although back then, there were "mixed feelings" about turning from the UK to the US, it turned out to be the right decision.

Local listings can provide an important steppingstone during companies' early growth. But it was Nasdaq that enabled GW Pharma's transformation from a development company to a $4.2bn market cap organization with two marketed products, including the first FDA-approved cannabinoid drug, Epidiolex, and a trans-Atlantic commercial infrastructure. Accessing the funds to become a fully integrated group that could exploit the full value of its pipeline "would have been challenging in London," said Gover. In 2016, the London listing was ditched.

A Nasdaq listing can turbo-charge stock-prices as new investors buy in, driving more activity and interest (*see Exhibit 2*). Trading volumes and liquidity tend to increase (there are sharper ups and faster downs); valuations tend to improve as the company is opened to a pool of capital up to 10 times larger than in the UK, and to an almost endless supply of specialist funds.

This opens up companies' strategic options. It puts them in a stronger negotiating position with potential product partners, for example, including enabling companies to retain a greater share of their pipeline assets, as Genmab is seeking to do. It reveals the potential buyer universe – Sanofi paid $4.8bn for Ablynx a year after US listing, beating suitor Novo Nordisk; UK-rooted gene-therapy firm Nightstar was acquired by Biogen for $877m in 2019, two years after its $76m Nasdaq IPO.

Not A Magic Solution

Of course, a Nasdaq listing itself is not a magic wand. The firms mentioned so far were well-established, waiting to break out. They had well-validated science, and most had partnered products on or near the market, and revenues. Some (like Ablynx), had spent years preparing the ground for their US debut; the doors were open.

They were also the survivors of a rough first couple of decades for the European biotech sector. "We were delusional, back then, thinking it was a good idea to take companies public on local listings," said one European-based VC. Many of Europe's locally listed biotechs floundered, hurt by a dearth of capital, of expertise and of liquidity. Yet the lack of private follow-on funding meant that "we had no choice" but to do a local IPO, the VC continued.

Times have changed. Private funding for European biotech reached a record of almost $3bn in 2019, according to *BioWorld*. And if the cohort of European biotechs survivors like Ablynx or Genmab came "late" to Nasdaq, some of their successors are trying to avoid making the same mistake. Young UK companies that have gone direct-to-Nasdaq, bypassing a local listing, include gene therapy players Orchard Therapeutics Ltd. and MeiraGTx Ltd. (which raised $186m and $80m, respectively, in 2018), chimeric antigen T-cell (CAR-T) company Autolus Therapeutics PLC (which raised $140m in 2018), and cancer-focused Bicycle Therapeutics.

These players are at a much earlier stage, some only in Phase I. They are working in hot but high-risk fields such as cell- or gene-therapy, developing entirely new drug modalities. They require investors with a sophisticated understanding of science, and an appetite for risk, both much harder to find in Europe. They also need to access funds quickly in order to have a chance of competing in fields marked by very rapid scientific and clinical advances. Going to the US "is about accessing capital at the same cost as competitors, but also about access to capital full stop," said Autolus CFO Andrew Oakley.

Broader biotech funding trends provide another Nasdaq tailwind. Crossover inves-

Exhibit 2

GW's Stock Price Progression Since 2013 Nasdaq Listing

SOURCE: Yahoo Finance

tors – who support companies through pre-IPO and post-IPO funding rounds – are more prevalent, and other private investors are also more likely to support the IPO rather than sell out. Since US investors win the numbers game – there are more, larger US crossover investors than European ones – the likelihood of Nasdaq success increases.

German cancer immunotherapy company BioNTech SE, for instance, raised a combined $600m in two private funding rounds in 2018 and 2019 – both led by US crossover investors. Fidelity Management led a $325m series B in July 2019 billed as one of the largest private biotech rounds ever in Europe; Redmile Group led the $270m series A in early 2018. So there was no surprise when the company listed on Nasdaq in October 2019 raising another $148m.

BioNTech was founded 10 years earlier, in 2008, with funding from the Struengmann family office (founders of generics giant Hexal AG, ultimately sold to Novartis). It has a full suite of technologies, from mRNA to cell therapies and antibodies, and a host of big-name partners. Most of its pipeline is still in Phase I or pre-clinical, however.

Yet BioNTech's American Depositary Shares (ADS) – dollar denominated shares of foreign companies – have more than doubled since the IPO. It has a market cap of close to $9bn. US specialist investors are better placed that some European investors to price risk, say CFOs – and therefore to drive valuations to match. Many European company investors and CFOs now say Nasdaq is the best – or even the only – way forward for ambitious R&D-focused European biotechs.

There remains some reluctance among European executives to acknowledge US dominance, but most no longer view going to Nasdaq as letting down the side. Europe's exchanges have tried – and, with one or two notable exceptions, failed – to compete with the fact that capital is global and Nasdaq is its hub. "It's perfectly legitimate to access funding in markets other than those in which you do R&D. There's no shame in it," said one UK-based private investor.

A Nasdaq listing does not need to involve moving the company wholesale to the US. In many cases R&D and most employees remain in the UK (or another European country), helping build the local talent ecosystem. This may be the best place for the science – in cases where a technology or asset emerged from local labs, for instance. But it can also bring significant tax and cost benefits to the company.

"Being UK domiciled but listed in the US is a very good outcome," said Autolus' Oakley. UK companies enjoy the generous R&D tax credit scheme, which can result in cash payments of up to a third of qualifying R&D spend. Office-space and company running costs are cheaper in the UK and most of Europe than in US hot-spots like Boston or San Francisco. PhD-qualified scientists may cost less, too, and are less likely to be poached by a nearby competitor.

Further, ex-US headquartered companies can take advantage of more relaxed reporting rules for foreign private issuers on Nasdaq.

MeiraGTx Ltd. has, like Autolus, structured itself to get the best of both worlds. "The majority of our employees and our infrastructure is in the UK," said CEO Alexandria Forbes. That is because MeiraGTx's ocular gene-therapy technology came out of University College London; the company also has ties to the nearby Moorfields Eye Hospital, through which it has established a gene therapy manufacturing facility. MeiraGTx remains UK-domiciled, but its headquarters are in New

FOREIGN PRIVATE ISSUERS

Non-US companies can list on Nasdaq as Foreign Private Issuers (FPI). This status comes with more relaxed, easier and cheaper reporting and disclosure requirements than for non-FPI. To meet FPI criteria, companies must have more than half their assets outside of the US, the majority of their directors must not be US citizens or resident, they must be principally administered outside the US, and/or no more than 50% of voting shares may be held by US residents.

It is the companies' responsibility to ensure they continue to meet FPI rules as they grow. Some Europe-headquartered biotechs choose to not take advantage of FPI even though they qualify, believing there is an advantage in having materials and accounts that look similar to those of any domestic (US) issuer.

York, where Forbes (who spent a decade as a buy-side investor in New York) and her management team are based.

Perhaps as a result of its CEO's own background, MeiraGTx's 2018 listing came fast, just three-and-a-half years after its foundation. Its most advanced program still in Phase I. "We wanted freedom to grow," said Forbes – and to capitalize on a reasonably healthy IPO window and enormous investor interest in gene therapy. There was no question where to list, since, by the time of the IPO, "our big investors were already mostly US," said Forbes. The company's programs "were further away [from the market] than the few investors in the UK would have been comfortable with." MeiraGTx raised $80m in February 2019 (led by JJDC) and almost as much again six months later.

Remaining European Union-domiciled can also open up funding opportunities that are not available to US companies. BioNTech pulled in €50m in December 2019 from the European Investment Bank – part of a scheme to boost the competitiveness of the European economy.

Some EU-rooted companies in the class of 2019 IPOs have become US incorporated ("Inc.'s"), however: Austrian-born infectious diseases vaccines company Hookipa Pharma Inc. and Swedish-born cancer-focused Aprea Therapeutics Inc., for example, which maintains research activities in Stockholm. As companies grow and expand their activities in the world's largest market, the benefits of a US listing multiply further, to include issuing stock options for US employees, and providing a currency for local acquisitions.

Dual Listing: Worth It?

Some ex-US companies maintain a dual listing after their US IPO. This allows them, in theory, to maintain stability among a local investor base as well as tap into deeper US pools. A loyal, local retail investor base can provide welcome support during a wider market downturn or after disappointing results, for instance.

But dual-listings can cause tensions. The US listing price itself can irk local shareholders if it's lower than the price at home: Germany's Biofrontera AG in 2018 had to fight off such a complaint from its local shareholder. On the other hand, some European CFOs suggest that local listings can be detrimental if they benchmark the company's valuation too low, with a knock-on effect on the Nasdaq price.

Dual listings can also be cumbersome. Reporting requirements differ slightly between US and European exchanges. Rules around what companies can or cannot do during closed periods either side of announcing results also vary – along with the length and timing of the closed period itself. "In the US, you can grant stock options during a closed period, but you can't even talk about them [during a closed period] in the UK," illustrated Piers Morgan, CFO at respiratory disease-focused Verona Pharma PLC.

Verona Pharma is, however, dual-listed on AIM and, since 2017, Nasdaq. Morgan does not want to de-list from the UK market at the moment, for fear of driving a large number of UK investors out of the stock, putting further downward pressure on a share price already well down on its 2018 highs. Respiratory-focused Verona is not working in a red-hot therapeutic area or with a new-fangled technology like gene therapy. It needs to convince backers on both sides of the pond that it can effectively compete in an area dominated by large players. The company's lead candidate, ensifentrine, a PDE3/4 inhibitor, has reported Phase IIb data as a maintenance therapy in chronic obstructive pulmonary disease (COPD).

Things may change if Verona's candidate progresses; GW Pharma found that almost all the trading activity in its shares moved to the US once it had its Nasdaq listing. When the company de-listed from AIM in 2016, it said that 94% of trading over the previous six months was on the US exchange. Anti-infectives focused Summit Therapeutics is following suit, with plans to de-list from AIM in February 2020, five years after its Nasdaq listing. Summit is majority funded by a single individual, reflecting the challenging nature of the anti-infectives market. But it wants to keep its US listing anyway, to keep open the option of future public offerings "without the costs of IPO," said CEO Glyn Edwards.

For Bicycle, whose lead candidate is

WHY CHI-MED IS STAYING ON AIM

When Hong-Kong-headquartered Chi-Med listed on AIM in 2006, it was all about increasing awareness of the group, said CEO Christian Hogg. The company (then worth less than $200m) did not raise much money there, either at IPO or afterwards. But "we built trust, and a strong reputation, among a small group of UK investors" who spread the word, he said.

Since 2016, Chi-Med – now worth $4bn- has been dual-listed on Nasdaq. That's where most of its freely floated shares are now traded. (The company's biggest shareholder remains Hutchison Healthcare Holdings Ltd.) Although Hogg acknowledges that the reasons to maintain a London listing are diminishing, one big benefit remains: a loyal and increasingly sophisticated base of (mostly institutional) shareholders, who hold about 15% of Chi-Med's shares.

only just in the clinic, the conversation about whether to dual-list was not a long one, according to CFO Lee Kalowski. Since many UK investors are now able to invest overseas, and more comfortable doing so, there appeared to be little benefit in a dual listing.

When Things Go Bad

Nasdaq offers biotechs a deep pool of long-term capital, but does not do so indiscriminately. Several companies – US and non-US – have tried and failed to list. French gene-therapy player GenSight attempted to join Nasdaq in 2015 but settled instead for a local Paris EuroNext listing the following year. Compatriot Poxel SA, which is developing drugs for metabolic diseases and NASH, announced plans for a US listing in 2016 which also came to nothing; it was a similar story for Copenhagen-listed Bavarian Nordic the same year. In 2019, Switzerland's ADC Therapeutics, whose lead antibody drug conjugate is in Phase II, pulled out of a planned $200m Nasdaq IPO. Many factors come into play in a decision to withdraw, to name a few: broader market conditions, driven by political and economic issues; investor appetite for a company's approach, team and therapy area focus; trial results; and how well the ground is prepared with US investors. Some Euro-centric boards and management teams are reported to have been reluctant to engage with American institutional investors.

Reverse mergers can provide a back-door onto Nasdaq. London-based, AIM-listed Mereo BioPharma Group reverse merged into struggling, Nasdaq-listed OncoMed in April 2019, having pulled an IPO attempt in 2018. Mereo identifies and develops clinical-stage rare disease assets; its lead compound is approaching a Phase III trial in brittle bone disease. (Reversing onto Nasdaq is not a new strategy: Germany's Micromet did the same in 2006, merging into CancerVax after the latter's lead drug failed. Micromet's CEO at the time: Christian Itin, who is currently running Autolus.) The trend continues: regenerative medicine company Histogen and rare diseases-focused Timber Pharmaceuticals both in late January 2020 announced plans to back onto US exchanges via struggling listed partners.

The last three years have been strong for both private and public biotech financing, with a record-breaking $76bn raised in 2018, according to Informa Pharma Intelligence's Strategic Transactions. Most of the single- or dual-listed UK and European biotechs have not yet experienced a significant market downturn.

When that time comes, will the non-US groups be at a disadvantage? Some talk of a 'European discount,' particularly for companies listed under the more relaxed foreign private issuer rules. But for the most part, investors and management point to the composition of institutional investors and the quality of individual companies as the key determinants of resilience during a downturn. If a European biotech "has a strong, highly educated institutional base with long-term funds, it will be treated exactly the same as the US companies those investors invest in," said Forbes. A predominance of shorter-term investors, like hedge funds, may lead to steeper price falls, but that is no different for US companies. "The market is sophisticated enough to judge the quality of the assets, and the company," said Syncona, UK-based investor whose portfolio includes Autolus (and did include Nightstar).

That means that even in a bull market, companies will be punished for poor results. Nasdaq "is a market that can bring significant reward, but also punish very harshly," said GW's Gover.

Nasdaq Will (Probably) Always Be The Way

Nasdaq's predominant position for biotech IPOs looks unlikely to fade. But that is not to say it is for all biotechs – or that the tides will not turn.

Lower-risk, revenue-generating services- or tools-based companies can do very well on local European exchanges. Examples include London Stock Exchange-listed protein research tools supplier Abcam PLC, or R&D technology and CRO firm Evotec, listed in Frankfurt. The local hero effect is still real for drug developers, too: Switzerland's Actelion became Europe's biotech success story with a single listing on the local exchange (confidential Nasdaq filings were prepared, but not used). Successor firm Idorsia, worth $3bn, is also doing just fine on the Swiss Exchange, where over half its shareholders are individuals based in Switzerland. The Belgian, Dutch, Danish, Swedish and French exchanges offer similar, mostly smaller, success stories – though they too are few in number. Meanwhile Asian exchanges – notably the Hong Kong stock exchange – have become more prominent listing venues, and Chinese investors are pouring money into innovation abroad, and at home.

And some investors remember 2009, when Nasdaq wasn't looking so good. That same year, Belgium-based Movetis, spun out of Johnson & Johnson (and now part of Shire Pharmaceuticals), raised $100m on Euronext Brussels. "I remember receiving calls from US investors asking how we managed it," recalled Antoine Papiernik, managing partner at VC Sofinnova Partners in Paris.

Markets are cyclical, and trends change. But right now, nowhere is close to rivalling Nasdaq for R&D-focused biotechs seeking access to public funds. January 2020 has already seen four biotech IPOs, according to Renaissance Capital. Among them: Cambridge, MA-based Black Diamond Therapeutics, which raised $201m and is still in preclinical.

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MANAGING DUAL LISTINGS

A German shareholder in dermatology player Biofrontera AG accused the company of setting too low a price for its January 2018 Nasdaq listing, and of refusing to allow existing shareholders to buy in at the lower price. The complaint was eventually dismissed by an independent legal expert who argued that "the purpose of the US placement is to attract US investors, not to broaden the circle of German investors."

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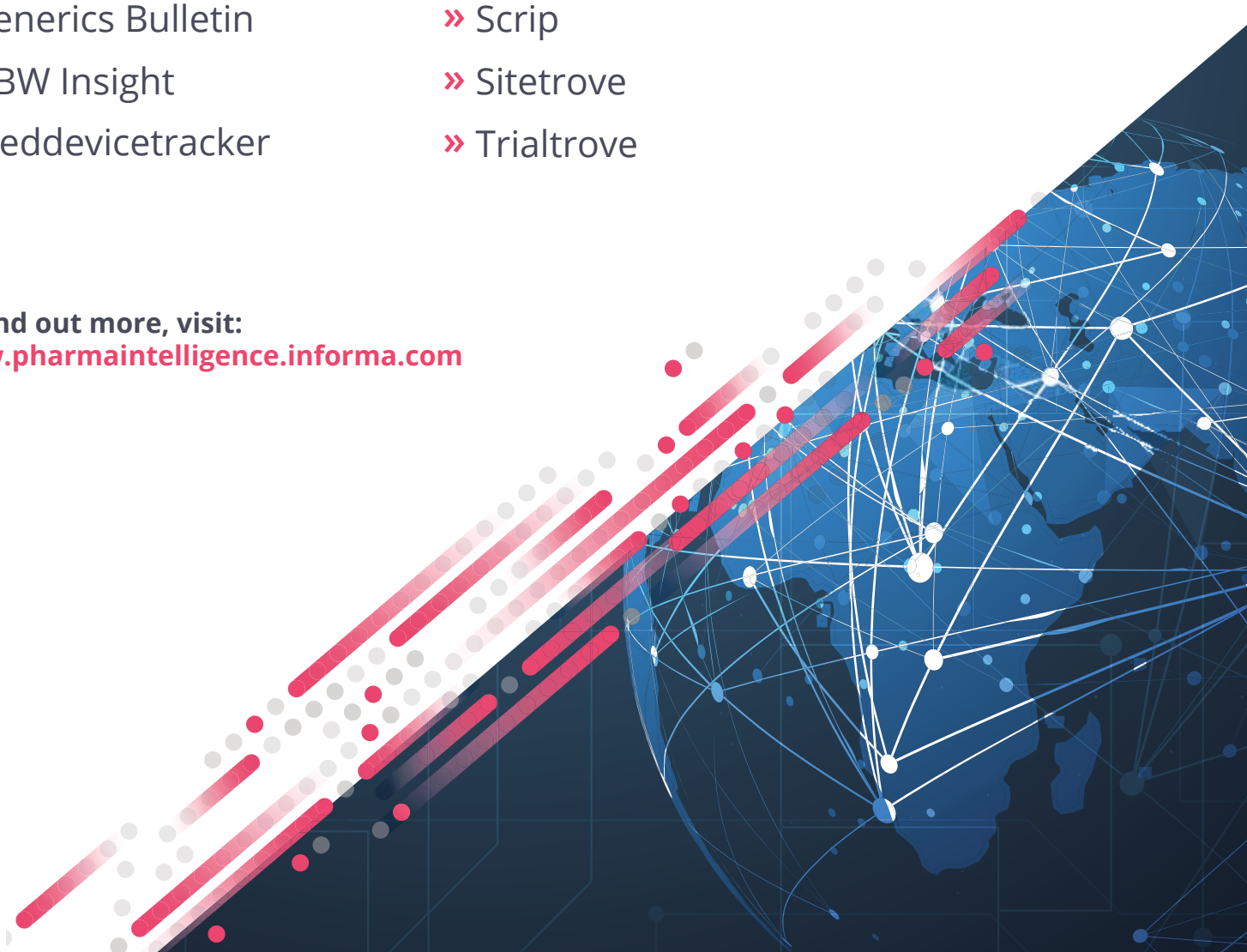

Investors And Deal-Makers See Medtech Continuing To Ride The Growth Wave Into 2020

The consensus among investors is that medtech has been the best-performing part of health care for the past three to four years, and investment levels remain good. Seemingly all-encompassing of late has been companies' preoccupation with digital strategies, but there is a lot more to this unique industry than just digital.

BY ASHLEY YEO

For investors, medtech may be behind biotech and pharma in terms of the weight of money invested, but combined with digital – now said to be truly coming of age – people are beginning to pay serious attention to medtech.

But there is also a lot more to medtech than just digital capabilities: how to bring devices to market in a complex health care landscape remains the province of the industry, which is acknowledged by the tech companies.

M&A deals remain notable in number – if smaller than in recent years – and the IPOs that are happening are mainly right-priced and are followed by a price uplift. This is contributing to the health of the innovative medtech sector, a stable and reliable industry for investors.

Pick your way through the complications and challenges faced by health care industries, and, as we move into the 2020s, investors will find medtech in a good place. Make that *continue* to find, because, many health care investors view medtech as the stand-out life sciences performer in the recent past.

This is seen in many aspects of performance, and not just in the pace of revenue growth. Levels of innovation, quality of management teams and capital deployment efficiencies, among others, have been appreciated and recognized in this sector.

It is a more predictable industry too, in the view of David Mardle, a partner in Goodwin's Technology and Life Sciences group. Mardle leads the law firm's newly opened Cambridge, UK office, where a team of life sciences and technology lawyers work on cross-border M&A, venture capital, intellectual property, licensing and regulations.

Medtech's relative stability is valued by investors and pension funds alike. The sector is in some ways seen as a safe haven – not as risky as biotech and pharma discovery, but offering more growth upside than other sectors, Mardle said in comments to *In Vivo*.

The composition of the top 25 global medtech companies has barely changed in the past year or two – in the most recent annual Medtech 100 ranking, the only change was the post-acquisition exit of St. Jude Medical Inc. But it is not a static industry: the big medtech M&A deals might have become rarer in 2019, but across the board deals have not significantly slowed (even if deal sizes have). Johnson & Johnson, with its milestone-enhanced $5.8bn purchase of surgical robotics company Auris Health Inc. a year ago; 3M Co., with two major deals in 2019; Stryker Corp. (regularly a key M&A player); and Boston Scientific Corp. (with 12 deals in the past 24 months), notably have continued

to fly the M&A flag in recent times.

Yet there are always new companies joining the industry and ready to address needs – societal as well as corporate. After shelter and food, health/health care are next on the list of priorities for the aspiring "middle class" globally, and medtech fits right in, addressing the needs of an aging population and unmet clinical needs with healthtech engineering.

The preoccupying theme at present for medtech corporates, the media, clinicians and caregivers alike, is the integration of digital solutions and strategies to cope with increased demand, more quickly, with fewer staff and at improved levels of quality. The digital revolution, the Internet of Medical Things (IoMT) and the power of artificial intelligence (AI) are transforming the industry. And where this is not quite happening in practice, it is transforming the way people perceive the medtech industry.

Digital Health Care Is "Finally Coming Of Age"

Add digital to medtech, and it becomes a life sciences investment proposition to rival biopharma for its size and potential, said Sophie McGrath, a fellow partner of Mardle's at Goodwin. McGrath's view is that "digital health care is finally coming of age." Medtech by itself still trails biotech and pharma, in the context of weight of money invested, but with digital, people are now paying serious attention to medtech, whereas it used to be fringe, and few knew how or even if it was regulated.

But there is now a constant sense that, with digital, health care is on the cusp of something transformative. The pool of investors in digital is broader, and tech investors in digital health are less risk averse on the technology. On the other hand, they are prone to underestimating the complexity of the health care regulatory landscape and how to sell into different jurisdictions.

However, it has not been all a digital show, said Jefferies Healthcare analyst Raj Denhoy at the investment house's 2019 conference in London. He added a counterbalance: the intricacies and methods of bringing medical devices to the market, the complexities of the health care landscape, and the structure of the sector, with its mix of hospitals, surgeons, payers and manufacturers, show there is a lot more to the medtech industry than just factoring in digital capabilities.

Current Trends In Medtech VC Investment

That was also clear at the 2020 LSX World Congress (4-5 February in London, UK), a forum for investors and life sciences innovators on leading industry themes, such as the medtech value proposition, M&A trends, commercial leadership and movements in the healthtech investment landscape.

Medtech has seen persistently strong investor interest and opportunity in the cardiovascular segment, said Swiss-based venture fund VI Partners' Arnd Kaltofen and Panakès Partners' Alessio Beverina, two participants on an LSX medtech investor panel.

There is a growing interest in robotics, which has become a major trend segment, with "four or five" major companies developing surgical robotics. But investors must proceed carefully here. Kaltofen said his firm had not yet found a robotics deal that it could be comfortable with. Electrophysiology and the convergence of tech and devices were other investment opportunities for his firm to consider.

Lightstone Ventures' Caroline Gaynor agreed that a glut of connected device technologies were coming to the fore, and the was a clear move towards more preventive medicine. She predicted that prevention is going to be "huge," and also highlighted a trend towards chronic care management packages. She added, The key was to cater for what insurance companies look for. "We are still seeing good deal flow," she said," but they are at later stage."

Looking at Europe specifically, Beverina observed that there has not been a "huge amount" invested in digital therapeutics, whereas there is a discernible trend towards that in the US. High-Tech Gründerfonds' Martin Pfister offered a similar view, saying his nine digital health portfolio companies find Europe hard to access because of the differing health care systems used around the continent.

Beverina was also somewhat downbeat on diagnostics, which in his view, did not seem to attract investors in large volumes. However, he noted great interest in the detection of sepsis, a huge burden for national health care systems.

Identifying the growth markets is seemly becoming clearer. OrbiMed Advisors' Anat Naschitz said the trick was gauging the number of people a company could access with its therapy. "The big medtechs are realizing that it's about 'touching' patients – companies that touch patients are more scalable, those that touch clinicians are less scalable."

"The IPOs that happened in 2019 were mostly around home care," she said. "Care is going into the home, and hopefully that's where this industry is going." Patient interaction with devices is a key factor, and devices offering this facility are setting the pace. Patients want smaller, easier-to-use devices that are less intrusive in their lives. But with cost of goods and cost-to-patient, a crucial ratio is at play: to drive and maintain patient adoption, prices must be appropriate and affordable to patients – manufacturers must broach that affordability challenge.

Management Skills A Vital Component

Companies wanting to attract investment need a very clear financing strategy and a very thoughtful management that either understands the needs immediately or has the ability to comprehend and adjust as the company progresses.

OrbiMed wants "the full package," which means looking for a team that can execute and has a clear understanding of regulatory and reimbursement pathways. Pfister noted that investors sometimes saw the need to bring more experienced executives into a company. Precommercial companies often needed to add management skills, he said, as they are "good at some things, but not always at ramping up sales."

Mardle noted the double benefit of this. "Talented, quality people not only bring themselves, but access to capital too," he said. They use their contacts to put together equity rounds that otherwise might not have been possible. "In such a capital-intense world, that can only be a good thing for early-stage and growth-stage companies," he added.

Goodwin itself has recently strengthened its life sciences team in Europe, with Mardle and McGrath joining the London office in 2019 and 2018, respectively. The

> *"It is certainly a very strong funding environment at the moment."*
>
> SOPHIE MCGRATH

expansion has given the firm what Mardle claims is the best and largest tech and life sciences team in Europe offering legal service to emerging growth companies and those that invest in them.

Silicon Valley Bank's (SVB) UK head of life sciences and health care Nooman Haque agreed that quality management was of "massive" importance from an investor's point of view. Speaking to *In Vivo*, Haque said investment was all about the people. "No credible investor would invest in great technology if the company had an inadequate team." This is because the path for innovation is so uncertain, and so much can go wrong along the way. There are no guarantees for anything, but management is a "must-have."

Haque was speaking after SVB had released its *2020 Healthcare Investments And Exits* report, which spoke of device investments in the US and Europe increasing for a second successive year, led by large, late-stage deals. While in 2019, medtech M&A had one of its weaker years for deal values, IPOs – eight in number – set new highs in pre-money values and proceeds, SVB reported. It predicts medtech IPO activity will be strong again in 2020.

Investment dollars in devices in 2019 increased by 15% and 43% compared with 2018 and 2017, respectively, according to SVB. In healthtech, devices with a software element and health care software jointly increased by 13% and 95% over the same periods. In many segments of medtech, it is increasingly rare that a standalone device does not have a digital component. There are exceptions, for example, there is yet to be a catheter that provides information on real-time blood flows. But it is probably only a matter time before this happens.

SVB's report valued VC deal activity in European medtech at $907m in 2019, up from $538m in 2018. This was skewed somewhat by two big "outliers," Babylon Health ($550m series C funding) and CMR Surgical Ltd. ($240m series C). "But strip those away and there is still a cascade effect," said Haque. The bigger trend is that technology investors, who never used to invest in health care, are now looking at driving health care investment returns in their portfolios, and through a channel that they understand – digital. That shows a convergence on the investor side, as well as on the technology side.

Haque said, "I still don't expect to see a healthtech investor invest purely in medtech, but if it's led by a digital component as a key part of the economic model, then that is something they'd be more attuned to getting into." Conversely, if the digital element was a bolt-on afterthought on a tangible medtech product, then it would be harder for a tech investor to address.

US medtech investments rose by $400m to $4.02bn in 2019. A significant amount of this was in "enabling technologies" – workflow and data management tools, security, etc. – as well as in the more front-facing technologies, and patient-doctor apps, etc.

As to which individual medtech segments are benefiting most, Haque said: "The increase is across the board." The US, in particular, realizes that there needs to be more investment in "efficiency" and in infrastructure components, where he said there has been "a bit of an uptick."

Goodwin's McGrath observed that a lot of investment is going into digital platforms, such as online treatment forums, professional telemedicine platforms and online interfaces for mental health users.

IPO Or M&A?

The received wisdom on product launches has for a long time been "Europe first, US later." But that might be changing. And most of the recent medtech IPOs have been in the US. IPOs are one route to liquidity, but the major option in Europe remains the M&A route.

Investors across the board are now seeing the M&A market as waiting a little longer before offers are being made for the younger companies, Naschitz said. She observed that, while private equity (PE) has always complained that the public corporates went in too early for M&A plays, leaving little, that is now changing too.

In addition, consolidation of the industry is narrowing the landscape of buyers in traditional medtech for exits of, say, between $300m and $500m, sometimes to just three to four companies per deal.

McGrath said Goodwin had seen a lot of activity in private investment across the whole sector – medtech, digital and biopharma. "It is certainly a very strong funding environment at the moment," she said. For her, how the exit market pans out this year is one of the big questions. Others are what will happen in the US IPO market, and whether M&A comes back to fill the breach potentially created by more challenging public markets?

There has been much talk of medtech companies' valuations being high, and a perceived wisdom that rounds are currently overvalued. But McGrath feels that the overvaluations are the outliers, and that a lot of "right-pricing" is being seen.

With low interest rates having been the norm for some time, medtech is being seen as a safe haven, with its growth upside, and biotech and discovery being seen as more risky. There is consequently pressure to invest in medtech and digital, from the pension funds' governance point of view. Many new funds have been set up, meaning there is a lot of money out there looking for good homes, according to Goodwin.

M&A Outlook: Bolt-Ons To Continue

There are still opportunities for larger mergers but medtech players are now being very thoughtful about where they want to succeed, what to divest and whether to acquire in more core areas. Whether mega or mid-cap, medtechs are regularly looking to see if they have non-core assets.

While mega-mergers are hard to predict, bolt-ons – adding adjacencies – will still be a factor in the next 12-24 months.

Bolt-ons are a way of addressing how a company can ensure sufficient product to distribute through often sophisticated sales and distribution channels. Stryker, for instance, is active in the M&A market not only to identify central acquisition targets but also to diversify into areas that are not so obvious.

But how do such groups find growth in a field where acquisitions are becoming more difficult? The chase for growth is the biggest and ultimate aim, and putting capital to work in ways that will leverage growth is, as most medtechs see it, the whole game.

M&A has always been a major component of the industry, and both the devices industry and the investment community have come to view the medtech sector as a growth engine. The accepted wisdom is that companies in this space should be able to grow in the mid-single digits, and much higher, currently, in the case of surgical robotics manufacturers.

Surgical robotics help to move people out of hospital much quicker, thereby transforming the delivery of health care at all levels, said Mardle. It continues to generate investor interest, even though the high upfront costs can be off-putting. Some technologies can be financed through opex (operating expenses) rather than capex (capital expenditure) in most countries. This offers greater budget flexibility, suggesting that these technologies could find it easier to get sales traction.

"There is huge potential in the displacement of humans as providers of care," said Mardle. The question with robotics is whether people are truly ready to accept the proposition of "taking the human out?" Robotics are a long-term proposition and the potential is still significant. A lot of capital going into robotics is actually "impact capital."

Impact capital is increasingly important for digital health propositions that focus on "mission-based" digital health wellness – rather than clinical care – enterprises which are socially- as well as commercially-driven, and address gaps in the market where pure private sector plays may not venture, due to lack of returns. Pure profit is not the sole aim of impact capital. "It's a sector that attracts people with social concern," said Haque, and capital seems to be responding.

Do Macro Factors Impinge On Investment?

The EU Medical Device Regulation (MDR) will come into effect on May 26 and has begun to cause mild-to-severe panic in some quarters, with observers fearing seriously negatives effects on innovation, company portfolios, companies' continued viability even, and the delivery of patient care. But Mardle believes that experienced investors will be more sanguine, taking the long view.

Haque added that it might happen that less experienced investors, who see in the MDR longer timescales and harder processes, back away. The fundamental question for him is: Does the landscape shift such that it does not make investor propositions feasible within the time frame of a fund? Many funds are 10-year vehicles, but if the MDR, say, doubles the regulatory timescale, then there might be huge implications for venture investors. The jury is still out on that.

Mardle's view is that the impact of MDR will be assimilated – albeit not without its chaotic moments – based on the significant weight of capital invested. As to Brexit's impact on the medtech industry, the UK is an established center of innovation and it seems probable that "it will retain that position," said Mardle, and will not be harmed irreparably.

> *"So long as interest rates remain low, we see no reason why the capital flows into innovative medtech won't continue very strongly."*
>
> DAVID MARDLE

Similarly, the US 2020 election is unlikely to have a material impact on early-stage investment. The market had managed an election every four years, said Mardle, who suspects that the outcome in late 2020 will drive any long-term trends. "We haven't seen any indications that people in this sector are changing their investment decisions over it." Investors fund great technology and great management teams, regardless of where they are physically located; and, because of the long lead times for commercialization, they are often not so focused on macro issues, especially in the earlier stages.

"So long as interest rates remain low, we see no reason why the capital flows into innovative medtech won't continue very strongly, with large amounts coming from the US and China," said Mardle. China is going through unusual times at present, with the Covid-19 virus disrupting normal business procedures, but in general, demand for improved patient outcomes in China is immense.

And the expectation of investment in healthtech is large. As such, the current coronavirus crisis is expected to drive those trends, not mitigate them. China has its own technology scene, with local rivals to the US-based global tech giants, but it's still an opportunity for investment.

The Long View Is A Priority

For the big corporates, the long view is the priority when balancing in-year operational issue with strategic growth initiatives. Back at the LSX World Congress,

Medtronic PLC's VP, strategy and business development, EMEA, Charity Kufass, said while there is so much uncertainty in the world, "we run the business in such a way as to focus on the long-term strategy and what we need to achieve."

J&J company group chair of medical devices, EMEA, Hani Abouhalka, agreed: "Industry factors are not impacted by events in a one- to two-year cycle. There will always be shocks along the way, and we manage for the long-term, as well as using commercial discipline."

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Biopharma M&A: Lessons From 2019, Trends For 2020

"Growth gaps" were the driver for a record-breaking M&A year – but CEOs must remain disciplined when pursuing opportunities, or pay the price down the line.

BY ANDREW MCCONAGHIE

2019 was a landmark year for biopharma M&A. Consultancy firm EY reported that the value of deals reached $357bn, even before December was added to the year's tally.

However, this new high was not due to a greater number of M&A deals, but rather a relatively small number of large deals. The year saw two mega-mergers: Bristol-Myers Squibb Co.'s acquisition of Celgene for $74bn, announced in January 2019, and AbbVie Inc.'s $63bn move for Allergan PLC, announced in June.

Alongside these were several other big-ticket purchases, including Eli Lilly & Co.'s $8bn acquisition of Loxo Oncology Inc., Roche's $4.3bn move on Spark Therapeutics and Pfizer Inc.'s buyout of Array BioPharma Inc. for $11.4bn.

What are the big driving forces behind biopharma M&A? EY unveiled its annual *Firepower* report on biopharma M&A trends in January 2020, based on industry metrics as well as a survey of dealmakers in the sector.

It identified four factors fueling last year's record-breaking activity: 1) readily available capital for deals, or "Firepower"; 2) slowing revenue growth at life sciences incumbents; 3) a recalibration of the US and European public markets; and 4) a desire to deepen therapy area focus.

The second of these factors is linked to what EY says are "growth gaps" – the difference between a company's revenue growth and the overall industry's sales expansion. Thirty-nine percent of the dealmakers who responded to the EY survey listed the need for revenue growth as one of the top two reasons for signing deals. (Access to new innovation or technology was the other top reason.)

EY found a number of companies falling into an "acute growth gap," where the difference in absolute dollars between their sales growth and the total industry's revenue growth exceeds 10% of the company's average annual revenue. Its analysis of the sector in 2017-2018 found that the majority of the sector's biggest companies – 18 of 23 (78%) – had acute growth gaps.

Of these 18 companies, nine signed deals in 2019, either through mega-mergers or bolt-on transactions, or a combination of the two. However, the research also concluded that these deals only reduced the growth gaps for five of the nine companies. A clear message that M&A – especially what EY calls the "traditional product focused M&A" – cannot help companies close this gap on its own.

Biotech Valuations Too High, Complains Pharma

While biopharma's 2019 started with a bang, with the BMS-Celgene and Lilly-Loxo deals both being announced in time for the J.P. Morgan Healthcare Conference in early January, the first two months of 2020 have been without any significant M&A deals.

A number of explanations have been proffered for this quiet spell, including concerns about the global economy and fears of a possibly pharma-unfriendly outcome to the US elections this coming November. Still, one of the more substantial reasons for the lack of deals so far in 2020 is that asking prices for mid-sized biotechs and their assets have become inflated, at least in the eyes of big pharma buyers. This view was confirmed in the EY survey, which found 69% of respondents saying that the "valuation gap" between buyers and sellers was the largest it has been since 2008.

That dynamic was revealed in a moment of humor during the J.P. Morgan meeting in San Francisco in January, at a satellite meeting held by venture capital firm Medicxi. Its partner Francesco De Rubertis was hosting a panel debate with a stellar line up of pharma execs – Giovanni Caforio, CEO of BMS, Jennifer Taubert, head of pharma at Johnson & Johnson and Novartis CEO Vas Narasimhan. Francesco made the audience laugh when he rather bluntly asked them to reveal what their next M&A targets were. But Novartis' CEO Vas Narasimhan shot back with his own zinger: "Francesco, can you tell me, don't you think biotech valuations have got completely out of hand?" Said in good humor, this theme is clearly near the top of minds in big pharma, who want to do the deals but often cannot justify paying multi-billion-dollar price tags on what could be risky or mediocre assets. And that is exactly what companies stand accused of when they unveil what is seen as a poor value deal. A recent example being Lilly's acquisition of Dermira and its atopic dermatitis drug candidate for $1.1bn.

M&A Is An Art, Not A Science

As much as investors, analysts and big pharma try to make the M&A process rational and numbers-driven, a good transaction remains as much an art as a science. That is because it involves a fine calibration of many factors: finance, opportunity, synergies between the two company portfolios, the potential to find hidden gems in pipelines and scientific platforms, cultural fit and, not least of all, timing.

"Gilead can bring new growth-driving products to market through both internal and external innovation, but the company has a high sense of urgency around business development. "We are going to take appropriate risks."

DANIEL O'DAY

Another factor watched closely is just how "leveraged" companies finances are in terms of balancing the spending of cash reserves against managing their debt. Opining on this subject recently was Roche's long-serving CEO, Severin Schwan, who said analysts were now concerned the company has not spent enough of its cash – whereas back when it acquired Genentech for $46.8bn in 2009, the worry was it was overstretching itself. Schwann said there was "no science" to deciding on how to strike this balance, but that that M&A was in any case more determined by market prices and opportunities.

"Late-stage assets remain very pricey, there is scarcity around those. And in most of those transactions we actually step out [of the bidding] for economic reasons," he commented at the company's 2019 Q4 earnings investor meeting.

"The focus continues to be on earlier stage deals, as typically that's where we can bring in our capabilities and assets, and be an interesting partner for those companies. It's not only about price, it's about bringing [that company] to the next inflection point and generating value for the partner rather than just the plain exit," Schwan said.

Nevertheless, he sees M&A as intrinsically opportunistic. "Then again, if there are opportunities we will seize them, and we will be very willing to take external innovation into the company. So that's opportunistic ... I don't see those dynamics changing."

Many M&A Deals Fail To Deliver Growth

One of the all-time most successful biopharma M&A deals was achieved by Gilead Sciences, when it purchased Pharmasset for $11bn in 2011. Many analysts at the time thought it had overpaid, but the deal brought with it the molecule which became Sovaldi (sofosbuvir), the beginning of a multi-billion-dollar hepatitis C franchise for the company.

Gilead has been under pressure for several years to replicate this success.

Exhibit 1
10 Major Biopharma M&A Deals In 2019

MERGER/ACQUISITION	DATE ANNOUNCED	THERAPY AREA/PLATFORM	VALUE
BMS + Celgene	January	Oncology/Hemato-oncology	$74bn
Eli Lilly + Loxo	January	Genetically defined oncology	$8bn
Roche + Spark Therapeutics	February	Gene therapy	$4.8bn
Merck & Co + Peloton Therapeutics	May	Small molecule oncology	$1.1bn
Pfizer + Array Biopharma	June	Small molecule oncology	$11.4bn
AbbVie + Allergan	June	Aesthetics, eyecare, neurology	$63bn
Mylan + Upjohn (Pfizer)	July	Generics	$12bn
Vertex + Semma Therapeutics	September	Stem cell therapy – type 1 diabetes	$950m
Novartis + The Medicines Company	November	RNAi	$9.7bn
Astellas + Audentes	December	Gene therapy	$3bn

SOURCE: In Vivo/Scrip

While the company has enormous M&A firepower thanks to its cash reserves, finding an opportunity as golden as Pharmasset has eluded it so far.

In 2017, under pressure from a hepatitis C franchise in freefall, the company bought cell therapy specialists Kite Pharma for $12bn. Nearly three years on, it is apparent that that acquisition is falling short of recouping this outlay. Kite's first product, chimeric antigen receptor T cell (CAR-T) therapy Yescarta is a groundbreaking innovation, and reached revenues of $456m last year. This is short of expectations, but worse still, Yescarta's growth looks to be stalling, putting its aspirations to reach blockbuster status in doubt.

Gilead has just taken a hefty $800m write-down on Kite Pharma, related to an abandoned program in indolent non-Hodgkin lymphoma. This adds to an $820m write-down last year related to Kite's abandoned multiple myeloma candidate KITE-585.

CEO Daniel O'Day has said Gilead can bring new growth-driving products to market through both internal and external innovation, but he acknowledged a "high" sense of urgency around business development. "We are going to take appropriate risks," he said on the company's 2019 Q4 results call.

Gilead will look to several key readouts from its existing pipeline to bring good news in 2020. Among these are the Phase III data for Yescarta in relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patients during the second half of 2020, while another CAR-T, KTE-X19, is under review in the US and EU for relapsed/refractory mantle cell lymphoma.

The company has set itself the target of launching "10 new transformative therapies" in 10 years, and aims to do so by expanding via internal and external innovation. On the 2019 Q4 results call with analysts, Gilead's leadership team pointed to 33 strategic partnerships and investment deals since January 2018, and said it would pursue more "transformative partnerships" such as that with Galapagos and small-to medium-sized bolt-on acquisitions. Analysts at Jefferies predict that the company is likely to make bolt-on acquisitions in 2020 in the gene-therapy and gene-editing space. The sell side analysts suggest Gilead should look out for some promising opportunities in a few "hot" therapy areas, such as CD20/CD-3 bi-specifics, other mid-stage oncology de-risked assets, as well as Phase I/II oncology assets in solid tumors and hematology.

More Regulatory Scrutiny

While M&A has become a way of life for the sector, it seems it may also have to accept increased scrutiny of its deal-making, with 2019 seeing an apparent sea change in market regulators' attitudes.

The Federal Trade Commission (FTC) approved Bristol-Myers Squibb's $74bn merger with Celgene in November, but only after a protracted review which concluded with it calling for the selling off of Celgene's psoriasis blockbuster Otezla, citing possible anti-trust concerns about the psoriasis market. This in turn created an opportunity for a competitor to buy up an established blockbuster, and in August Amgen snapped up Otezla for $13.4bn.

The need for this sell-off was the FTC's insistence that BMS's Phase III TYK-2 inhibitor BMS-986165 was an advanced late-stage candidate that could compete directly with Otezla (apremilast).

This kind of granular intervention from

regulators was virtually unheard of before last year, but now looks like a trend, as AbbVie also faced similar probes into its $63bn acquisition of Allergan. In September, the FTC filed a second request for information on the AbbVie-Allergan proposed deal, potentially prompted by calls from consumer groups to examine or even block the merger on anti-trust grounds. This prompted Allergan to volunteer the sell-off of two drugs, brazikumab and Zenpep (pancrelipase).

A third deal which was also much delayed in gaining anti-trust clearance was Roche's acquisition of gene therapy company Spark Therapeutics for $4.3bn.

The Federal Trade Commission (FTC) and the UK's Competition and Markets Authority (CMA) both probed the transaction, with final clearance given in December 2019 without either authority demanding the sale of any assets.

The authorities' original line of inquiry was not clear, but it transpired that one concern was that Roche might sabotage Spark's hemophilia program in order to maintain the market share of its new hemophilia biologic Hemlibra (emicizumab).

The FTC eventually concluded that Roche would have no incentive to delay or terminate Spark's hemophilia A gene therapy, and waved the deal through.

Given the disappointing performance seen in similar acquisitions of cutting-edge platforms, such as Gilead's acquisition of cell therapy company Kite, the onus is now on Roche to make the takeover work. Speaking at Roche's recent 2019 Q4 investor meeting in London, its pharma division head Bill Anderson said: "We expect big things from Spark in the future."

One company which does look to have cracked the commercial challenge of gene therapy is Roche's neighbor and rival, Novartis, which has seen its spinal muscular atrophy (SMA) gene therapy Zolgensma (onasemnogene abeparvovec; acquired with AveXis for $8.7bn) get off to a flying start following its US launch last year.

Roche will look to match this kind of success, though in the hemophilia gene therapy space it is trailing significantly behind BioMarin, which is set to gain the first approval later this year.

Anderson commented: "We have spent a considerable amount of time with the leadership at Spark already this year, helping to plan how we use their resources and the worldwide resources of Roche to help accelerate the programs they have ongoing, and additional investment for Spark in Philadelphia to expand into new disease areas."

Alternative Strategies: Gilead And Galapagos

Armed with plentiful cash, but with few sure-fire M&A opportunities that are worth the risk and major undertaking of an outright acquisition, companies are looking at alternative deal-making strategies. One very notable example of this was the deal struck between Gilead and Belgium/Netherlands-based biotech Galapagos in July 2019.

The deal is a novel approach to big pharma-biotech tie-ups – de-risking the expenditure for Gilead and allowing Galapagos to retain its independence. It comprised a $3.95bn upfront payment, a $1.1bn equity investment stake in Galapagos (22% of the company) plus opt-in payments covering six molecules currently in clinical trials, and more than 20 preclinical programs. Importantly for Galapagos, the agreement also includes a "standstill" guarantee that Gilead will not move to acquire it over a 10-year period. For Gilead, the deal looks like a wiser bet than an all-out acquisition, allowing it to keep its options open on Galapagos's promising but still risky antibody pipeline.

Speaking at the Jefferies Healthcare Conference in London in November, Galapagos CEO Onno van de Stolpe said: "I hope this model is followed more in the industry, rather than the outright acquisitions that we've seen in the past, where innovation is sort of secondary. Nothing good comes out of these big pharma acquisitions."

Key to the success of the partnership is the approval of JAK1 inhibitor filgotinib in rheumatoid arthritis, for which Gilead submitted its data to the FDA in December. Also expected this year is Phase III data with the compound in ulcerative colitis.

A deal of similar proportions and significance for the future direction of the sector was that struck between US big biotech Amgen and China's BeiGene. The companies signed a very substantial $2.7bn equity and co-development and co-marketing deal which should help Amgen break into the increasingly important China market, and help fuel BeiGene's aspiration to be a fully-fledged global pharma company. In return, Amgen gains a 20.5% stake in BeiGene.

BeiGene will commercialize three Amgen products in China including Xgeva/Prolia (denosumab) and two others – Kyprolis (carfilzomib) and Blincyto (blinatumomab) – which are in Phase III development in China.

More unusually, the deal also sees BeiGene take over development for the Chinese market, taking on 20 Amgen preclinical molecules. Altogether, BeiGene will set aside $1.2bn for the development costs of the candidates, which might also include Amgen's KRAS mutation-targeting drug AMG510.

Opportunism Versus Franchise Building

As Roche's Schwan pointed out, many M&A deals are driven by timing and opportunity, but EY says that a planned strategy to build expertise in key areas is becoming more common – and with good reason.

EY's analysis suggests that companies which pursue this strategy see stronger returns on their investments. It says that in 2019, almost every major biopharma acquisition increased both the buyer's overall therapeutic focus and its projected five-year compound annual growth rate. It found that 20 of the 25 deals it analyzed had high overlap in terms of the therapy area or indication of the buyer's existing portfolio and the target company's lead product. Such deals accounted for nearly 45% of last year's M&A total, with two notable exceptions: AbbVie's acquisition of Allergan, and Vertex's acquisition of Semma Therapeutics.

AbbVie's CEO Richard Gonzalez rationalized its move for Allergan and its blockbuster Botox franchise as a deliberate diversification beyond its dependence on Humira. However, there was more than a touch of opportunism in the move as well.

Allergan's stock had lost more than half its value from its peak in 2015, the year when Pfizer had been ready to pay triple that price, only for the deal to fall through.

All the same, while Gonzalez saw the Allergan acquisition as something of a bargain, many investors were far from convinced, judging Allergan's declining valuation very warranted.

When the deal was announced in June last year, AbbVie saw its share price plummet 16%. Like several other peers who splashed out in 2019, AbbVie will be under scrutiny to wring as much value from this deal as possible, once it gains anti-trust clearance, which is expected in early 2020.

The other exception to the rule identified by EY is Vertex's acquisition of Semma Therapeutics. Vertex gained US approval for its triple therapy for cystic fibrosis, Trikafta (elexacaftor/tezacaftor/ivacaftor) in October. This is a blockbuster in the making, but one that the company will most likely find difficult to surpass in terms of treating CF. This therefore requires the company to broaden its horizons into other disease areas. Semma is pursuing the ambitious goal of finding a cure for type 1 diabetes.

The company is focused on transforming undifferentiated pluripotent stem cells into insulin-producing pancreatic beta cells that could be transplanted into patients. This is a move into cutting edge, disruptive innovation, a high stakes bet increasingly seen across the industry. In terms of timing, then, Vertex hopes to avoid the kind of problem now plaguing Gilead, which is still looking for its next big product long after its flagship hepatitis C franchise has already declined. But as Gilead has seen, these big bets don't always pay off.

"AbbVie's CEO Richard Gonzalez rationalized its bid for Allergan as a deliberate diversification beyond Humira. However, there was more than a touch of opportunism in the move as well."

Big Pharma Is Streamlining

The flipside of concentrating on key areas of expertise and high growth, innovative therapy areas, is the disposal of non-core assets and divisions. A prime example of that is Pfizer, which has been in the process of disposing its non-pharma divisions for a number of years. This process continued in 2019, with the spin-off of its generics portfolio, Upjohn, into a merger with Mylan, with Pfizer receiving a $12bn payment.

Another downsizer is GlaxoSmithKline, which recently provided more detail on the planned spinout of its consumer health division joint venture with Pfizer. This process will give a slimmed down prescription medicines and vaccines focused GSK more flexibility to invest more into innovative medicines.

The company is still integrating its $5bn buyout, oncology-focused Tesaro but it seems highly likely that the company is clearing the decks, and setting aside capital, to make another strategic acquisition to bolster its pipeline.

While this process of divestment and acquisition, diversification and specialization is cyclical in the sector, this latest round of changes is being driven, at least in part, by an acceleration in science – such as genomics, big data analytics and artificial intelligence, as well as new platforms such as cell and gene therapy. This gathering pace in innovation, along with the ever-present need for revenue growth, will help transform the sector over the coming decade, with M&A an integral part of the process.

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2019 Global Biopharma R&D Productivity And Growth Ranking

An analysis of the R&D productivity of the world's 30 largest public pharmaceutical companies reveals an overall drop in R&D productivity, but this should not hide the fact that some companies are still performing extremely well.

BY MARKUS THUNECKE AND ERIKA KUCHEN

The top companies in Catenion's annual survey have traditionally been emerging and mid-size players rather than big pharma. The same is true in 2019 as 6/10 qualify as mid-sized in the R&D ranking and 7/10 in the company ranking (that includes historical and forecast growth in sales, profit and market cap). Emerging mid-size pharma company Alexion Pharmaceuticals Inc. (a first-time entrant) and Regeneron Pharmaceuticals Inc. top the company performance ranking, but only Regeneron is in the top 10 in the R&D ranking (#8, Alexion #13). Both companies are now enjoying the fruits of their strong R&D from previous years, at the same time both are struggling to replenish their pipelines with high value assets (*see Exhibit 1*).

Alexion is feeling the heat as activist investor Elliott Management has a different view of the outlook than management, and the board and is pushing for a sale now. The journey from one-product success to becoming a sustainable biopharma is not an easy road, and only few companies, such as Regeneron, have succeeded without being acquired along the way. Alexion has been able to establish an industry leading complement factor franchise with Soliris (eculizumab) and Ultomiris (ravulizumab) that are expected to combine for more than $5bn in sales by 2021. It also successfully launched Strensiq (asfotase alfa) for hypophosphatasia that is expected to achieve blockbuster sales by 2024. The issue is that there is only one higher value asset, an SOD-1 inhibitor for amyotrophic lateral sclerosis (ALS) and Wilson's disease, in its pipeline.

Another company that is struggling to maintain its strong performance is Gilead Sciences Inc. It is still high in the ranking (R&D productivity #3), but mostly based on HIV and hepatitis C marketed products reflected in a strong long-term NPV, while the pipeline position (#16) is already pointing towards future troubles. In line with this, Gilead is also not present in the company top 10 ranking anymore (#12). After the rapid decline of its sofosbuvir hep C franchise, Gilead is highly dependent on the performance of HIV combo pill Biktary that is responsible for a massive $54bn in value or ca. 65% of its market cap and is forecast to peak at $11bn in sales. Gilead's diversification strategy into oncology, culminating in the acquisition of Kite Pharma for $11.9bn in 2017, will have to accelerate if this area is to become a serious second pillar next to its virology stronghold. CD-19 CAR-T therapy Yescarta (axicabtagene ciloleucel) is forecast to achieve blockbuster sales, but there is still a long way to go to expand patient populations and clear supply chain and reimbursement hurdles; third quarter sales in 2019 came in at only $118m.

Oncology Is Leading The Way

In the 2019 R&D productivity ranking, oncology makes up 46% of the value across the top 30 pharma companies, dwarfing all other areas (the next in line is systemic anti-infectives with 11% and endocrine with 9%). Oncology has also seen the biggest absolute increase in value from 2018 to 2019 (followed by CNS). This value distribution is a result of the industry's increasing focus on high-unmet need specialty indications such as oncology and rare diseases.

The dominance of oncology has reached a point where it could be questioned whether industry is over-spending on oncology at the expense of other areas of unmet need. On the other hand, the increasing scientific understanding of oncogenic pathways, the explosion of immuno-oncology as well as the ability to stratify patient populations make oncology fertile hunting grounds for countless biotechs and pharma companies. The analyst consensus forecast for oncology of more than $240bn by 2024 reflects this increasing translation of scientific advances into clinical benefits.

ABOUT THE AUTHORS:
Markus Thunecke, PhD (markus.thunecke@catenion.com), is a founding senior partner of Catenion, a biopharma focused strategy consulting firm. Erika Kuchen, PhD, is an analyst at Catenion (erika.kuchen@catenion.com).

Where Are Novartis And Roche?

Novartis AG and Roche are frequently cited as examples of outstanding R&D productivity, so why are these two companies only in the mid-field in the R&D ranking (#15 and #14)? Both had considerable success with new product launches and lifecycle extensions, but what is often overlooked is that R&D productivity is based on both value created by the pipeline and products launched in recent years, as well as the sum of R&D costs, plus adjusted costs of M&A over a 10-year period.

Both Novartis and Roche have spent considerable amounts on R&D and bolt-on acquisitions making them top spend-

Exhibit 1

R&D Productivity And Corporate Growth Ranking

R&D PRODUCTIVITY				COMPANY PERFORMANCE			
Final NPV Rank	Company	Momentum (Pipeline NPV)	Long-Term (All NPV)	Final Corp. Growth Rank	Company	Past Performance	Forecast Performance
1	AstraZeneca	12	3	1	Alexion Pharmaceuticals	1	1
1	Biogen	3	6	2	Regeneron Pharmaceuticals	4	5
3	Gilead Sciences	16	2	3	Novo Nordisk	5	6
3	Eli Lilly	1	7	4	Johnson & Johnson	11	9
3	Novo Nordisk	19	1	5	Amgen	7	14
6	Amgen	6	9	5	Bristol-Myers Squibb	9	12
7	Merck & Co	23	5	5	Allergan	2	19
7	Regeneron Pharmaceuticals	26	4	8	Merck & Co	14	8
9	GlaxoSmithKline	7	12	9	Eli Lilly	14	10
10	Astellas Pharma	5	15	9	Eisai	23	1

TOP 5

SOURCE: Catenion

ers over the 10-year period included in this analysis: in 2018 Roche spent $9.8bn on pharma R&D (#1) and Novartis $8.2bn (#3). To create value through such enormous R&D spending, the portfolio value *increase* has to match at least the $8bn-$10bn p.a. plus a large sum (more than $1bn) that is typically spent on bolt-on acquisitions. It is tremendously difficult to implement a scalable model of superior R&D productivity.

Productivity Champions

There are four large pharma companies that have high positions in the 2019 R&D ranking, the most notable one is back-to-back winner AstraZeneca PLC, sharing the #1 spot with Biogen Inc. The only reason why AstraZeneca does not have a top spot in our Corporate performance ranking is its poor past performance (#26), while the forecast performance reflects its strong R&D productivity (#4) spot.

AZ's impressive turnaround story that started with the arrival of Pascal Soriot from Roche continues: its two biggest products both in terms of value and potential are EGFR inhibitor Tagrisso with $40.4bn in value and $8bn in forecast peak sales, followed by PD-L1 inhibitor Imfinzi (durvalumab) with $24bn in value and $5bn in forecast peak sales. The AstraZeneca case exemplifies that a complete turnaround is possible even for big pharma companies that many people had already written off. The mixture of strong leadership who realize the solution is not another round of mega mergers but a focus on R&D rejuvenation could be a template for other large organizations who find themselves in a similar position.

Biogen's top position may seem unexpected when considering the initial difficulties with its Alzheimer's antibody aducanumab that had been discontinued after an interim futility analysis in Phase III in March of 2019. Since then, the events took an unexpected turn upon re-analyzing the data and finding a positive signal in one of the two Phase III studies in October 2019. Consultations with the FDA led to the decision to file for approval. It was one of the most unusual biopharma stories of 2019, especially as this is not only about aducanumab but also about the validity of the beta-amyloid hypothesis, that was largely dismissed after the nth Phase III

Exhibit 2
Method Used To Calculate R&D Productivity

R&D PRODUCTIVITY RANKING

MOMENTUM RANKING	LONG-TERM RANKING
Dec 2019 pipeline eNPV (analyst consensus)	Dec 2019 pipeline + marketed eNPV (analyst consensus)*
Sum of 2009-2018 R&D expenditures (WACC 7%)	Sum of 2003-2012 R&D expenditures (WACC 7%)

Primary deal driver	Commercial	Hybrid	Pipeline
Rationale for M&A (value drivers)	Marketed products and >€1bn pharma sales pa	Marketed products and <€1bn pharma sales pa	No marketed products
% M&A costs incl. premium allocated to R&D costs	25%	50%	80%

Ranked independently and then combined – Momentum ranking 1/4 + Long-term ranking 3/4

CORPORATE GROWTH RANKING

Calculate historical and forecast CAGRs for:
- Pharmaceutical Sales
- EBITDA
- Market Cap (historical only)

Rank companies independently for historical and forecast data

Calculate overall ranking – the three metrics are weighted equally

SOURCE: Catenion

failure in a row.

Beta-amyloid has now staged a comeback, and many stock analysts have re-entered aducanumab into their Biogen valuation models as the lone high value asset in the pipeline ($2.2bn peak sales to Biogen, $4.4bn NPV). Due to the uncertainty of the drug reaching the market and the high pipeline value concentration, Biogen's current position as a top company is definitely at risk as recently launched spinal muscular atrophy blockbuster Spinraza (nusinersen) may not be sufficient to compensate a declining portfolio of multiple sclerosis blockbusters. Biogen's difficulties are typical symptoms shared by many of the mid-sized outperformers of the last years that face huge challenges. Simply put, it is difficult to maintain the creative culture and performance focus that made these companies great as they go through periods of hyper-growth.

Novo Nordisk Sits Pretty In Top 5

Novo Nordisk AS is the only company that has defended a top five position in the ranking since its inception in 2014. In this year's survey, Novo Nordisk is the only company to be in the top five in both the R&D Productivity and Company Performance rankings. Novo Nordisk is a prime example of the power of highly focused R&D in the endocrinology space as 80% of sales stem from internal R&D and 86% fall into the endocrinology area, mostly peptides and proteins. Its largest product is Ozempic (semaglutide), the leading GLP-1 agonist in an ever growing diabetes market ($25.9bn in value and $7.4bn in peak sales), the oral version of which has just been approved in the US (Rybelsus) and is forecast to be another mega-blockbuster ($14.5bn in value and $5.6bn in peak sales).

The main strategic question for Novo Nordisk is whether they can keep up that kind of outperformance. The mid-term outlook appears very strong as loss of exclusivity of semaglutide is not before 2031, this should give Novo Nordisk enough runway to diversify into other areas such as obesity, NASH and diabetic complications. Interestingly, Novo Nordisk has unsuccessfully tried several times already to diversify into areas such as inflammation, oncology or neuroscience. Perhaps its lack of traction in these areas is unsurprising given the enormous success of its core franchises (Clayton Christensen's innovators dilemma comes to mind). One of the key drivers of Novo Nordisk's long-term success is its unique model and set-up as a public company that is fully controlled by a foundation. The Novo Foundation protects Novo Nordisk from being acquired while ensuring that its unique mixture of altruistic and business motives embedded in the "Novo Nordisk Way" are kept alive.

Lilly Enters Top 10

Lilly Research Laboratories's #3 spot in R&D Productivity comes as a real surprise (last year #10) as its R&D organization has kept a very low profile over the last few years. A closer look reveals that its strong performance is fueled by a successfully growing diabetes franchise, with GLP-1 agonist Trulicity (dulaglutide) leading the way; this asset has seen a massive increase in value from 2018 to 2019, representing $23bn in value and $6.7bn in projected peak sales. Strengthening the GLP-1 franchise is tirzepatide that was not included in most analyst models last year but is expected to become a large product with $8.9bn in value.

Lilly's second largest product Taltz (ixekizumab), a psoriasis antibody, has also increased since last year to $2.5bn in peak sales and $8.2bn in value. As Lilly is new to the top five, it will be interesting to see how sustainable this much-improved performance is, in 2019 it has already translated into a top 10 spot in the Corporate Performance ranking (#9).

The most exciting move the company has done in a long time was the acquisition of Loxo Oncology for $8bn, even though the lead product Vitrakvi (larotrectinib) was already licensed to Bayer. Lilly will get royalties and an interesting pipeline of targeted therapies in oncology such as a next generation BTK inhibitor. The acquisition is a first step towards an increasing focus on oncology, a theme seen with the other major turnaround story in this year's ranking, AstraZeneca.

What Really Matters?

In spite of industry-wide problems with R&D productivity, Catenion's annual survey has demonstrated over the years that it is possible to outperform and to create substantial value for patients and shareholders. So what are the common denominators among the top ranked companies? Catenion has identified a few elements that contribute to sustainable R&D outperformance that translate into superior growth and profitability:

- A science-driven innovation culture and model: a prime example is Regeneron whose model resembles the Genentech of the 90s with its focus on people and culture as competitive advantages.
- Establishing a clear competitive advantage: building disease area strongholds and industry leading R&D capabilities. Examples are Novo Nordisk in endocrinology and proteins or Gilead in virology.
- Focus on high unmet need specialty indications: the market growth of oncology as well as the rich scientific and drug target landscape make it the industry's most popular area. The role of oncology in AstraZeneca's turnaround story is an illustration of this approach. Smaller bolt-on acquisitions: instead of major M&A, smaller bolt-on acquisitions complemented by licensing has been the strategy of choice for most top 10 companies, the notable exceptions being Novo Nordisk and Regeneron that have completely relied on internal R&D strength.
- Strong presence in US market: the US is responsible for a disproportionate part of the global biopharma profit pool. In addition, hotbeds such as Boston ensure the US keeps a leading position in the global biopharma innovation system in terms of talent and output.
- Effective portfolio decision-making: the much-cited truth seeking versus progression seeking behaviour is at the root of effective portfolio governance that was a main factor in the turnaround of AstraZeneca. This is one of the most underutilized and cost-effective levers that exists.

The examples of R&D productivity champions create hope for those companies that find themselves at the bottom of the ranking. The AstraZeneca case study demonstrates that R&D productivity is not just based on luck but on strong leadership. This emphasizes the importance of people, culture and model as the foundations of competitive strategy.

Methodology:

R&D Productivity Ranking

In order to evaluate the R&D productivity of the world's 30 largest public pharmaceutical companies, as judged by total pharmaceutical sales, the Catenion methodology takes an approach that focuses on value. It compared the total R&D spending from 2009-2018 including costs from M&A (*see Exhibit 2*) and a 7% cost of capital with the total net present value (eNPV) today of compounds marketed in the last five years and all pipeline products.

Using this data, two distinct rankings were calculated – a "Momentum" and a "Long-Term" ranking. The Momentum ranking aims to capture the value a company is forecasted to generate by taking the current eNPV of its entire pipeline and dividing by the firm's R&D and M&A costs, both adjusted for cost of capital, as described above. By contrast, the Long-Term ranking focuses on the value a company has already generated in the recent past, specifically the eNPV of products marketed in the last five years are added to the pipeline eNPV whilst those marketed six to eight years ago are also added but with the contribution tailing off by 33% per year. This is then divided by the total costs as per the Momentum rank.

The overall R&D Productivity rank was then generated by weighting the momentum rank ¼ vs. ¾ for the long-term rank.

To fairly allocate M&A costs to the R&D costs, each deal was defined by its primary driver. If the acquired firm had pharma sales >€1 bn then was said to be commercial and thus 25% of the deal total deal value was added to the R&D costs for that year. By contrast a deal involving a firm with no marketed products is, by definition, a pipeline driven deal, thus 80% of the deal costs were taken. In addition, if the total cumulative sales of the target company up until the deal date were <20% of the deal value then these were also considered to be a pipeline driven deal (e.g. AbbVie Inc.'s acquisition of Pharmacyclics). Finally, if a firm had pharma sales <€1bn then it is considered a hybrid of the two deals and thus 50% of the M&A cost were used.

Corporate Growth Ranking

To evaluate the corporate performance of each firm, the historical and forecasted CAGR for pharmaceutical sales, EBITDA and market cap (historical only) was calculated. Each company was ranked independently on each of the five metrics before they were combined with equal weighting to generate the overall corporate growth ranking.

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Investing In People: Aligning VCs And Today's Entrepreneurs

In the latest instalment of our VC playbook series, *In Vivo* sits down with Roel Bulthuis, managing partner at INKEF Capital, to discuss the group's approach to health care investing in Europe, the importance of funding a team not just a project and how life sciences venture capital is evolving with the emergence of health tech.

BY LUCIE ELLIS

Roel Bulthuis, who previously established Merck Serono's corporate venture fund M Ventures, talks to *In Vivo* about what he seeks in a new investment opportunity for INKEF Capital and why VC funds need to keep up to date with the interests of emerging entrepreneurs.

Bulthuis joined INKEF in 2019, and his focus on building teams and fostering talent aligns with the firm's goal of backing "mission-driven entrepreneurs who are ready to take the next step to grow their business."

INKEF is focused on early-stage investments, where it is unlikely there will be a fully built team. He seeks individuals who are committed to the work, know their value and understand the need to expand on that.

Founded in 2010 by ABP/APG, INKEF Capital currently invests out of a €500m ($549m) fund. Co-managing partner Roel Bulthuis, who has more than 15 years' experience across venture capital, pharma business development and investment banking, joined the company in January 2019. Prior to joining INKEF he was a senior vice president and managing director of M-Ventures, which he created and developed into a leading corporate VC fund.

In an exclusive interview with *In Vivo*, Bulthuis discusses INKEF's strategy, his valuation methodology and red flag warnings that make him avoid a project.

***In Vivo*: What is INKEF Capital and what is your investment motto?**

Roel Bulthuis: INKEF is an Amsterdam based European VC focused on health care and tech. I am one of two managing partners and I run the health care side of the firm. My colleague Robert Jan Galema runs tech investments. Across the board, we want to be an investor that helps entrepreneurs build companies. That could sound simplistic, but a lot of the venture community has a shorter-term vision and are focused on a relatively quicker investment cycle. However, INKEF runs a long-term fund, we have a 20-year fund cycle and we commit significant amounts to our portfolio companies.

We start our investments early; we prefer to get in at the seed or series A round and from there we want to stick with our companies long term. We typically reserve €15m to €30m over the life cycle of a company, but we can go beyond that. It is great when there is an early interest from potential buyers, and that may make sense in some cases, but we want to be in the position to support our companies and enable them to grow into European leaders.

How is INKEF's approach different from that of its peers?

The way we see our firm, we are a bit of a different animal in terms of our heritage. We inherited a commitment to impact investing from the pension fund that started INKEF and we still have that fund as our LP. That pension fund came into this wanting to create a strong environment for entrepreneurs. We don't think we should be bound by the conventions that exist in the venture community. We have a different take on fund cycle, management and on how we incentivize our investors.

The performance for European VC funds has not been overwhelming to suggest the current short-term model is working. Fund managers, and we are seeing this in the corporate VC space, are starting to look at our type of model.

How did you personally enter the VC field?

I originally wanted to become a scientist but failed miserably. I did a master's degree in pharmaceutical sciences and started research in molecular biology – but it wasn't for me. Then I got a job as a junior business developer in a biotech company and did that for just under a year before being recruited to join a bank, where I was a health care investment banker for five years. I did a lot in capital markets but also M&A work in the health care sector in Europe and the US.

I quit banking just before the financial crisis and did my MBA before joining Serono, that was about 12 years ago now. I worked on M&A for Serono and then the company was acquired by Merck KGaA. For the next two years I ran part of their business development group, the structured deals group. Part of my mandate in BD was to find solutions for deprioritized assets.

I had a whole portfolio of molecules that were deprioritized for strategic reasons – these were good pharma grade assets that were looking for a new environment. Rather than out-licensing those programs, I found a way to finance them externally, in some cases by merging them with existing venture-backed businesses and in some cases creating new vehicles.

Before this, the corporate board of Merck looked at the venture community as a bit of a strange animal – there was not the perception that these were funds that could add value to asset development. We showed them with those projects that bringing in VCs helped raise the development quality of those assets. I used those experiences to make a proposal to the board of Merck to start a corporate venture fund.

"I would invest in a great team with a science project that needs work, but I would never invest in an absolutely fantastic science project with a mediocre team around it."

ROEL BULTHUIS

My entry into venture was through convincing the corporate board of a very conservative German company that they should do venture capital – which they did, reluctantly. For the last 10 years my work in venture capital has been building up a corporate venture fund, initially in therapeutics but also in other sectors in life sciences technologies, in new materials, etc. INKEF was the transition from running a corporate venture fund that became a quite large organization – when I left we were 35 people with four funds, invested in more than 60 companies – to a group where I would have my hands free. Somewhere I could play a significant role in defining where we go with our investments, with our strategy and with our vision of how we want to work with entrepreneurs.

What are some of the skills from your BD or CVC roles that you still find yourself going back to?

For me, the most important theme when we invest in companies is "How can I help you translate this unique science into a drug that is going to have an impact for a patient in such a way that a physician will prescribe it and an insurance company will pay for it?" It may sound trivial, but the emphasis has to be on making something commercially relevant and doing it in such a way that you can resource it in a biotech environment.

In a pharma setting you often have a big portfolio of assets going into clinical trials, whereas in a biotech setting you often have one or two shots on goal. We're less focused on later stage development, a partner could do that, but the earlier-stage clinical development, the Phase I/II trials – I can only finance those if I get relevant data along the way.

To give you an example, if I'm going to invest in cell therapy, I find that hard as a VC as I will not see relevant data preclinically because animal models do not tell

me anything. I will have to make a huge investment in manufacturing, and then do a Phase I trial – the only thing I will know is that I am not killing any patients. Then immediately I need to move to a combined Phase II/III study. So, the first time that I see any validation for my hypothesis, I've burned through $60m, $70m, $80m.

Do you have a tick list of "must-haves" to help evaluate an asset at the early stages?

The important thing for us is that, although we spend a lot of time with people to develop their hypothesis, neither me nor my team (who are very smart) are smart enough to be able to immediately see the opportunity from a given piece of science.

So, ticking the box: I need a vision on what you are going to make and what your product is going to be. I don't want a data download, I don't want the elevator pitch that gives me so much information that I can't handle it all. I want to get a vision of what your product is. Another important point, we invest early stage, where it is unlikely there will be a fully built team. But I want to see an individual, or a group of individuals, who are totally committed to the work, who know what their value is and who understand that there is a need to expand on that.

I want to see commitment, but I also want to see a realistic view. I want to be a value-added investor working with entrepreneurs who want to get value out of me beyond the cash. If you're looking for cash only, and you don't consider the investor a relevant part of the equation to develop a company and develop a product, then I'm not the right investor. I would invest in a great team with a science project that needs work, but I would never invest in a fantastic science project with a mediocre team around it.

What excites you when seeking new investment opportunities?

We invest in teams and we invest in science. The assumption is often – when working with an academic with a great piece of science – that they are going to be fundamental for the future of the company but probably in a CSO-style position. At some point, a new CEO needs to be brought in.

> *"When you have that founder who steps up to the role of CEO, it leads to a very different dynamic and culture within the team."*

Sometimes though, with first-time entrepreneurs, people step up and surprise you. VCs then must change their mind-set – which we don't do enough as a community – and realize this is someone who is going to take the role of a CEO and do it well. The impact of that is tremendous because when you have that founder who steps up to the role of CEO, it leads to a very different dynamic and culture within the team – you can build a stronger and more committed organization. You build an expectation with the people on that team that if the CEO and founder can grow and get the support of the board, then there are other opportunities. I love those situations.

Can you highlight an INKEF investment that stands out to you as a success story?

Before my time, INKEF made a number of really smart investments. One example: the firm was convinced by an entrepreneur to invest in the field of hearing loss many years ago, before everyone else started to jump into that field. This was working with a serial entrepreneur, who had set up a virtual company with very few resources, and we invested and were the largest shareholder in that company. It was a field that not many people were getting into at the time.

The preclinical models had relatively little validation. With herd mentality, VCs tend to run after the same thing, and this was contrary to anything that was happening in the market. It takes time to develop an asset, but we're close to seeing Phase II clinical data on that program. This puts us on par with some significantly funded companies in the US right now, some of which have listed on Nasdaq with impressive valuations. I think the good thing for us is that we're getting to a market environment where this is actually a hot topic, there are a lot of investors that are looking at this right now, there are a lot of pharma companies that are looking at opportunities in hearing loss too.

How much of that is luck and how much of it is skill, to get ahead of the game at the right time?

There is always a factor of luck. In this instance, the bet was on us knowing this entrepreneur; we like what he does, we like his way of looking at a company. The

science was solid, the translation of the plan to something that could move on was solid. There is a skill in selecting an opportunity, and there's a skill in making decisions.

One of the hard things to do in a venture environment is to make that judgement call. What I tell my team is we are in the business of making decisions on the basis of too little information. Many of the projects that come to us have many years of work behind them, very committed entrepreneurs behind them. If we were to spend enough time with every opportunity to fully understand them, then this would be a different issue. But if I get 2,000 to 3,000 business plans per year, I'm not going to be able to do that. That's an important skill in VC, to make quick decisions while accepting that we will be wrong from time to time. We often tell entrepreneurs that we hope that they prove us wrong when we pass on an opportunity. We have to make a judgement call, we have to focus our attention on the 30 to 40 companies that we can spend enough time with on an annual basis, which then leads us on to the five to eight investments that we make a year.

What are the red flags that could put you off an asset or opportunity?

I don't like to get invited to a C or a D financing round because that often means there is a problem to be solved with the investors rather than an opportunity to be developed in the company. There are some investors that do that very well, but it's not our cup of tea. We like to be with the company early on and have an impact.

Another concern is when a company claims something is "new" and "unique" without being able to explain why that is relevant in a commercial setting. We're not investing in academic projects; we're investing in companies. It needs to have an application. It is interesting that we see some tech investors coming into the health care sectors. In tech you sometimes hear the argument that "Well you may not believe this now, but if you took that position when looking at Google early on you would have been wrong." That's not a real argument. Yes, Google was very successful, but there were 30 other companies at that time that were trying to do something that we didn't understand yet. In tech, there is a lot of focus on product marketing, that is a softer approach. When we develop drugs, devices and technology for a health care setting, I need to understand the application.

Assessing the current European environment, how do you think it has changed in the last few years for health care investing?

The environment has changed tremendously, mostly in a positive way. One very important point, across Europe, but especially in a few locations such as the UK, Benelux and the Nordics, there has been the emergence of some really strong seed-stage, early-stage investors. Investors that are fully focused on company creation. They add tremendous value to the sector.

With some larger VCs, it is nice to see that they have stuck to mantras of making early-stage investments in a balanced way. These are the firms that have – to a large extent – survived the crisis and are the ones that are now accelerating their growth and raising bigger funds.

There is one other change I find to be very important at the level of entrepreneurship. In many European countries we still have a challenge. Our industry is fully focused on science and for new ideas we rely heavily on the academic community. I still feel that in many European countries the older generation of academics – and many of those in senior positions in academia today – frown upon the opportunity to become an entrepreneur.

Not everyone needs to be an entrepreneur, but they don't always see it – social status wise – on a similar level to academic positions. This holds a lot of people back from taking that step. We could significantly increase the creativity and drive if there was more cross-movement between people who are academics and who are entrepreneurs.

In the US, I invested in a professor who then started a company and did that for five years before going back into academia. In Europe that reverse move would be unthinkable, though the interesting thing is that he felt that with his startup experience, he became a much more creative and productive scientist. The output of that is significant. The younger generation, the post-docs who come out of university right now, have a different view on life. They realize that not everyone is going to be a Nobel Prize winner, that a career in academia is only for a few and that becoming an entrepreneur is actually a very positive aspiration. This generation does not feel bad saying that they want to make a living out of science, they don't feel bad saying that they want to be millionaires, they want to be an Elon Musk.

I think this change drives a different sort of entrepreneur in health care.

Where would you like to see INKEF in five years' time?

I joined INKEF because I wanted to help build a leading European venture platform. I want us to be one of the leaders in creating new health care and tech companies in Europe and to be part of creating a stronger sector in Europe, without preconceptions about how we *should* do venture. We're not stuck with the conventional model, we do what's best for the venture firm, and that's always in the context of what's best for our portfolio companies.

IV124444

Additional reporting by William Masters

Comments:
Email the author: *Lucie.Ellis@Informa.com*

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On the Move

Recent executive appointments in the life sciences industry

RAMZI BENAMAR

JENNIFER CHIEN

PETER GARCIA

BERTIL LINDMARK

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Sandra E. Poole	Advantagene Inc	Chief Operating Officer	LogicBio Therapeutics	Chief Operating Officer	10-Jan-20
Andreas Harstick	Affimed Therapeutics AG	Chief Medical Officer	Molecular Partners AG	Chief Medical Officer	1-Mar-20
Pascal Juery	Agfa-Gevaert NV	Chief Executive Officer	Carbios	Director	1-Feb-20
Peter S. Garcia	ALX Oncology	Chief Financial Officer	PDL BioPharma	Chief Financial Officer and Vice President	7-Jan-20
Peter N. Laivins	Alzheon Inc	Head, Commercial Strategy and Planning	Tesaro Inc	Senior Vice President, Strategic Development Program	7-Jan-20
John Chin	Antengene Corp	Chief Business Officer	Celgene China	General Manager	6-Jan-20
Steve Hughes	Arcturus Therapeutics Ltd	Chief Development Officer	Organovo	Chief Medical Officer	8-Jan-20
Ivor Macleod	Athersys Inc	Chief Financial Officer	Eisai Inc	Chief Financial Officer and Chief Compliance Officer	31-Jan-20
Erick J. Lucera	Aveo Oncology	Chief Financial Officer	Valeritas Inc	Chief Financial Officer and Executive Vice President	6-Jan-20
Ed Vertatschitsch	Bardy Diagnostics Inc	Chief Operating Officer	Varian Medical Systems	Vice President, Global Portfolio Solutions	2-Jan-20
M. B. Chinappa	Biocon Biologics India Ltd	Chief Financial Officer	Syngene International Ltd	President (Finance) and Chief Financial Officer	6-Jan-20
Robert Green	Cambrex Corp	Chief Financial Officer and Executive Vice President	General Electric Corp	Chief Financial Officer, GE Power	6-Jan-20
Tom Wilton	Carisma Therapeutics Inc	Chief Business Officer	LogicBio Therapeutics	Chief Business Officer	6-Jan-20

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Take an interactive look at recent executive-level company changes and promotions in the biopharma, medical device and diagnostics industries.
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DAVID MOFFAT

PAULA BROWN STAFFORD

LAURENCE TURKA

TOM WILTON

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Ramzi Benamar	DBV Technologies	Chief Financial Officer and Member of Executive Committee	Spark Therapeutics	Vice President and Head, Financial Planning and Analysis	6-Jan-20
Scott Holmes	Disarm Therapeutics	Chief Financial Officer	Kiadis Pharma	Chief Financial Officer	13-Jan-20
Michelle Robertson	Editas Medicine Inc	Chief Financial Officer	Momenta Pharmaceuticals Inc	Chief Financial Officer	9-Jan-20
David Meek	FerGene	Chief Executive Officer and President	Ipsen Group	Chief Executive Officer	14-Jan-20
Enrique Conterno	FibroGen Inc	Chief Executive Officer and Director	Eli Lilly & Co	President, Lilly USA	6-Jan-20
Ritesh Khullar	Foundation Medicine Inc	Chief Commercial Officer	Flatiron Health	Vice President, Provider Solutions	13-Jan-20
Bertil Lindmark	Galecto Inc	Chief Medical Officer	eTheRNA	Chief Medical Officer	3-Feb-20
Michael Cooke	IFM Therapeutics llc	Chief Scientific Officer	Magenta Therapeutics	Chief Scientific Officer	7-Jan-20
Onaiza Cadoret-Manier	Ionis Pharmaceuticals Inc	Chief Corporate Development and Commercial Officer	Grail Biosciences	Chief Commercial Officer	9-Jan-20
Jorgen B. Hansen	Ivenix Inc	Chief Executive Officer	Cantel Medical Corp	Chief Executive Officer and President	13-Jan-20
Jennifer Chien	Krystal Biotech Inc	Chief Commercial Officer	Sanofi Genzyme	Vice President and Head, Genetic Diseases, US Rare Disease	20-Jan-20
Istvan Molnar	Lantheus Medical Imaging	Chief Medical Officer	Fusion Pharmaceuticals	Chief Medical Officer	13-Jan-20

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Venkat Reddy	Macrophage Pharma	Chief Scientific Officer	Glenmark Pharmaceuticals Ltd	Senior Vice President and Global Head, Translational Sciences	9-Jan-20
Diane M. Bryant	Neural Analytics	Chairman and Chief Executive Officer	Google Cloud	Chief Operating Officer	9-Jan-20
Andrew Macan	Neuronetics Inc	Chief Compliance Officer and Senior Vice President, General Counsel and Corporate Secretary	US Silica Holdings Inc	Senior Vice President, General Cousel and Corporate Secretary	21-Jan-20
Han Myint	NexImmune Inc	Chief Medical Officer	Celgene	Vice President, Global Medical Affairs	8-Jan-20
John Trainer	NexImmune Inc	Chief Financial Officer	MedImmune	Vice President and Head, Partnering and Strategy	8-Jan-20
Matthew K. Harbaugh	NuVasive Inc	Chief Financial Officer and Executive Vice President	Mallinckrodt plc	President, Specialty Generics	2-Jan-20
Helge Lubenow	ProteoMediX AG	Chief Executive Officer	Epigenomics AG	Director	1-Jan-20
Jason Hoitt	Provention Bio Inc	Chief Commercial Officer	Dova Pharmaceuticals	Chief Commercial Officer	8-Jan-20
Peter Buhler	Quotient Ltd	Chief Financial Officer	Zaluvida AG	Group Chief Financial Officer	5-Feb-20
Maged Shenouda	Relmada Therapeutics Inc	Chief Financial Officer	AzurRx Biopharma	Executive Vice President, Corporate Development	10-Jan-20
Steve Arkinstall	Revitope Oncology Inc	Chief Executive Officer	Elstar Therapeutics	Chief Executive Officer	8-Jan-20
Laurence Turka	Rubius Therapeutics Inc	Chief Scientific Officer	Rheos Medicines	Co-founder and Chief Scientific Officer	21-Jan-20
Gaurav Agarwal	Vyaire Medical	Chief Executive Officer	KCI	President and Chief Operating Officer	21-Jan-20
Keri P. Mattox	Zimmer Biomet Holdings Inc	Chief Communications Officer and Senior Vice President, Investor Relations	W2O Group	Global Lead, Integrated Corporate Communications	8-Jan-20

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
Jennifer Buell	Agenus Inc	Chief Operating Officer and President	Chief Operating Officer	9-Jan-20
Shawn P. Cavanagh	Cambrex Corp	Chief Operating Officer, President and Director	Chief Operating Officer and Executive Vice President	6-Jan-20
Stephan Haitz	Cambrex Corp	President, CDMO Sales and Marketing	Vice President, Sales and Business Development	6-Jan-20
Darin Johnson	Exactech Inc	Chief Executive Officer and President	Senior Vice President, Extremities	6-Jan-20
David Hale	Guerbet	Chief Executive Officer	Chief Commercial Officer	1-Jan-20

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
David Moffat	Macrophage Pharma	Chief Technology Officer	Director, Chemistry	9-Jan-20
Thomas Hoover	Millendo Therapeutics Inc	Chief Commercial Officer	Senior Vice President, Commercial Strategy	9-Jan-20
Paula Brown Stafford	Novan	Chief Executive Officer	President and Chief Operating Officer	2-Feb-20
Marsha Smith	Siemens	Chief Financial Officer, Siemens Mobility North America and Siemens USA	Chief Financial Officer, Siemens Mobility North America	1-Jan-20
Patrick Weiss	Twist Bioscience	Chief Operating Officer	Senior Vice President, Research and Development and General Manager, Data Storage	13-Jan-20

DIRECTORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Vincent Milano	Aclaris Therapeutics Inc	Director	7-Jan-20
George Golumbeski	Aura Biosciences Inc	Chairman	7-Jan-20
Jean-Luc Boulnois	BioDirection Inc	Director	7-Jan-20
Jeryl Hilleman	Cardiva Medical Inc	Director	10-Jan-20
Heinz Jacqui	Distalmotion SA	Director	14-Jan-20
Reinhard Mayer	Distalmotion SA	Director	14-Jan-20
Daniel Alberttis	Exactus Inc	Director	16-Jan-20
James A. Schoeneck	FibroGen Inc	Chairman	6-Jan-20
Scott Biller	Foghorn Therapeutics	Director	9-Jan-20
Yunshu Zhou	Jiangsu Hengrui Medicine Co Ltd	Chairman	17-Jan-20
Elizabeth O'Farrell	PDL BioPharma Inc	Chairman	1-Jan-20
Gayle Crowell	Pliant Therapeutics	Director	8-Jan-20
Russell H. Ellison	Rockwell Medical	Director	9-Jan-20
James P. Panek	Sutro Biopharma Inc	Director	8-Jan-20

ADVISORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Christian Grimm	Casma Therapeutics Inc	Scientific Advisory Board Member	13-Jan-20
Martin Kampmann	Casma Therapeutics Inc	Scientific Advisory Board Member	13-Jan-20
Yves Henrotin	GeneQuine Biotherapeutics GmbH	Advisory Board Member	13-Jan-20
James P. Allison	Lava Therapeutics BV	Advisory Board Member	8-Jan-20
Padmanee Sharma	Lava Therapeutics BV	Advisory Board Member	8-Jan-20

Deal-Making

Covering deals made February 2020

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.

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MEDICAL DEVICES

MERGERS & ACQUISITIONS

Anika pays up to $100m for **Arthrosurface**

Anika buys **Parcus Medical** for up to $95m

RTI Surgical sells OEM biz to Montagu for $490m

ALLIANCES

Bayer receives US license to **Dare**'s vaginal contraceptive ring *Ovaprene*

Sebacia acquires **Sienna**'s SNA001 laser light hair removal device

FINANCINGS

SeaSpine Holdings nets $79.9m via FOPO

SI-Bone nets $50.3m via FOPO

PHARMACEUTICALS

MERGERS & ACQUISITIONS

Lilly buys **Dermira** for $1.1bn

Neuraxpharm buys Austrian OTC/generics firm **easypharm**

ALLIANCES

Almirall gains worldwide license to **23andMe**'s bispecific mAb

Allergan divests two exocrine pancreatic insufficiency products to **Nestle**

Almirall collaborates with, gains option to acquire **Bioniz** outright

Almirall uses **WuXi**'s *WuXiBody* to discover multiple bispecific antibodies for skin diseases

Amunix licenses *XTEN* technology **Roche**

Ocuphire gets rights to **Apexian**'s APX3330 for ophthalmic indications

Apollomics, **GlycoMimetics** co-develop blood cancer therapies

Ionis uses **Aro**'s *Centyrin* platform to develop antisense oligonucleotides in $1.4bn collaboration

AZ sells hypertension products to **Atnahs Pharma**

Kyorin Pharma gets Japanese rights to **aTyr**'s ATYR1923

Axsome gets exclusive US rights to reboxetine and esreboxetine from **Pfizer**

Bayer partners with **Evotec** for the third time, in polycystic ovary syndrome

BeiGene gets Chinese license to two **EUSA** drugs

BeiGene gets rights to **Leap**'s DKN01 in Asia Pacific region

Biogen, **CAMP4** pen CNS deal

Biogen pays up to $710m for **Pfizer**'s CK1 inhibitor for CNS conditions

Takeda and **Charles River** enter drug discovery collaboration

Eagle to co-promote **Tyme**'s cancer metabolism candidate in the US

Pfizer gets worldwide rights to **eFFECTOR**'s cancer candidates

Empirico to use *Precision Insights Platform* to identify antisense targets for **Ionis**

Ocumension gets rights to **EyePoint**'s *Dexycu* in Greater China

Kyverna pens option agreement with **Gilead**

Incyte pays big for rights to **MorphoSys**'s tafasitamab

Novartis grants **Iovance** license to its IL-2 analog to develop as cancer immunotherapy

J&J gets option to kinase inhibitors from **Pulmatrix**

Mereo grants **Oncologie** exclusive rights to Phase I ovarian cancer project

Merck pens KRAS inhibitor development deal with **Astex** and **Taiho**

Regenerative Medicine of China signs 30-yr. deal to sell **Zhittya**'s biologics in China territories

Regenerative Medicine of Latin America signs 30-yr. deal to sell **Zhittya**'s biologics in Latin America

Chugai licenses dual RAF/MEK inhibitor CH5126766 to **Verastem**

FINANCINGS

Public offering nets $79m for **Adaptimmune**

Aligos gets $125m in series B financing

Apellis nets $332m through FOPO

Applied Therapeutics nets $134.8m via FOPO

Aptinyx nets $33.6m through FOPO

Armata raises $25m via PIPE

Autolus nets $75m through public offering

Black Diamond goes public via $187m IPO

Blueprint Medicines nets $308.7m via public stock sale

FOPO nets $61m for **Concert Pharmaceuticals**

Global offering nets $144.5m for **DBV Technologies**

Denali nets $169.2m through FOPO

Hutchison China MediTech nets $103.4m through public offering

I-Mab goes public, nets $96.4m

FOPO nets $98m for **Immunogen**

Infinity enters into $20m royalty sale agreement with BVF

Leap closes $27m private placement

Matinas nets $47m via FOPO

Public offering nets $324.3m for **Mirati**

Public offering nets $45m for **Mirum**

Novome brings in $33m via series A

Onconova closes another PIPE; nets $9.3m

Osmotica nets $28m through FOPO

Trillium Therapeutics nets $110m through public offering of common and preferred shares

Xenon nets $56.4m through FOPO

Zymeworks nets $301.6m through public offering

MEDICAL DEVICES

MERGERS & ACQUISITIONS

ANIKA THERAPEUTICS INC.
ARTHROSURFACE INC.

Anika Therapeutics Inc. is acquiring closely held orthopedic company **Arthrosurface Inc.** for $60m in cash up front and up to $40m in regulatory and commercial milestones. (Jan.)

Founded in 2002, Arthrosurface has a portfolio of over 150 surface implant curvatures for conditions--such as trauma, injury, and arthritic disease--of the upper and lower extremities including knee, shoulder, hip, ankle, wrist, and toe. Its *HemiCAP* implants are a minimally invasive alternative to total joint replacement and enable patients to have increased range of motion with reduced pain. Arthorsurface's products will join the Anika portfolio of more than 20 products for joint preservation and regenerative medicine which are based on Anika's hyaluronic acid platform. Anika concurrently acquired sports medicine company **Parcus Medical** for $35m up front and up to $60m in potential earn-outs. Investment Banks/Advisors: SVB Leerink (Anika Therapeutics Inc.)

ANIKA THERAPEUTICS INC.
PARCUS MEDICAL LLC

Expanding its offerings in the fast-growing ambulatory surgical center market, **Anika Therapeutics Inc.** is paying $35m in cash up front to acquire **Parcus Medical LLC**. Anika could shell out another $60m in commercial-based earn-outs. (Jan.)

Founded in 2007, Parcus offers a variety of products for use in surgical procedures of the shoulder, knee, hip, and distal extremities. Parcus' portfolio of polyetheretherketone (PEEK)- based products includes *Draw Tight* suture-based anchors, the *AcTiFlip* button fixation system, *SLiK* knotless screw-in anchors and fix screw-in tenodesis system, and the *V-LoX* screw-in suture anchors. Parcus Medical estimated 2019 revenues to be $12-13m, which was 15% more than 2018. Concurrent with the acquisition, Anika paid $60m in cash and could pay up to $40m in regulatory and commercial milestones for private orthopedic company **Arthrosurface Inc.** Both transactions allow Anika to expand its offerings of products for joint preservation and restoration. Investment Banks/Advisors: SVB Leerink (Anika Therapeutics Inc.)

RTI SURGICAL INC.

RTI Surgical Holdings Inc. (implants) sold its original equipment manufacturing (OEM) business to private equity firm Montagu for $490m in cash. (Jan.)

RTI will use proceeds from the sale to repay debt and invest in its global spine portfolio. Following the divestiture, RTI becomes a pure play spine company and will focus on growth and innovation. For year-end 2019, RTI's spine business generated $118.5m. With its expertise in tissue, biologics, and hardware, the OEM biz will continue supporting RTI with certain contracted product development and manufacturing. During each of the next two years, RTI anticipates launching at least ten new products. The OEM business generated about $189m in revenues for 2019.

ALLIANCES

BAYER AG
DARE BIOSCIENCE INC.

Dare Bioscience Inc. licensed **Bayer AG** US rights to its investigational vaginal silicone ring *Ovaprene*. (Jan.)

Bayer made an up-front payment and provides Dare with clinical and marketing expertise. Dare is in charge of remaining development, including the completion of the pivotal contraceptive effectiveness and safety trial (planned for the second half of 2020), and gaining approval. In order to make the license effective, Bayer has to pay Dare $20m (which Dare will put toward development costs) once the pivotal trial is completed, and then the Big Pharma will commercialize the device, handing over another $310m in sales milestones plus double-digit tiered royalties. *Ovaprene* is a non-hormonal contraceptive ring that provides a month's long contraception through the use of a permeable mesh that creates a partial barrier for sperm from the cervical canal. The ring also releases the locally acting spermiostatic agents ascorbic acid and ferrous gluconate. Dare, which holds exclusive global rights to *Ovaprene* under a 2017 agreement with **ADVA-Tec**, expects to file an investigational device exemption in the first half of 2020. This is Bayer's second women's health-focused deal of 2019 to date. A week before it signed the alliance with Dare, Bayer teamed up with **Evotec** (for the third time) to develop candidates against multiple targets in polycystic ovary syndrome. The Big Pharma already has a strong women's health portfolio, led by the intrauterine device *Mirena*, a billion-dollar product, and another contraceptive *Yaz*. It has been a year since Bayer withdrew its permanent birth control device *Essure* from the market for business reasons, including low sales due to adverse events.

SEBACIA INC.
SIENNA BIOPHARMACEUTICALS INC.

Sebacia Inc. acquired **Sienna Biopharmaceuticals Inc.**'s SNA001, a topical silver photoparticle therapy for the reduction of light-pigmented hair, and all related assets. (Jan.)

SNA001 uses Sienna's *Topical Photoparticle Therapy* platform, which incorporates engineered silver photoparticles to absorb laser light and convert the light energy into heat, which is then applied to a targeted area. In September 2019, Sienna submitted a 510(k) application for SNA001 in the light hair removal indication and a commercial launch is anticipated early this year. SNA001 is also undergoing pivotal trials in acne. The current deal resolves all ongoing patent litigation between Sienna and **Massachusetts General Hospital**, which owns certain patents licensed by Sebacia. SNA001 complements Sebacia's own *Microparticles*, a gold microparticle/laser energy system that reduces oil production in the sebaceous glands to prevent and treat acne. The divestiture of its aesthetics device enables Sienna (which had been looking to offload SNA001) to focus on its *Topical by Design* dermatology drug pipeline.

FINANCINGS

SEASPINE HOLDINGS CORP.

SeaSpine Holdings Corp. (medical devices for spinal disorders) netted $79.9m in a follow-on public offering of 6.8 million common shares at $12.50. (Jan.)

Investment Banks/Advisors: BTIG LLC; Canaccord Genuity Inc.; Ladenburg Thalmann & Co. Inc.; SunTrust Banks Inc.

SI-BONE INC.

SI-Bone Inc. (devices for musculoskeletal disorders of the sacropelvic anatomy) netted $50.3m through a follow-on public offering of 2.49 million common shares at $21.50. The company will use some of the proceeds for commercial expansion of its *iFuse* system for treating sacroiliac joint dysfunction. Stockholders sold another 1.81 million shares. (Jan.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Canaccord Genuity Inc.; JMP Securities LLC; Morgan Stanley & Co.

PHARMACEUTICALS

MERGERS & ACQUISITIONS

ELI LILLY & CO.
DERMIRA INC.

Eli Lilly & Co. agreed to pay $18.75 per share (a 21% premium) or $1.1bn to acquire public dermatology company **Dermira Inc.** (Jan.)

The deal helps Lilly expand its immunology offerings, particularly with the addition of Dermira's monoclonal antibody lebrikizumab, an IL-13 inhibitor in Phase III trials for moderate-to-severe atopic dermatitis. **Almirall** has rights in Europe under a deal signed in February 2019. (Dermira licensed the candidate from **Roche** in 2017; milestones and royalties under that arrangement still apply.) In-

jectable lebrikizumab is complementary to Lilly's Phase III *Olumiant* (baracitinib), an oral JAK 1/2 inhibitor for AD. The ability to offer patients both an oral and injectable AD therapy is an attractive option as Lilly faces competition in the AD space from **Sanofi**/**Regeneron**'s twice-monthly injection *Dupixent* (dupilumab). The deal also gives Lilly access to Dermira's marketed medicated cloth *Qbrexa* (glycopyrronium) for excessive underarm sweating (primary axillary hyperhidrosis). The acquisition will take place via tender offer, which has been unanimously approved by Dermira's BOD. Bay City Capital and New Enterprise Associates, which together own 13% of the company, have also entered into a Tender and Support Agreement. The transaction is expected to close by the end of Q1 2020. Investment Banks/Advisors: Evercore Partners (Eli Lilly & Co.); Citigroup Inc.; SVB Leerink (Dermira Inc.)

NEURAXPHARM ARZNEIMITTEL GMBH
EASYPHARM OTC GMBH

CNS-focused spec pharma **neuraxpharm Arzneimittel GmbH** agreed to acquire privately held Austrian consumer healthcare company **easypharm OTC GmbH**, which will be launched as **Neuraxpharm Austria**, and retain easypharm's existing management. (Jan.)

Easypharm's CNS OTC brands include *easysleep* (melatonin, valerian, and hop) aid for insomnia (available as a tablet, a tea, and a sleep-spray formulation) to shorten falling asleep time and contribute to healthy sleep and *easyrelax* (passion flower, valerian, lemon balm, lavender, and saffron), a dietary supplement to reduce stress, nervous tension, and restlessness. These products will boost neuraxpharm's existing CNS consumer healthcare franchise of nutraceuticals. Easypharm also has a portfolio of neurology/psychiatry prescription generics--including aripiprazole, levetiracetam, memantine, olanzapine, quetiapine, risperidone, and venlafaxine--distributed in Austria by partner **Aristo Pharma**. In addition, easypharm offers respiratory, cough, sore throat and pharyngitis, and cold sore OTC products as well as the *ERAPROTECT* medical device pen for UV radiation protection to prevent cold sores. Easypharm's local sales force and distributor resources will facilitate the commercialization in Austria of neuraxpharm's own probiotic product *NeuraxBiotic Spectrum* (Lactobacillus plantarum PS128), a psychobiotic that modulates the gut-brain-axis, first launched in the UK last year. Neuraxpharm has over the past four years expanded with acquisitions across Europe; the current deal marks its twelfth European country, further extending the company's Central European reach.

ALLIANCES

23ANDME INC.
ALMIRALL SA

Almirall SA licensed exclusive development and commercialization rights to **23andMe Inc.**'s bispecific monoclonal antibody (mAb) that blocks all three isoforms of IL-36 cytokine. (Jan.)

Although a specific candidate wasn't disclosed, IL-36 belongs to the IL-1 cytokine family, which is associated with various inflammatory diseases, including some dermatological conditions. With its database containing genotypic information, along with billions of phenotypic data points, 23andMe identifies targets from which it generates lead compounds and then conducts preclinical research to support further development. Almirall plans to progress this 23andMe preclinical IL-36 inhibiting mAb through clinical trials and commercialization. This deal, along with concurrent dermatology partnerships with both **Bioniz** and **WuXi**, further boosts Almirall's early-stage pipeline programs.

ALLERGAN PLC
NESTLE SA

To satisfy regulators ahead of its acquisition by **AbbVie**, **Allergan PLC** is selling **Nestle SA** its FDA-approved *Zenpep* (pancrelipase) delayed-release capsules. (Jan.)

Zenpep is indicated for treating exocrine pancreatic insufficiency due to cystic fibrosis and other conditions. In 2018, the drug generated $237.7m in sales. Nestle is also acquiring *Viokace*, an uncoated immediate- release drug, also for exocrine pancreatic insufficiency. Concurrently, Allergan is divesting to its **AstraZeneca** its IL-23 inhibitor brazikumab, which is in Phase IIb/III trials for Crohn's disease and Phase II for ulcerative colitis. Financial terms of both agreements were not disclosed.

ALMIRALL SA
BIONIZ THERAPEUTICS INC.

Almirall SA and **Bioniz Therapeutics Inc.** entered a collaboration and option agreement in which Almirall paid $15m for the option to acquire Bioniz outright. (Jan.)

Through its multi-cytokine inhibitor technology platform, Bioniz has developed peptides that selectively inhibit functionally redundant cytokines, with a present focus on the IL-2 cytokine family, to treat immuno-inflammatory diseases and T cell malignancies. Bioniz's pipeline includes BNZ1 (an IL-2, IL-9, and IL-15 inhibitor in Phase I/II for cutaneous T cell lymphoma (CTCL), Phase I for alopecia areata, and preclinical for other T cell leukemias/lymphomas); BNZ2 (an IL-15 and IL-21 inhibitor in preclinical development for celiac disease and inflammatory bowel disease); and BNZ3 (also an IL-15 and IL-21 inhibitor in preclinical development for autoimmune diseases). Following the availability of Phase I/II trial results of BNZ1 in CTCL and dependent on other defined regulatory conditions, Almirall may exercise its option to buy Bioniz, paying an exercise fee of $47m, plus additional milestones and royalties. As part of the agreement if the option is exercised, Almirall will also start a research collaboration to expand its early-stage pipeline. Almirall will form a new company (that will retain Bioniz's technology platform), with which it will collaborate to discover other multi-cytokine inhibitors for dermatology indications, with a goal of delivering at least three IND-approved candidates. The newco will be eligible for development and regulatory milestones upon IND submission. This deal is concurrent with Almirall's announcement of dermatology partnerships with both **WuXi** and **23andme**.

ALMIRALL SA
WUXI PHARMATECH INC.
WuXi AppTec Inc.
WuXi Biologics

Almirall SA and **WuXi Biologics** agreed to collaborate on the discovery of multiple bispecific antibodies that target dermatologic diseases using WuXi's *WuXiBody* platform. (Jan.)

The *WuXiBody* engineering platform enables the assembly of almost any monoclonal antibody (mAb) sequence pair into a bispecific construct with a structural flexibility that enables the building of various formats with different combinations of valencies (multiple binding sites). Under the deal, Almirall will gain access to WuXi's antibody technologies, including *WuXiBody*, paying WuXi an up-front fee and potentially providing development, regulatory, and commercialization milestones and royalties on global sales for each resulting bispecific antibody project generated under the agreement. Almirall's aim is to discover multiple bispecific antibodies for skin diseases, including atopic dermatitis, to which it will have development rights. Almirall concurrently announced dermatology partnerships with both **Bioniz** and **23andMe**.

AMUNIX PHARMACEUTICALS INC.
ROCHE

In their second collaboration in as many years, **Roche** received a license to **Amunix Pharmaceuticals Inc.**'s *XTEN* technology. (Jan.)

Roche's **Genentech Inc.** teamed up with Amunix in 2017 to discover and develop drugs in undisclosed therapy areas. Under the new partnership, Roche has rights to use *XTEN* to discover and develop candidates in non-oncology indications against certain unknown targets. Amunix receives $40m up front, up to $1.5bn in development and sales milestones, and royalties. *XTEN* creates protein polymers that are recombinantly fused to therapeutic products

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(such as T-cell engagers, cytokines, and checkpoint inhibitors); the fused entity--called an XTENylated drug--as a result has increased half-life and decreased immunogenicity. The most advanced *XTEN* molecule in the pipeline currently is **Sanofi**'s BIVV001, an engineered Factor VIII therapy for hemophilia A. Sanofi got the program through its 2018 acquisition of BioVerativ (Amunix originally licensed the therapy to **Biogen** in 2011).

APEXIAN PHARMACEUTICALS INC.
OCUPHIRE PHARMA INC.

Apexian Pharmaceuticals Inc. granted **Ocuphire Pharma Inc.** an exclusive global sublicense to APX3330 for all ophthalmic and diabetic indications. (Jan.)

APX3330 is an oral apurinic/apyrimidinic endonuclease 1/reduction-oxidation effector factor-1 (APE1/Ref-1) inhibitor in preclinical studies for diabetic retinopathy (DR) and diabetic macular edema (DME). Future indications for the compound may include wet age-related macular degeneration and retinal vascular occlusion. Apexian is also developing APX3330 for cancer. Based on the positive results of a recently completed Phase I oncology trial (APX-CLN-0011) and ten other Phase I and Phase II prior trials conducted by Apexian, Ocuphire plans to commence a Phase II proof-of-concept trial (ZETA-1) in non-proliferative DR and DME in 2020. APX3330 will join Ocuphire's ophthalmic pipeline which is led by *Nyxol*, a Phase IIb eye drop for front-of-the-eye disorders, including night vision disturbances, reversal of mydriasis, presbyopia, and normal-tension glaucoma. APX3330 was licensed to Apexian from **Eisai** in 2008 and incorporates IP that Apexian licensed from **Indiana University** in 2017.

APOLLOMICS INC.
GLYCOMIMETICS INC.

Apollomics Inc. licensed exclusive rights to co-develop and commercialize **GlycoMimetics Inc.**'s blood cancer candidates uproleselan and GMI1687 in China, Hong Kong, Macau, and Taiwan. (Jan.)

GlycoMimetics gets $9m up front, up to $180m in milestones, and tiered royalties. Apollomics is responsible for all costs related to development and commercialization of the E-selectin inhibitors in its territories and will receive the candidates from GlycoMimetics under a supply agreement. IV-administered uproleselan is in Phase III for acute myelogenous leukemia, and has received Breakthrough Therapy designation from the FDA, while GMI1687 is in IND-enabling preclinical studies. The latter is also indicated for AML but is delivered via subcutaneous injection with equivalent activity to uproleselan at a 250-fold lower dose. Apollomics adds the projects to a pipeline that holds three targeted cancer candidates (a c-Met inhibitor, an epidermal growth factor receptor inhibitor, and a multi-kinase inhibitor) and three monoclonal antibodies (anti-PD-1, anti-PD-L1, and cytotoxic T-lymphocyte-associated protein 4).

ARO BIOTHERAPEUTICS CO.
IONIS PHARMACEUTICALS INC.

Ionis Pharmaceuticals Inc. and **Aro Biotherapeutics Co.** will collaborate on the development of RNA-targeted therapeutic candidates, combining the former's antisense oligonucleotides with Aro's *Centyrin* protein drug platform. (Jan.)

A 2017 start-up established and backed in part by Johnson & Johnson Innovation - JJDC Inc., Aro holds an exclusive worldwide license from **J&J** to use the *Centyrin* technology--which was discovered by Aro's CSO Karyn O'Neil, PhD, and her team at **Janssen Pharmaceutical Co.**--to develop, manufacture, and commercialize protein therapeutics. *Centyrins* are small, non-antibody protein scaffolds with the ability to simultaneously target multiple cell surface receptors to deliver complex drug payloads in high concentration to specific cell types and tissues, while lowering the toxicity in non-diseased organs. Because of its structurally simple, ultra-stable, and highly soluble properties that can be expressed in various formats, this platform is expected to facilitate the discovery of medicines with new mechanisms of action. Using the *Centyrin* platform, Aro will be responsible for discovery. The partners will together collaborate to create for further development a defined number of lead *Centyrin* drug conjugates (in a variety of diseases with high unmet medical need) designed to achieve--via systemic administration--tissue-specific, therapeutically effective gene knockdown in extra-hepatic tissues. Ionis will lead development and will have worldwide exclusive commercialization rights for each resulting drug conjugate. Aro and Ionis will also collaborate on additional discovery programs. In exchange, Aro gets an up-front cash payment, R&D funding, and up to $1.4bn in specific development and commercial milestones, plus royalties on net sales. Ionis has a diverse pipeline of antisense oligonucleotides across multiple therapeutic areas, with several programs set to enter pivotal studies this year. Aro is developing its own pipeline of *Centyrins* for oncology and immunology.

ASTRAZENECA PLC
ATNAHS PHARMA

AstraZeneca PLC divested a portfolio of non-core mature hypertension brands to **Atnahs Pharma**, which paid $350m. The rights to Atnahs are global excluding the US and India (previously divested), and Japan (where AZ will retain rights). (Jan.)

Atnahs could also hand over up to $40m in sales milestones during the next two years. The deal includes the beta blockers *Inderal* (propranolol), *Tenormin* (atenolol), and *Tenoretic* (atenolol/chlorthalidone fixed-dose combination), which are all indicated for angina, hypertension, and arrythmias, as well as the ACE inhibitors *Zestril* (lisinopril) and *Zestoretic* (hydrochlorothiazide/lisinopril, fixed-dose combination). (*Zestril* treats hypertension, congestive heart failure, diabetic related conditions and hypertensive renal disease, while *Zestoretic* treats hypertension.) In the licensed territories, the five products brought in $132m in sales in 2018. Atnahs' business model is to acquire established branded drugs from large and specialty pharmacos. The company's therapy areas of focus encompass women's health and endocrinology, neurology and pain, gastroenterology, and oncology.

ATYR PHARMA INC.
KYORIN PHARMACEUTICAL CO. LTD.

ATyr Pharma Inc. licensed **Kyorin Pharmaceutical Co. Ltd.** exclusive rights to develop and commercialize its lead program ATYR1923 for interstitial lung diseases (ILDs) in Japan. (Jan.)

In exchange for the rights, Kyorin will pay aTyr $8m up front, up to $167m in development, regulatory, and sales milestones, plus royalties, as well as tiered royalties on net sales in Japan. Kyorin will fund all R&D and commercialization activities, and aTyr will supply the therapeutic. ATYR1923 is a fusion protein comprised of the immuno-modulatory domain of histidyl tRNA synthetase fused to the FC region of a human antibody. It is a selective modulator of neuropilin-2 that downregulates the innate and adaptive immune response in inflammatory disease states. ATYR1923 is currently in Phase I/II trials for pulmonary sarcoidosis.

AXSOME THERAPEUTICS INC.
PFIZER INC.

Pfizer Inc. licensed **Axsome Therapeutics** exclusive US rights to nonclinical and clinical data, and intellectual property surrounding the norepinephrine reuptake inhibitor reboxetine--the active ingredient in Axsome's narcolepsy candidate AXS12--and esreboxetine (renamed AXS14) for fibromyalgia and other indications. (Jan.)

Axsome issued Pfizer $8m in stock and paid $3m in cash up front. Pfizer is also eligible for up to $323m in regulatory and sales milestones, plus tiered sales royalties in the mid-single to low-double-digits (*Strategic Transactions* estimates 4-29%). Pfizer gets a right of first negotiation on any potential collaborations involving AXS12 or AXS14. In December 2019 Axsome announced positive results from the Phase II CONCERT trial of AXS12. It plans to move the candidate into Phase III in 2020. AXS12 was granted orphan drug designation in 2018 and has two

patents pending in the US. Pfizer currently markets reboxetine as *Edronax* outside the US for depression. Esreboxetine, a more selective and potent version of reboxetine, demonstrated efficacy in previous Phase II and Phase III fibromyalgia trials. According to Biomedtracker, Pfizer had suspended development of esreboxetine in early 2009 because they considered it unlikely that the compound would provide meaningful benefit to patients beyond the current standard of care. Concurrent with the agreement, Pfizer sold **Biogen Inc.** its casein kinase 1 (CK1) inhibitor PF05251749 for Alzheimer's and Parkinson's diseases. That deal could be worth up to $710m.

BAYER AG
CELMATIX INC.
EVOTEC SE

For the third time, **Bayer AG** and **Evotec SE** are collaborating, this time in a five-year, multi-target agreement to develop candidates for polycystic ovary syndrome (PCOS). (Jan.)

The companies first teamed up in 2012 for a multi-target deal in endometriosis; that agreement has resulted in many molecules advancing into Phase I and II. In 2016 they partnered again in the area of kidney diseases, including chronic kidney disease in diabetes. In the current alliance, Bayer and Evotec will each provide drug targets and high-quality technology platforms. Evotec's contributions will also include targets identified through its partnership established in October 2019 (expanded in December 2019) with **Celmatix Inc.** to produce preclinical programs in women's health conditions based on Celmatix's proprietary multi-omics *Reproductive Atlas* database. Bayer and Evotec will jointly conduct preclinical studies, after which the Big Pharma takes over clinical development and commercialization, in exchange for €6.5m up front ($7.2m) and €10m in R&D funding over five years (Evotec will share this with Celmatix in return for novel target identification and prioritization work). Bayer will also pay Evotec and Celmatix over €330m in preclinical, clinical, and sales milestones, plus up to low double-digit sales royalties. (In comparison, Bayer and Evotec's 2012 endometriosis deal was worth $761m in total potential value, while the kidney one was $351m.) There are a handful of older hormonal drugs that are used for PCOS, but the disease is often underdiagnosed and there are no products specifically approved for the condition. Presently there are only six PCOS candidates in the pipeline (two of which are the Evotec/Bayer and Evotec/Celmatix assets). The most advanced--**AbbVie**'s elagolix, a luteinizing hormone releasing hormone antagonist, and **Ogeda**'s fezolinetant, a neurokinin 3 receptor antagonist--are in Phase II trials.

BEIGENE LTD.
EUSA PHARMA

EUSA Pharma licensed **BeiGene Ltd.** exclusive rights to develop and commercialize the biologics *Sylvant* (siltuximab) in China, Hong Kong, Macau, and Taiwan, and *Qarziba* (dinutuximab beta) in China. (Jan.)

EUSA will receive up to $160m in the form of an up-front payment and regulatory and commercial milestones. It is also eligible for tiered sales royalties. BeiGene will fund and perform all clinical development, regulatory, and commercial activities. *Sylvant* is approved in over 40 countries for treating idiopathic multicentric Castleman's disease, which is an orphan condition affecting the lymph nodes and related tissues. EUSA acquired worldwide rights to *Sylvant* for $115m in cash from **Janssen Sciences Ireland** in July 2018. *Qarziba* is the only EMA-approved targeted immunotherapy for treating high-risk neuroblastoma, the most common solid tumor affecting children which originates outside of the brain. Both drugs have been submitted for fast track approval in China. Investment Banks/Advisors: Jefferies & Co. Inc. (EUSA Pharma)

BEIGENE LTD.
LEAP THERAPEUTICS INC.

Leap Therapeutics Inc. granted **BeiGene Ltd.** an exclusive option to license development and commercialization rights to DKN01, a Phase II anti-Dickkopf-1 (DKK1) antibody for gastric cancer, in Asia (excluding Japan), Australia, and New Zealand. (Jan.)

Leap gets $3m up front and will receive additional money if BeiGene exercises its option following initial proof-of-concept studies. Leap is also eligible for up to $132m in development, regulatory, and commercialization milestones, plus tiered sales royalties. Additionally, BeiGene has agreed to make a $5m investment in a concurrent private placement of Leap's. BeiGene is interested in the potential combination of DKN01 with its own anti-PD-1 inhibitor tislelizumab. During the option period, Leap will conduct studies on the DKN01/tislelizumab combo in 40 patients with second-line gastric cancer/gastroesophageal junction cancer whose tumors express high levels of DKK1 in an effort to bolster research suggesting positive outcomes with the combination of DKN01 and PD-1 inhibitors. These trials are expected during the first half of 2020.

BIOGEN INC.
CAMP4 THERAPEUTICS

CAMP4 Therapeutics and **Biogen Inc.** are teaming up to discover and develop therapies for neurodegenerative and neurological diseases. (Jan.)

CAMP4 will contribute its *Gene Circuitry Platform* which can map the transcriptional machinery and network of signaling pathways that control gene expression across any cell in the human body. The collaboration seeks to identify targets that can be engaged to either dial up or down unhealthy gene expression within microglial cells, which are the primary immune cells of the central nervous system. Biogen is an ideal partner with its expertise in developing therapies for CNS conditions. Biogen will pay CAMP4 $15m up front in addition to research funding. Biogen gets the option to license initial targets and would pay up to $96m in development milestones for each, plus sales royalties. CAMP4 would get up to $173m for each additional target selected by Biogen, plus royalties. In addition to microglial cells, the parties may also examine other CNS cell types.

BIOGEN INC.
PFIZER INC.

Biogen Inc. is acquiring **Pfizer Inc.**'s casein kinase 1 (CK1) inhibitor PF05251749 for patients with behavioral and neurological symptoms across diseases of the central nervous system. (Jan.)

Biogen paid Pfizer $75m up front and could shell out another $635m in development and commercial milestones, plus tiered royalties in the high-single digits to sub-teens (*Strategic Transactions* estimates 7-12%). PF05251749 had demonstrated an acceptable safety profile and proof-of-mechanism in a Phase Ia trial. Biogen plans to commence a Phase Ib study in Q4 2020 as a treatment of sundowning (also known as late-day confusion) in Alzheimer's disease and irregular sleep wake rhythm disorder (ISWRD) in Parkinson's disease. Biogen seeks to develop PF05251749 to improve behavioral disturbances of sundowning by correcting circadian rhythm, and to treat ISWRD symptoms and improve daytime wakefulness, sleep quality, behavior, and daily function. According to Biomedtracker, Pfizer lists PF05251749 as a discontinued project in its pipeline following a January 2018 decision to exit their internal neuroscience discovery and early development efforts. Concurrent with the agreement, Pfizer licensed **Axsome Therapeutics** exclusive US rights to nonclinical and clinical data, and intellectual property surrounding reboxetine, which is the active ingredient in Axsome's narcolepsy candidate AXS12. Axsome also received exclusive US rights to esreboxetine (renamed AXS14) for fibromyalgia. The deal could be worth up to $334m.

CHARLES RIVER LABORATORIES INTERNATIONAL INC.
TAKEDA PHARMACEUTICAL CO. LTD.

Takeda Pharmaceutical Co. Ltd. penned a deal with CRO **Charles River Laboratories Inc.** for the discovery of preclinical programs across Takeda's four areas of

focus--oncology, gastroenterology, neuroscience, and rare diseases. (Jan.)

Throughout the deal, Charles River will use its end-to-end integrated drug discovery platform to identify new potential candidates and bring them into preclinical development. Takeda retains options to license any projects it wishes to advance further. It made an undisclosed up-front payment and will hand over in excess of $50m per program in development milestones per compound, up to $120m in sales milestones, and royalties on projects that make it to the market. Takeda is consistently working to enhance its pipeline and strengthen the company's offerings in core disease areas. The deal with Charles River was announced shortly after Takeda penned two other alliances; in December, it entered into a potential $1bn agreement with **Turnstone Biologics** under which Takeda took exclusive global rights to Turnstone's vaccinia virus-based cancer immunotherapy RIVAL01 (and options to license additional candidates), and it also signed a deal with **Cerevance** to discover and develop new treatments for CNS-based gastrointestinal disorders.

EAGLE PHARMACEUTICALS INC.
TYME TECHNOLOGIES INC.

Eagle Pharmaceuticals Inc. has agreed to co-promote in the US **Tyme Technologies Inc.**'s oral cancer candidate SM88 (racemetyrosine) for advanced cancers. (Jan.)

SM88 is a *Cancer Metabolism-Based Therapy* (*CBMT*) in Phase II/III development by Tyme that has demonstrated complete or partial response in 15 different types of solid and blood cancers including pancreatic, prostate, sarcoma, breast, and lung. Under terms of the ten-year agreement, Tyme will be responsible for all development, regulatory, commercial, marketing, reimbursement, and manufacturing activities. It also reserves the right to repurchase Eagle's co-promotion rights for $200m. Eagle pays $20m up front via an equity investment (10 million Tyme shares at $2, a 65% premium), and will make a $20m milestone payment ($10m cash and $10m equity) upon completion of one of three events: achievement of the primary endpoint of overall survival in a pivotal trial with SM88 for pancreatic cancer, achievement of the primary endpoint of overall survival in the Phase III *Precision Promise* registration arm of a trial with the Pancreatic Cancer Action Network, or FDA approval of SM88 in any cancer indication. Once launched, Eagle will carry out 25% of the promotional sales efforts in the US oncology market and receive 15% of net revenues. The companies could also study SM88 in combination with Eagle's oncology pipeline, with potential trials in breast, lung, and other cancers.

EFFECTOR THERAPEUTICS INC.
PFIZER INC.

Pfizer Inc. licensed excusive global rights to **eFFECTOR Therapeutics Inc.**'s small-molecule inhibitors of eukaryotic initiation factor 4E (eIF4E). (Jan.)

Pfizer will pay $15m up front plus up to another $492m in R&D funding and development and sales milestones, plus sales royalties. EFFECTOR has an option to co-promote in the US and would share in profit and losses with Pfizer. The Big Pharma will develop the eIF4E inhibitors for various treatment-refractory cancers. In the past, development of such small molecules has proven challenging because of the nature of its binding site.

EMPIRICO INC.
IONIS PHARMACEUTICALS INC.

Empirico Inc. signed a three-year deal to identify targets for indications and tissues of interest to **Ionis Pharmaceuticals Inc.** in its development of antisense therapeutics. (Jan.)

Ionis made a $10m up-front payment to Empirico in the form of an equity stake (as part of Empirico's concurrent/separate $17m series A-2 round), and will be responsible for $30m in near-time operational and preclinical milestones, $620m in clinical development, regulatory, and commercial milestones, plus sales royalties. Ionis may select up to 10 targets to bring into preclinical and clinical studies. Empirico has the option to license, develop, and sell a therapy directed at a collaboration target, in exchange for milestone payments and royalties. In addition, the partners plan to apply human genetics evidence to existing Ionis candidates, and will together perform target validation, indication and biomarker selection, and patient stratification. Ionis' current pipeline spans multiple indications in rare and more common conditions within the neurological, cardiometabolic, renal, and oncology areas. Empirico, founded in 2017, will leverage its *Precision Insights Platform*, which aggregates big data, human genetics, and programmable data (statistical and machine learning algorithms) to identify and prioritize therapeutic targets that have the highest probability of success based on the roles that genes and targets play in disease. Internally, Empirico has used the technology to generate preclinical candidates in multiple areas including immune, dermatology, cardiometabolic, and ophthalmology. The same day as the current alliance, Ionis also signed a separate partnership with **Aro Biotherapeutics** to combine antisense oligonucleotides with Aro's protein therapeutics platform *Centyrin*.

EYEPOINT PHARMACEUTICALS INC.
OCUMENSION THERAPEUTICS

EyePoint Pharmaceuticals Inc. licensed **Ocumension Therapeutics** exclusive rights to develop and commercialize the ophthalmic product *Dexycu* (dexamethasone) intraocular suspension 9% in China, Hong Kong, Macau, and Taiwan. (Jan.)

EyePoint will receive $2m up front, up to $12m in predetermined development, regulatory, and commercial milestones, plus sales royalties. *Dexycu* is indicated for treating post-operative inflammation following ocular surgery. EyePoint already sells *Dexycu* in the US and will exclusively supply Ocumension with the product. *Dexycu* is a single-dose sustained release therapy that provides long-lasting benefit for up to 22 days. It will offer patients an alternative to a burdensome steroid eye drop regimen, which has low patient compliance due to its complex dosing schedule. In November 2018, EyePoint licensed Ocumension exclusive rights to develop and commercialize its three-year posterior segment uveitis micro insert (sold as *Yutiq* in the US) in China, Hong Kong, Macau, and Taiwan. That agreement could be worth up to $11.75m.

GILEAD SCIENCES INC.
KYVERNA THERAPEUTICS

Cell therapy start-up **Kyverna Therapeutics** penned a deal with **Gilead Sciences Inc.** through which the companies will develop engineered T-cell therapies for autoimmune diseases. (Jan.)

Kyverna will use its synthetic Treg platform and the *SynNotch* synthetic gene expression technology (belonging to Gilead's **Kite** division) to conduct research and initial clinical studies through proof-of-concept. Gilead holds an option to license rights to further develop and sell the resulting projects. It paid Kyverna $17.5m up front and committed to up to $570m in development and sales milestones. Gilead also took part in Kyverna's concurrent $25m series A round.

INCYTE CORP.
MORPHOSYS AG

In a deal potentially worth up to $2bn, **Incyte Corp.** licensed exclusive global rights to develop and sell **MorphoSys AG**'s anti-CD19 antibody tafasitamab, an Fc-engineered antibody for B-cell cancers. (Jan.)

Incyte paid $900m up front ($750m and a $150m equity investment through the purchase of MorphoSys American Depositary Shares). The deal also calls for up to $1.1bn in development, regulatory, and commercialization milestones, plus tiered royalties on ex-US sales ranging from the mid-teens to the mid-twenties (*Strategic Transactions* estimates 14-26%). The partners will co-commercialize tafasitamab in the US, where MorphoSys

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will book all revenues. Commercialization activities there will be shared, and the companies will share profits and losses 50:50. Costs associated with development both globally and in the US will be split 55% Incyte and 45% MorphoSys, though Incyte agreed to cover all future trials specific only to ex-US countries. MorphoSys filed a BLA for tafasitamab in combination with lenalidomide for relapsed/refractory diffuse large B-cell lymphoma; additional development is planned in combination studies with Incyte's PI3K-delta inhibitor parsaclisib in follicular lymphoma, marginal zone lymphoma, and chronic lymphocytic leukemia. The deal adds another late-stage program to Incyte's coffers. Tafasitamab could see approval later this year, as could the company's pemigatinib for cholangiocarcinoma and capmatinib for non-small cell lung cancer.

IOVANCE BIOTHERAPEUTICS INC.
NOVARTIS AG

Iovance Biotherapeutics Inc. gained development and commercialization rights to an antibody cytokine engrafted protein from **Novartis AG**. (Jan.)

Novartis' compound, which Iovance will name IOV3001, is an engineered IL-2 non-complementarity determining region (CDR) graft, which targets IL-2R beta-gamma-expressing cells and limits regulatory T cell (Treg) activation. Iovance is developing cancer immunotherapies based on tumor infiltrating lymphocytes (TILs), in which immune cells are extracted from a patient's tumor and then those cells are infused back into the patient's own tumor tissues where they attack cancer. The biotech will take over GMP manufacturing during 2020 and expects to initiate IND-enabling activities by next year. Iovance provides an up-front payment; development and regulatory milestones in the low-single-digits triggered by the initiation of dosing in various development phases and approvals in the US, EU, and Japan; as well as low-to-mid-single-digit sales royalties (1-6%). The deal will expand the company's existing TIL pipeline, which includes candidates for metastatic melanoma, cervical, head and neck, non-small cell lung, and blood cancers. In a separate concurrent collaboration, Iovance licensed exclusive worldwide rights to **Cellectis'** *TALEN* technology to develop gene-edited TILs.

JOHNSON & JOHNSON
PULMATRIX INC.

Pulmatrix Inc. granted the Lung Cancer Initiative at **Johnson & Johnson** an option to license exclusive global rights to RV1162/PUR1800 and a portfolio of related narrow spectrum kinase inhibitors in development for lung cancer interception. (Jan.)

J&J will pay $7.2m up front, a $2m milestone upon completion of the Phase Ib trial (to be conducted by Pulmatrix), and up to $91m in development and commercial milestones if the option is exercised. Pulmatrix will also get sales royalties in the low-single-digits. RV1162/PUR1800 incorporates Pulmatrix's *iSPERSE* (*inhaled Small Particles Easily ReSpirable and Emitted*) dry powder inhalation technology. The Phase Ib study in stable patients with chronic obstructive pulmonary disease is expected to commence in Q1 2020 and trial data is anticipated in Q3 2020.

MEREO BIOPHARMA GROUP PLC
ONCOLOGIE INC.

Mereo BioPharma Group PLC granted **Oncologie Inc.** exclusive global rights to develop and commercialize navicixizumab, an anti-DLL4/VEGF bispecific antibody in Phase I for refractory solid tumors including ovarian cancer. (Jan.)

Mereo gets $4m up front, a $2m payment related to a CMC (chemistry, manufacturing, and controls) milestone, and up to $300m in development, regulatory, and sales milestones. The company is also eligible for tiered royalties ranging from mid-single-digits to sub-teens (*Strategic Transactions* estimates 4-12%). Navicixizumab is in a Phase Ib trial in combination with paclitaxel for heavily pretreated ovarian cancer and has also completed a Phase Ia monotherapy study in other solid tumors. Mereo gained the project through the merger last year with OncoMed Pharmaceuticals; as a result of the current alliance, former OncoMed stockholders are now eligible to receive cash payments under the terms of a CVR agreement signed in accordance with that merger. Oncologie adds navicixizumab to a pipeline that includes three other cancer projects--bavituximab (glioblastoma, advanced hepatocellular carcinoma, and gastric cancers), varisacumab (solid tumors), and lefitolimod (various solid tumors, developed in partnership with **Mologen**.) For Mereo, the out-licensing allows the company to further focus development efforts on its lead rare disease candidate setrusumab, which is approaching a pivotal Phase III pediatric trial for osteogenesis imperfecta.

OTSUKA HOLDINGS CO. LTD.
Astex Pharmaceuticals Ltd.
Taiho Pharmaceutical Co. Ltd.
MERCK & CO. INC.

Merck & Co. Inc. signed a deal with **Otsuka Pharmaceutical Co. Ltd.** divisions **Taiho Pharmaceutical Co. Ltd.** and **Astex Pharmaceuticals Ltd.** for the development and commercialization of small-molecule inhibitors of KRAS and other targets. The heavily backloaded deal has a potential value topping $2.5bn. (Jan.)

All three firms agreed to combine preclinical candidates, data, and research. Merck will fund all research and will pay the two partners $50m up front, up to $2.5bn in clinical, regulatory, and commercialization milestones for multiple projects, and tiered sales royalties. The Big Pharma gets exclusive global rights, while Taiho retains co-promotion rights in Japan and an option to rights in specific Southeast Asia territories. Taiho and Astex are both active in the cancer drug development space, and look forward to the leverage a partnership with Merck will provide in bringing their preclinical candidates into further development. KRAS is one of the most common mutations found in a variety of cancers, especially pancreatic. Merck joins a number of competitors in the KRAS space, including **Amgen**, **Mirati**, **Novartis** (in partnership with **Cancer Research UK**), **Lilly**, and **J&J**.

REGENERATIVE MEDICINE OF CHINA INC.
ZHITTYA GENESIS MEDICINE INC.

Regenerative Medicine of China Inc. (RMC) licensed over a 30-year term exclusive marketing rights in China, Taiwan, Hong Kong, and Macao to biological drugs developed by **Zhittya Genesis Medicine Inc.** (Jan.)

RMC pays Zhittya $75m up front and could provide future milestones up to $75m. Zhittya's drug development efforts span multiple therapeutic areas focusing on disorders caused by insufficient blood perfusion. Zhittya's approach use different formulations of fibroblast growth factor 1 (FGF-1) to trigger the angiogenesis process, which stimulates growth of new blood vessels, provides nourishment, removes waste products, and re-establishes normal cellular functioning in diseased tissues that have become ischemic due to lack of blood flow. Although specific candidates weren't disclosed, Zhittya has eight active preclinical development programs--in diabetic foot ulcers, venous leg ulcers, coronary artery disease, peripheral artery disease, stroke, vascular dementia, Alzheimer's disease, and Parkinson's disease. Zhittya contracts with a cGMP biologics drug manufacturer to produce clinical and preclinical lots to support its programs.

REGENERATIVE MEDICINE OF LATIN AMERICA INC.
ZHITTYA GENESIS MEDICINE INC.

Regenerative Medicine of Latin America Inc. (RMLA) licensed over a 30-year term exclusive marketing rights in Mexico and all Latin American countries south of Mexico to biological drugs developed by **Zhittya Genesis Medicine Inc.** (Jan.)

RMLA pays Zhittya $76.5m up front and could provide future milestones up to $75m. Zhittya's pipeline, which includes eight preclinical development programs--in diabetic foot ulcers, venous leg ulcers, coronary artery disease, peripheral artery disease, stroke, vascular dementia, Alzheimer's disease, and Parkinson's disease--focuses on disorders caused by insufficient blood perfusion. Zhittya uses different formula-

tions of fibroblast growth factor 1 (FGF-1) to trigger angiogenesis to stimulates growth of new blood vessels and re-establish normal cellular functioning in diseased tissues that have become ischemic due to lack of blood flow. Zhittya contracts with a cGMP biologics drug manufacturer to produce clinical and preclinical lots to support its programs. Earlier this month, Zhittya signed a 30-year agreement with similar terms in which it granted **Regenerative Medicine of China Inc.** exclusive marketing rights in China, Taiwan, Hong Kong, and Macao to biologic drugs it produces.

ROCHE
Chugai Pharmaceutical Co. Ltd.
VERASTEM INC.

Roche's **Chugai Pharmaceutical Co. Ltd.** licensed **Verastem Inc.** (also known as Verastem Oncology) worldwide rights to develop and sell its Phase I dual RAF/MEK inhibitor CH5126766 (CKI27; RO5126766; RG7304) for KRAS-mutant solid tumors. (Jan.)

Verastem will pay $3m up front plus sales royalties. Under a Phase I trial that began in December 2017 and is sponsored by Verastem, Chugai, the UK's **National Health Service**, and the UK's **Institute of Cancer Research**, the companies are studying a combination of CH5126766 and defactinib (Verastem's oral small-molecule focal adhesion kinase (FAK) inhibitor in Phase II) for KRAS-mutant advanced solid tumors, including low-grade serous ovarian cancer, non-small cell lung cancer, and colorectal cancer. The MEK/FAK combination is believed to be beneficial, as MEK inhibition activates FAK signaling as a potential escape mechanism for drug resistance and cell survival. According to Verastem, it will be looking at potential partnering strategies for CH5126766. Roche had been developing a companion diagnostic for the candidate, but the current status is unknown. KRAS-targeting therapies in the pipeline have been an active area for development because of positive clinical results. There are currently no approved KRAS drugs, and the lead program on the horizon is **Amgen**'s AMG510 in Phase II for colorectal and non-small cell lung cancers.

FINANCINGS

ADAPTIMMUNE THERAPEUTICS PLC

Adaptimmune Therapeutics PLC (cancer immunotherapies) netted $79m through a public offering of 21 million American Depositary Shares (representing 126 million ordinary) at $4 per ADS. Adaptimmune believes that the net proceeds from the offering, combined with existing cash and expected collaboration revenues, will fund company operations into the second half of 2021. (Jan.)

Investment Banks/Advisors: Cowen & Co. LLC; Roth Capital Partners

ALIGOS THERAPEUTICS INC.

Aligos Therapeutics Inc. (therapies for hepatic diseases and viral infections) raised $125m in an oversubscribed series B financing led by Wellington Management and an undisclosed investment management firm, which were joined by first-time backers Janus Henderson Investor, Boxer Capital of Tavistock Group, Cormorant Asset Management, Pivotal bioVenture Partners, and Logos Capital, and returning series A investors Vivo Capital, Versant Ventures, Novo Holdings, Roche Venture Fund, and an undisclosed healthcare fund. The company was founded in 2018 when it raised $100m in a series A round. (Jan.)

APELLIS PHARMACEUTICALS INC.

Apellis Pharmaceuticals Inc. (complement system inhibitors) netted $332m in a public offering of 9.5 million shares at $37. The company will use the proceeds to fund continued development and potential commercialization (including build-out of a commercial infrastructure and sales force) of lead candidate pegcetacoplan (APL2), a C3 inhibitor, in Phase III for multiple indications. Concurrent with the financing, Apellis announced topline results from a Phase III study in paroxysmal nocturnal hemoglobinuria, for which the candidate has a 66% likelihood of approval (7% above average). (Jan.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Citigroup Inc.; Evercore Partners; JP Morgan & Co.; Robert W. Baird & Co. Inc.

APPLIED THERAPEUTICS INC.

Applied Therapeutics Inc. (developing therapies for cardiovascular, metabolic, and ophthalmic diseases) netted $134.8m through an upsized follow-on offering of 3.15 million shares (including full exercise of the overallotment) at $45.50 each. The company plans to use the funds to advance Phase I/II AT007 for galactosemia and to prepare for commercial launch; for ongoing development and potential pre-launch activities for Phase II/III AT001 for diabetic cardiomyopathy; to advance its preclinical AT003 through Phase I for diabetic retinopathy; and for additional R&D activities. (Jan.)

Investment Banks/Advisors: Barclays Bank PLC; Cowen & Co. LLC; Goldman Sachs & Co.; UBS Investment Bank

APTINYX INC.

Neurology-focused **Aptinyx Inc.** (N-methyl-D-aspartic acid (NMDA) receptor discovery platform) netted $33.6m through the public sale of 11.7 million shares (including the overallotment) at $3. The company will use the proceeds to advance its NMDA receptor modulator pipeline, including NYX2925 (Phase II for diabetic peripheral neuropathy and fibromyalgia indications and preclinical for chemotherapy-induced peripheral neuropathy); NYX783 (Phase II for post-traumatic stress disorder and preclinical for alcohol use disorder); and NYX458 (Phase II for Parkinson's diseases and preclinical for traumatic brain injury). (Jan.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Cowen & Co. LLC; Wedbush PacGrow Life Sciences

ARMATA PHARMACEUTICALS INC.

Armata Pharmaceuticals Inc. grossed $25m through a two-tranche private placement of 8.7 million common shares at $2.87 (market average) to **Innoviva Inc.** Armata also issued warrants to purchase up to another 8.7 million shares exercisable at the same price. The company plans to use the proceeds for R&D activities including first-in-human studies of its lead program APPA02 for Pseudomonas aeruginosa as well as preclinical APSA02 for Staphylococcus Aureus. Innoviva will appoint two directors to Armata's board. (Jan.)

AUTOLUS LTD.

Autolus Therapeutics PLC (T-cell immunotherapies for cancer) netted $75m through the public offering of 7.25 million American Depositary Shares (1:1 to ordinary) at $11 apiece. Funds will support ongoing development activities, including work on AUTO1 for adult acute lymphocytic leukemia, AUTO3 for diffuse large B-cell lymphoma, and AUTO4 for peripheral T-cell lymphoma. (Jan.)

Investment Banks/Advisors: HC Wainwright & Co.; JP Morgan Chase & Co.; Jefferies & Co. Inc.; William Blair & Co.

BLACK DIAMOND THERAPEUTICS INC.

Black Diamond Therapeutics Inc. (precision oncology) netted $187m through its initial public offering of 10.6 million common shares at $19. The company had originally file to sell 8.9 million shares at a range of $16-18. (Jan.)

Investment Banks/Advisors: Canaccord Genuity Inc.; Cowen & Co. LLC; JP Morgan Chase & Co.; Jefferies & Co. Inc.

BLUEPRINT MEDICINES CORP.

Blueprint Medicines Corp. (precision therapeutics for genomically defined cancers and rare diseases) netted $308.7m through a public offering of 4.7 million common shares at $69. Funds will support build out of the company's global commercial infrastructure to support regulatory filings and upcoming launches for *Ayvakit* (avapritinib, gastrointestinal stromal tumors) and pralsetinib (RET-altered non-small cell lung cancer, medullary thyroid carcinoma, and other solid tumors) in the US and Europe. Proceeds will also go towards additional drug development and manufacturing costs. (Jan.)

Investment Banks/Advisors: Canaccord Genuity Inc.; Cowen & Co. LLC; Goldman Sachs & Co.; JMP Securities LLC; Raymond James & Associates Inc.

CONCERT PHARMACEUTICALS INC.

Concert Pharmaceuticals Inc. netted $61m through the public offering of 4.75 million shares at $9.92 and pre-funded warrants to purchase 1.8 million shares at $9.919. The company will use the proceeds to advance CTP543 (a deuterium-modified version of ruxolitinib) into Phase III for alopecia areata and to fund pipeline development, including CTP692 (a deuterium-modified form of D-serine) for schizophrenia through Phase II, for which topline data is expected by year end. (Jan.)

Investment Banks/Advisors: HC Wainwright & Co.; JMP Securities LLC; Jefferies & Co. Inc.; Mizuho Bank Ltd.

DBV TECHNOLOGIES SA

DBV Technologies SA (food allergy immunotherapies) netted $144.5m through a global offering of 7.5 million ordinary shares: 4,535,581 ordinary shares in the form of 9.1 million American Depositary Shares (ADSs) in the US, Canada and certain countries outside of Europe at a public offering price of $10.25 per ADS and 2.96 million ordinary shares at a public offering price of €18.63 ($20.49) per ordinary share to qualified investors in Europe (including France). Proceeds will support the upcoming launch of *Viaskin Peanut* (2H 2020, if approved), and additional R&D activities. (Jan.)

Investment Banks/Advisors: Citigroup Inc.; Goldman Sachs & Co.; HC Wainwright & Co.; JMP Securities LLC; Kempen & Co.

DENALI THERAPEUTICS INC.

Denali Therapeutics Inc. netted $169.2m through the public offering of 7.8 million shares at $23. The company will use the proceeds to fund further development of its LRRK2 inhibitor program, including completion of Phase I and Phase Ib trials for DNL151 in Parkinson's disease (expected in mid-2020) and the advancement of either DNL201 or DNL151 into Phase II/III trials in PD; a Phase I/II trial of enzyme replacement DNL310 (ETV:IDS) in Hunter syndrome planned for 1H 2020; a Phase I study of EIF2B activator DNL343 in amyotrophic lateral sclerosis expected in early 2020; and RIPK1 inhibitors DNL747 and SNL758 (in collaboration with partner **Sanofi**); and to advance other candidates, including IND-enabling studies for PTV:PGRN and ATV:TREM2 for AD, which are partnered with **Takeda**. Denali also plans to potentially use some of the monies to support future development and early-stage R&D programs. (Jan.)

Investment Banks/Advisors: Goldman Sachs & Co.; HC Wainwright & Co.; JP Morgan & Co.; Janney Montgomery Scott Inc.; Jefferies & Co. Inc.; Nomura Securities International Inc.

HUTCHISON CHINA MEDITECH LTD.

Hutchison China MediTech Ltd. (Chi-Med) netted $103.4m through the public offering of 4.4 million American Depositary Shares (representing 22 million ordinary) at $25 per ADS. The company is developing immunotherapies for cancer and autoimmune diseases, and will put the proceeds towards ongoing development, manufacturing, and commercialization activities. (Jan.)

Investment Banks/Advisors: Bank of America Merrill Lynch; CLSA; Canaccord Genuity Inc.; Deutsche Bank AG; Goldman Sachs & Co.; HSBC; Morgan Stanley & Co.; Panmure Gordon

I-MAB BIOPHARMA CO. LTD.

I-Mab Biopharma Co. Ltd. netted $96.4m through its initial public offering in the US of 7.4 million American Depositary Shares (representing 17 million ordinary shares) priced at $14 per ADS. (Jan.)

Investment Banks/Advisors: China Renaissance; Jefferies & Co. Inc.

IMMUNOGEN INC.

ImmunoGen Inc. sold 24.5 million common shares (including the overallotment) at $4.25 in a public offering that netted $98m. The company is developing antibody-drug conjugates for cancer, and will use the funds to support clinical trials, supply, and pre-commercialization activities. (Jan.)

Investment Banks/Advisors: Cowen & Co. LLC; Jefferies & Co. Inc.; William Blair & Co.

INFINITY PHARMACEUTICALS INC.

Infinity Pharmaceuticals Inc. entered into a $20m non-dilutive royalty financing with its largest shareholder BVF Partners. BVF will realize royalties due Infinity from **PellePharm** for future sales of the hedgehog pathway inhibitor patidegib, which is in Phase III to reduce the basal cell carcinoma burden in patients with Gorlin syndrome. (BVF could also make a $5m payment for positive Phase III data of the candidate.) Infinity has the right to repurchase the rights for $20m plus interest during the next three years. The financing will support key data readouts from now until the second half of 2021 on five ongoing solid tumor trials with sole candidate IPI549, a PI3K-gamma inhibitor. (Jan.)

LEAP THERAPEUTICS INC.

Leap Therapeutics Inc. grossed $27m through a private placement of convertible preferred shares. Raymond James was the placement agent. (Jan.)

Investment Banks/Advisors: Raymond James & Associates Inc.

MATINAS BIOPHARMA HOLDINGS INC.

Matinas BioPharma Holdings Inc. (treatments for cardiovascular, infectious, and metabolic diseases) netted $47m in a follow-on public offering of 32.26 million common shares at $1.55 each. The company will use most of the proceeds for development of its lead clinical program MAT9001 for hypertriglyceridemia. (Jan.)

Investment Banks/Advisors: BTIG LLC; HC Wainwright & Co.; Maxim Group LLC; Piper Jaffray & Co.; Roth Capital Partners; SunTrust Banks Inc.

MIRATI THERAPEUTICS INC.

Mirati Therapeutics Inc. (oncology) netted $324.3m through the public sale of 3.5 million common shares (including the overallotment) at $97.50. Some of the proceeds will support continued development of solid tumor candidates MRTX849 and sitravatinib, in addition to other preclinical and manufacturing activities. (Jan.)

Investment Banks/Advisors: Cowen & Co. LLC; Credit Suisse Group; Goldman Sachs & Co.; SVB Leerink

MIRUM PHARMACEUTICALS

Mirum Pharmaceuticals Inc. (liver disease therapies) netted $45m through a public offering of 2.4 million common shares at $20. Funds will support continued development of maralixibat for Alagille syndrome, progressive familial intrahepatic cholestasis, and biliary atresia, as well as volixibat for intrahepatic cholestasis of pregnancy and primary sclerosing cholangitis. (Jan.)

Investment Banks/Advisors: Citigroup Inc.; Evercore Partners; Guggenheim Partners LLC; Raymond James & Associates Inc.; Roth Capital Partners

NOVOME BIOTECHNOLOGIES INC.

Three-year-old **Novome Biotechnologies Inc.** raised $33m in its series A financing led by DCVC Bio, which was joined by 5AM Ventures, Alta Partners, Alexandria Venture Investments, and **Mayo Clinic**. A representative from DCVC Bio and Alta Partners will join the board. (Jan.)

ONCONOVA THERAPEUTICS INC.

Oncology firm **Onconova Therapeutics Inc.** netted $9.3m through a private placement to two health care-focused institutional investors of 27.66 million common shares at $0.3615 (a 6% premium). HC Wainwright was the placement agent. The company recently netted $4.65m through a separate PIPE that closed last month. (Jan.)

Investment Banks/Advisors: HC Wainwright & Co.

OSMOTICA PHARMACEUTICALS PLC

Osmotica Pharmaceuticals PLC (specialty extended-release generics) netted $28m through the public offering of 6 million ordinary shares at $5. In November 2019, Osmotica announced the FDA accepted its NDA filing for RVL1201 (oxymetazoline hydrochloride) ophthalmic solution, 0.1%

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for acquired blepharoptosis (droopy eyelid or ptosis) with a PDUFA goal date of July 16, 2020. (Jan.)

Investment Banks/Advisors: Jefferies & Co. Inc.; RBC Capital Markets; SVB Leerink; SunTrust Banks Inc.

TRILLIUM THERAPEUTICS INC.

Immuno-oncology firm **Trillium Therapeutics Inc.** netted $110m through a public offering of common and preferred shares. The company sold 41.3 million common (including the overallotment) at $2.75 and also issued 1.25 million series II non-voting convertible first preferred shares at $2.75. Proceeds will support development of the company's CD47 programs including TTI621 in patients with B- and T-cell lymphomas and other blood cancers, and TTI662 for lymphoma and myeloma. (Jan.)

Investment Banks/Advisors: Bloom Burton & Co.; Cowen & Co. LLC

XENON PHARMACEUTICALS INC.

CNS-focused **Xenon Pharmaceuticals Inc.** (small-molecule ion channel drug development) netted $56.4m through the public offering of 3.75 million shares at $16. The company will use the proceeds to support clinical development related to Kv7 potassium channel modulators XEN1101 (Phase IIb for epilepsy) and XEN496 (ezogabine; in preclinical studies for KCNQ2 epileptic encephalopathy in pediatric patients) and Cav2.1 calcium channel modulator XEN007 (flunarizine; in Phase II for epilepsy and preclinical development for hemiplegic migraine and alternating hemiplegia, orphan CNS conditions); fund discovery activities; and potentially expand its business through the in-licensing or acquiring of candidates, products, or companies. (Jan.)

Investment Banks/Advisors: Guggenheim Partners LLC; Jefferies & Co. Inc.; Stifel Nicolaus & Co. Inc.

ZYMEWORKS INC.

Zymeworks Inc. (multifunctional biologics for cancer) netted $301.6m through a public offering of 5.8 million common shares (including the overallotment) at $46.50 and 1.07 million pre-funded warrants priced at $46.4999. Funds are earmarked for continued development of ZW25 as a single agent and combination therapy for HER2-expression tumors including gastroesophageal, biliary tract, breast, and others, and will also support work on ZW49 for locally advanced or metastatic HER2-expressing cancers that have progressed following treatment with existing approved therapies. (Jan.)

Investment Banks/Advisors: Citigroup Inc.; JP Morgan Chase & Co.; Raymond James & Associates Inc.; Stifel Nicolaus & Co. Inc.; Wells Fargo Securities LLC

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Phil Jarvis

EDITORIAL OFFICE
605 Third Avenue, Floor 20-22
New York, NY 10158
invivo.pharmaintelligence.informa.com

CUSTOMER SERVICE
clientservices@pharma.informa.com

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US Toll-Free: +1 888 670 8900 | US Toll: +1 908 547 2200 | UK & Europe: +44 (20) 337 73737

Australia: +61 2 8705 6907 | Japan: +81 3 6273 4260

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