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DIGITAL HEALTH

Leveraging data to power and personalize the patient experience

Will Advanced Technology Simulations Lead To More And Better Drugs? Start-Up Schrodinger Says It Can.

Data And The Digital Horizon: Perspective From The Agency C-Suite.

Digital And Connected Care Are Pushing On An Open Door – But Is Medtech Ready?

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THE DIGITAL HEALTH ISSUE

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DEPARTMENTS

EXCLUSIVE ONLINE CONTENT

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From The Editor

DENISE PETERSON

Development of digital health technologies has drawn more than $1 billion in private sector investment worldwide over the past five years, according to an analysis by *In Vivo*'s John Hodgson.

But despite this impressive figure, an EY executive survey reveals life sciences execs are taking a measured approach to the opportunities promised. While they foresee digital as being more disruptive to their sector compared to execs in other industries, life sciences management teams intend to allocate relatively less of their budgeted acquisition capital to digital and expect fewer of their M&A transactions in the next two years will be digital related, EY's Arda Ural reports.

This month, *In Vivo* takes a step back from the buzzwords and brouhaha to look more closely at digital health, including where the true transformations may soon start to be delivered and where biopharma and medtech companies are just starting to "scratch the surface" of the possibilities. We look at how digital technologies are being employed in every stage of biopharma, from the use of computational chemical simulation software to enhance drug discovery to the use of digitally obtained insights and connections to enhance post-marketing engagement with patients, providers and patients.

As always, we bring you perspectives from thought leaders and key discussion forums. For example, Bill Looney interviews Christina Kim, SVP for data solutions at Omnicom Health, for a wide-ranging Q&A on topics including how digital is delivering insights on customer motivation. Ashley Yeo takes the pulse of medtech in conversations with leaders at several industry conferences. While some remain wary, Yeo finds an emerging viewpoint that companies soon will be unable to take an "either/or" approach to digital strategy, but rather must decide "when" – when to jump in fully or perhaps get left behind.

To help readers delve deeply and thoughtfully into current trends and turning points, we plan three additional theme issues this year. Upcoming issues will center on clinical trials (May), drug delivery (September) and market access (November). I invite you to connect with us directly if you have ideas or questions you'd like us to tackle in these theme issues, or more generally in *In Vivo*. I can be reached at denise.peterson@informa.com

For now, we join leaders at the Medtech Europe's Forum in asking whether digital health's "big moment" has arrived. Turn the page and start deciding for yourself.

Up-Front

SNAPSHOTS FROM MARCH'S CONTENT

Schrodinger's computational software is used by researchers in 70 countries, with a customer base of more than 400 commercial enterprises, including the 30 largest big pharma, as well as 1,500 government and academic institutions. Page 12

UK&I Solutions Lead Stephen McMillan says that while industry is doing a very good job of digitizing particular modalities, in imaging, say, and is "at the forefront of something enormous with digital genomics and pathology," it is not yet doing a very good job of connecting these digitized diagnostics by joining up information and getting meaningful use out of it. "Using AI and presenting the results back to clinicians in such a way that they can make decisions from it remains a technology challenge at the end of the day." Page 18

The impending next wave of mobile technology or 5G capability will allow for much more efficient and prompt device-to-device communication, thus making the medical Internet of Things an operational reality. In the upcoming decade, the medical device industry will be differentiated largely by consolidating mIoT into its product design. Page 4

Despite hurdles, some winners in the digital and connected health landscape are starting to emerge. They are able to show significant health outcomes and garner the attention of the payer and provider communities. Reimbursement seems possible, as payments will follow the data and the evidence that comes with it.
See http://bit.ly/2DID1S3

"Digital is only a tool – a means to an end. The client needs to identify that end in advance: what do you want to achieve? The wrong approach is to throw a lot of technology out there and hope it will cover all the options," says Omnicom's Christina Kim. Page 24

Around The Industry

Digital Deals And Life Sciences: Avoiding Death By A Thousand Pilots

For some years now, the application of digital technology in health care has promised to advance patient-focused outcomes to reduce costs across a very fragmented ecosystem. To their credit, life sciences companies have made investments in this area, to some success. But they have yet to move beyond pills and apps at the pilot stage to fully embrace a business model geared to an at-scale state of convergence between health care and digital. Instead, life sciences companies have largely opted to acquire or partner with technology innovators for point solutions.

EY's 2018 Digital Deal Economy Study surveyed 900 global executives, including more than 70 in life sciences. Its findings portray how digital technology increasingly drives the strategy behind biopharma deal-making activity. Several observations emerged, demonstrating the role digital is playing to meet competitive challenges in this highly regulated, competitive and fragmented industry.

Beset by rising costs and administrative inefficiencies, patients and payers are demanding action from the health care industry. Over the past 10 years, digital technologies have enabled the gathering and exchange of massive amounts of health-related data to address previously unanswerable questions along with targeted and timely services at the personal-care level. These new capabilities are attracting the interest of a number of big pharma players. In February, **Roche** doubled down on its investment in precision medicine following its investment in **Foundation Medicine Inc.** in 2015 by acquiring **Flatiron Health Inc.** for $1.9 billion. (*Also see "Deal Watch: Roche Goes All-In On Real-World Data With Flatiron Acquisition" - Scrip, February 19, 2018.*) The acquisition of this oncology focused electronic health record (EHR) company gives Roche access to real-word evidence (RWE) data it hopes to use to inform better clinical trial design and outcomes, cementing its place as a leader in oncology therapeutics.

Other large pharma companies are turning to digital start-ups looking to upend traditional therapeutic approaches, evidenced by **Novartis AG**'s recent digital medicine partnership deal with **Pear Therapeutics Inc.** to develop new mobile apps that provide FDA-approved interactive digital programs for patients with schizophrenia and multiple sclerosis. (*Also see "Novartis Teams With Pear Therapeutics In Neurological Digital Health Pact" - Scrip, March 1, 2018.*) The recent announcement of an alliance between an online retailer, an insurance conglomerate and an investment bank also has a disruptive potential to the complex and fragmented health care ecosystem. (*Also see "Mysterious Amazon/Berkshire/JPMorgan Partnership Could Disrupt Health Care, Pharma" - Scrip, January 30, 2018.*)

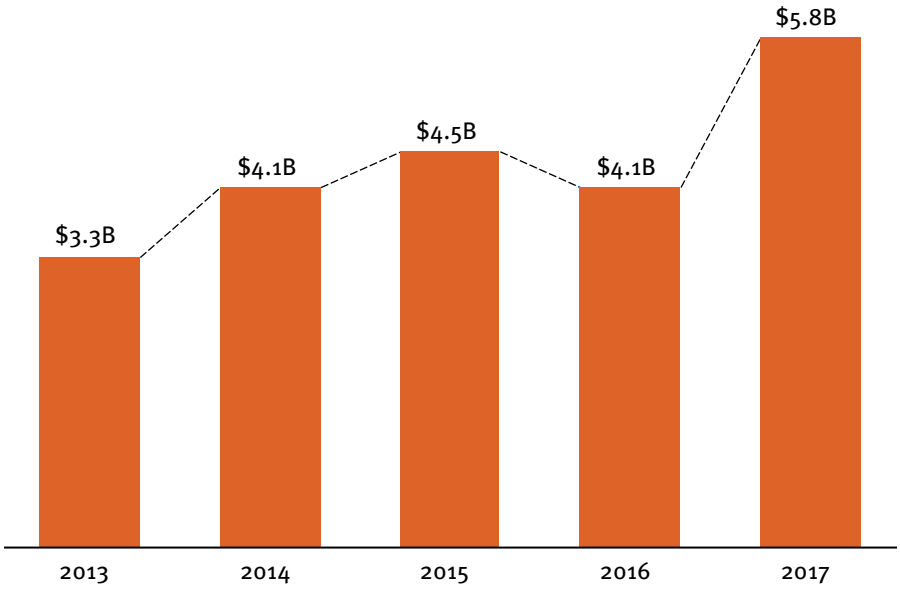
Two major strategic questions emerged from our survey, as follows:

Where does the life sciences industry need to focus to benefit from the convergence of health care, digital and services?

Having tried brand-focused point solutions, life sciences executives should consider platform strategies that would embed their digitally enabled therapeutic solutions into today's value-driven ecosystem. This may include complementary services powered by data and analytics, as well as partnerships with other players, such as risk-bearing providers and payers. The industry can leverage its implicit firepower to design business models in which all parties win, including patients. Using

Exhibit 1

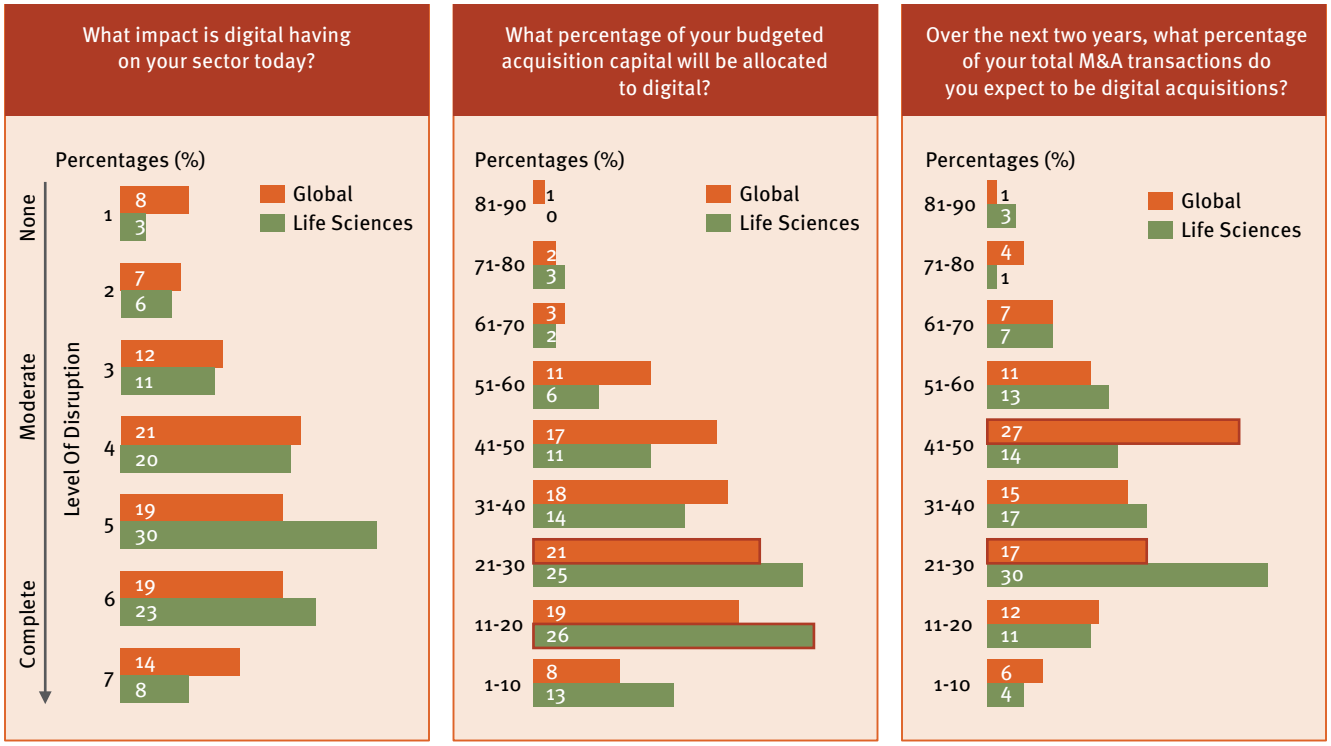
Digital Health Venture Funding (2013-17)



SOURCES: Rock Health and EY analysis

Exhibit 2

Industry Views On Capital Allocation And Digital M&A



SOURCE: EY Digital Deal Economy Survey

acquisitions, joint ventures and other risk-sharing partnerships with health care technology players can generate a differentiated market position and help redefine life sciences companies' role in the new health care ecosystem. This may position them as solution providers and thus change the perception of such firms from being contributors to health care costs to being essential players in helping deliver improved health outcomes.

EY's Digital Deal Economy survey findings also reported that more than 60% of life sciences companies expect to look externally, through M&A, outsourcing, alliances and joint ventures to drive their digital strategy. Digital health venture funding has continued to grow at a CAGR of 15% over the last five years to $5.8 billion in 2017, according to Rock Health and EY analysis. (*See Exhibit 1.*) In comparison the life sciences M&A for therapeutic assets totaled $200 billion, other analyses found. Fueled with the provisions of the tax reform, such as the lowered corporate tax rate on earnings and ability for a one-time offshore repatriation in 2018, life sciences companies are expected to pursue deals at a higher rate. This war chest will allow them to bet increasingly on digital technology strategies, seek scale to combat payer pressure and customer consolidation in a fragmented landscape, and pilot new value-driven business models.

> Life sciences companies plan to allocate relatively less of their acquisition capital to digital and expect fewer digital M&A transactions in the next two years.

Yet, ever-increasing valuations will require a rigorous strategic and financial rationale, reinforcing the need for life sciences companies to deploy their corporate development deal savvy toward digital assets. Projecting from the statistics about participation in the *Healthcare Information and Management Systems Society (HMSS) 2018 Annual Convention* (reported by Mark Anderson in GLG Conference on HIMSS 2018 Outlook: Trends to Watch), we expect the funding to continue to flow to primarily six areas: (1) analytics and big data, (2) health care consumer experience, (3) digital medical devices, (4) telemedicine, (5) personalized medicine, and (6) population health management.

We also expect this trend to accelerate with the impending next wave of mobile technology or 5G capability to allow for much more efficient and prompt device-to-device communication, thus making the medical Internet of Things (mIoT) an operational reality. In the upcoming decade, the medical device industry will be differentiated largely by consolidating mIoT into its product design.

Life sciences companies can leverage this transformative health care technology wave by creating interconnected ecosystems and exploring promising

technology assets from a pool of thousands as a source of growth and innovation to insert their products and solutions into the value chain. They can then integrate digital health care technology to augment an existing product's revenue, or bring in health care technology-enabled services to supplement the market position of a traditional pharma or medical device product.

How are life sciences companies deploying capital strategies and M&A to further digital transformation today?

Herein lies the dilemma. Although life sciences companies view digital as being more disruptive to their sector than their peers in other industries, life sciences companies plan to allocate relatively less of their budgeted acquisition capital to digital and consequently expect fewer of their M&A transitions in the next two years will be digital related. (*See Exhibit 2.*)

Relative to peers in other industries, life sciences respondents consider their customer-facing digital capabilities in digital customer experience, mobile application, Internet of Things and advanced analytics as market leading. However, fewer life sciences companies generally view their applications of digital to talent and skills, sales and marketing, manufacturing, back office, and automation and robotics as market leading relative to their peers in other industries.

The life sciences industry is in a period of experimentation and is willing to make one-off bets on at-scale assets to help embed these capabilities into its therapeutic business models. Those life sciences companies that apply their M&A skills to the digital space will gain even more through greater operational agility and competitiveness as they seek market-disrupting opportunities.

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The views reflected in this article are the views of the author and do not necessarily reflect the views of the global EY organization or its member firms.

Digital's Big Moment Has Arrived Say CEOs At Medtech Europe Panel

Digital technologies, artificial intelligence and value-based healthcare both create opportunities to improve health care delivery and affordability, and also provide the tools to make those positive changes happen. These were absorbing themes for the record number of medtech industry attendees at the Medtech Europe Forum 2018, convened January 23-25 in Brussels, Belgium.

Connected care is no longer the future, according to a panel of CEOs comprising Siemens Healthineers' Bernd Montag, AdvaMed Chairman and **CVRx Inc.** President and CEO Nadim Yared and former **bioMerieux SA** President and CEO Jean-Luc Bélingard: it is the present. Fast- and future-thinking players are already factoring this long-awaited efficiency tool into their business strategies.

For "digital" is a method, a means to an end – the facilitator of cheaper, faster, more reliable health care. That was the essence of Bernd Montag's comments to the Medtech Forum. The event convened this year in Brussels once more, but next year moves to Paris to entice more input from the vibrant local medtech community and thereafter to Germany.

Montag of course has much on his mind besides digital strategies and macro industry trends: Siemens Healthineers AG announced its keenly anticipated IPO in mid-February, which the CEO described as an opportunity to create a dedicated pure play in medical imaging and diagnostics. (The shares were listed in Frankfurt on March 16 at an initial price of €28 per share - valuing its equity at €28 billion and yielding gross proceeds of €4.2 billion – $5.2 billion). But globally, he identifies three overriding medtech trends.

> "We need to think differently – the winners will be those who can adapt; the losers will be those clinging to old models."
>
> – CVRx President and CEO Nadim Yared

One is the rise of personalized medicine, where there has been a switch from talking and concepts to reality. Another is consolidation among providers, as the logic of health care delivery changes. "We are looking now at the overall picture as we move from fee-for-service to value-based health care," Montag told the MTF audience. This has everything to do with the rising power and influence of the patient as a consumer of health care – providers have reacted and "are really putting this on their agenda now."

And underlying it all is digital and AI, and the past year was *the* "big moment" when these tools became the main event, says Montag. CVRx's Nadim Yared agrees, believing that "we are only just scratching the surface" of the potential of the Internet of Things. Devices in the future will all

"We are still not forward-looking enough, and there should be more spent on prevention."

– Siemens Healthineers CEO Bernd Montag

have some form of connectedness, says Yared, who is mid-way through a two-year term as AdvaMed chairman. Today connected health care technologies are outside the body, but eventually they will also move inside the body, he believes.

One key advantage that digital will bring to researchers and clinicians is the ability to "make sense out of biological complexity with data analytics." So says Jean-Luc Bélingard, who believes that the sector is undergoing change that goes beyond merely the impact of digital. He says the future of health care will be "transversal," where medtech will be combined with other elements of health care in the drive toward patient centricity. Bélingard stepped down from the BioMerieux in December 2017.

"Planning for the future is probably the most difficult job role right now," he says, an assertion that will do little to comfort those traditional medtechs yet to devise a digital strategy. These are precisely the organizations that risk missing the boat. (*Also see "Winners Are Beginning To Emerge In Digital Health – But Without Planning Medtechs Risk Missing The Boat" - In Vivo, March 2018.*)

One of our duties is to make sense out of the data, says Bélingard. It needs to be brought together, and the industry has initiatives to do just that, but this is a delicate issue, because once companies start talking to patients on data harvesting, this can prompt the regulators to start stepping in. Montag agrees. Healthineers is striving to be "more relevant" when it comes to clinical decision-making. Some 240,000 patients every hour come into contact with Siemens systems, he says, and in the past, there had been "no learning" from these interactions and decisions. While that's probably overstating it a little, the difference now is that the data can be turned into knowledge, which is the core of what Montag says Siemens is aiming for.

But this is not a revolution that can be carried by industry alone. Other stakeholders need to be brought along too. "Are we prepared?" asks Yared, answering his own question in the negative, but adding quickly that the sector is making steps in the right direction. New players like Google and IBM Watson are also showing the value of data generated by biomedical devices, but there is an education piece to maintain, especially regarding politicians in the US and elsewhere.

THE EDUCATION PIECE – VITAL FOR DIGITAL AND MEDTECH THEMES ACROSS THE BOARD

Which is not to say that it's a thankless or fruitless task. Far from it. Yared recalls for the MTF audience the original meeting some four and a half years ago between AdvaMed and US members of Congress that in April 2014 led the then-House Energy and Commerce Committee Chairman Fred Upton (R-MI) to announce the launch of the 21st Century Cures Act. This is proof, were it needed, of the value of lobbying and education and medical breakthroughs; and meetings like MTF and AdvaMed are useful in getting policymakers on board.

Industry fears competition still, and naturally so, but there is a greater need for collaborations and partnerships, says Yared. And this is happening at the highest level. The FDA is becoming more collaborative with companies, simplifying processes and reducing the timelines. Bélingard agrees, adding, "The FDA comes to us to ask us about data analytics." Europe, sadly, appears to be going in the opposite direction and adding layers of complexity. Where can that lead? Yared notes that the FDA is now aiming for first-in-man studies to be done in the US, which used to be the province of Europe. Where the US gets pressure from industry groups, the EU gets pressure from politicians, Yared suggests. "I'm very worried about what is going on in Europe," he confided to the Brussels audience.

PRICING, GETTING PAID AND INVESTMENT

The pressure in fact comes from all sides. While the public debate on health care cost often defaults to pharma pricing, it has not gone unnoticed that medtech prices have been rising below inflation in recent years. Thus, the industry is losing ground, even though it re-invents products, incrementally, at least, every 2.5 years on average. "Prices are going down but we get the same amount of pressure from the public as does pharma, where prices are rising 9% year-on-year," claims the AdvaMed chairman.

More strategically, the medtech industry sees the need ultimately for a change in the way technologies are paid for in the future. Pricing depends to a large extent on the prevailing health care structures, but who pays over the longer term? "We need to think differently – the winners will be those who can adapt; the losers will be those clinging to old models," says Yared.

But it's not quite happening yet, not in the US at least. Montag notes that there has *not yet* been a fundamental shift in US decision-making. But Siemens Healthineers, a company where 55% of the revenues come through services and reagent sales, has an insurance against the vagaries of pricing and the investment climate. "There is procedure growth and typically, we are not in a pricing discussion," he asserts, even if SMEs and small companies would disagree.

In the discussion on the affordability of value-based health care, IVD tools, which optimize the notion of cost-effective care, says Bélingard. "It very important that we position our industry as one that is affordable, and we need to think of both value and cost." Pricing is structural, and pricing will go down further in medtech, he forecasts. Industry should be ready for pressure on pricing in the US as well, he warns. A new approach is needed. The perception is that the industry typically sets a price and adds to the cost to the health care system. Instead, it should get ahead of the game, talk to the authorities about pipeline needs and address the demand

side in ways that have never been done before. "It needs to be tested at least."

Montag echoes the sentiment. "We do need to look at how money is spent in health care. We are still not forward-looking enough, and there should be more spent on prevention. More pathology tests will lead to more imaging and the ability to get the right diagnosis, at the right time, at the right place."

HEALTH CARE NEEDS MORE MEDTECH, NOT LESS

Technology is increasingly sophisticated, and medtech research is aimed at the continual improvement of treatment, but the fact is that health care needs more medtech, not less, says Montag. It has so many fundamentals – emerging economies' demand, demographic change, growing knowledge and power of the customer base – that make for an attractive industry and an investment opportunity. But views on investment trends differ, depending on where a company sits in the wider industry.

Siemens Healthineers' CEO does not think that medtech is being left behind in investment trend comparisons with other industries. But the CVRx boss has a different take. Yared's company is still in the start-up and investment phase. CVRx manufactures implantables to treat high blood pressure and heart failure and is said to be a top-five medtech company in terms of VC raised. (*Also see "CVRx Funding Boost Will Sustain Barostim Heart Failure Device To US Launch" - In Vivo, September 2016.*) But funding for the wider medtech start-up ecosystem, as different from large cap investment, has not been very good for several years.

Smaller entities often need 12 years before reaching liquidity, hence a VC investment for any shorter period "does not add up." The cost of creating a start-up, from inception to IPO or to exit, as measured by the venture investment that needs to be made in these companies, has risen from $32 million in 2004 to $74 million in 2014 (*see box*). Compared to 10 years ago, there are a quarter of the number of medtech companies being set up today.

But this should be seen as an opportunity, for now is a good time to come into medtech, says Yared. "We as an industry are still undervalued and we are living in exciting days." And in the transition to digital, the industry is barely scratching the surface. There is all to play for as the medtech industry continues to evolve.

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ASHLEY YEO

COST FROM INCEPTION TO EXIT

The rise in costs to fund a medtech company's lifecycle from inception to IPO or exit over the past 10 to 15 years have been driven by:

- demand for larger clinical trials,
- lengthier duration of regulatory and reimbursement pathways,
- "frothiness" of consolidators to acquire businesses earlier (many acquirers are requiring small companies to prove the adoption of a novel technology, which entails the small firm investing in distribution channels and manufacturing before being acquired), and
- the slow to non-existent IPO market for pre-revenue companies.

SOURCE: CVRx President and CEO Nadim Yared

DEALS OF THE MONTH

In Vivo's editors pick February's top alliance, financing and M&A deals.

TOP ALLIANCE:

Gilead/Kite Licenses Sangamo's Gene Editing Technology

Gilead Sciences Inc. will pay up to $3.16 billion for exclusive rights to gene editing pioneer **Sangamo Therapeutics Inc.**'s zinc finger nuclease technology to help its **Kite Pharma Inc.** subsidiary create better T cell therapies for cancer. In seeking a partner, Gilead eschewed newer gene editing plays, describing Sangamo's ZFN technology as "the optimal gene editing platform." The partners have identified some initial oncology targets for specific therapeutic programs and will also attempt to develop CAR-T therapies for solid tumors.

TOP FINANCING:

Moderna Raises Another Big, Private Round

mRNA drug developer **Moderna Therapeutics LLC** added $500 million to its already-full coffers in early February. New investors Abu Dhabi Investment Authority, BB Biotech, Julius Baer, Singapore-based EDBI and Sequoia Capital China joined existing investors Fidelity Management & Research, Pictet, Viking Global Investors, ArrowMark Partners and Alexandria Venture Investments. The funds will support Moderna's 19 development programs; discovery for prophylactic vaccines and therapeutics for rare diseases; plus, its technology platform infrastructure.

TOP M&A:

Roche Acquires RWE With Flatiron Buy

Roche agreed to acquire all outstanding shares of **Flatiron Health Inc.** for $1.9 billion in cash. The acquisition stems from an existing partnership – Roche previously held a 12.6% equity interest in Flatiron, which operates as a technology platform providing oncology-specific electronic health record software and a suite of software products for advancing real-world evidence of cancer research. The deal is structured so that Flatiron will continue to operate autonomously and it will maintain its network of partnerships.

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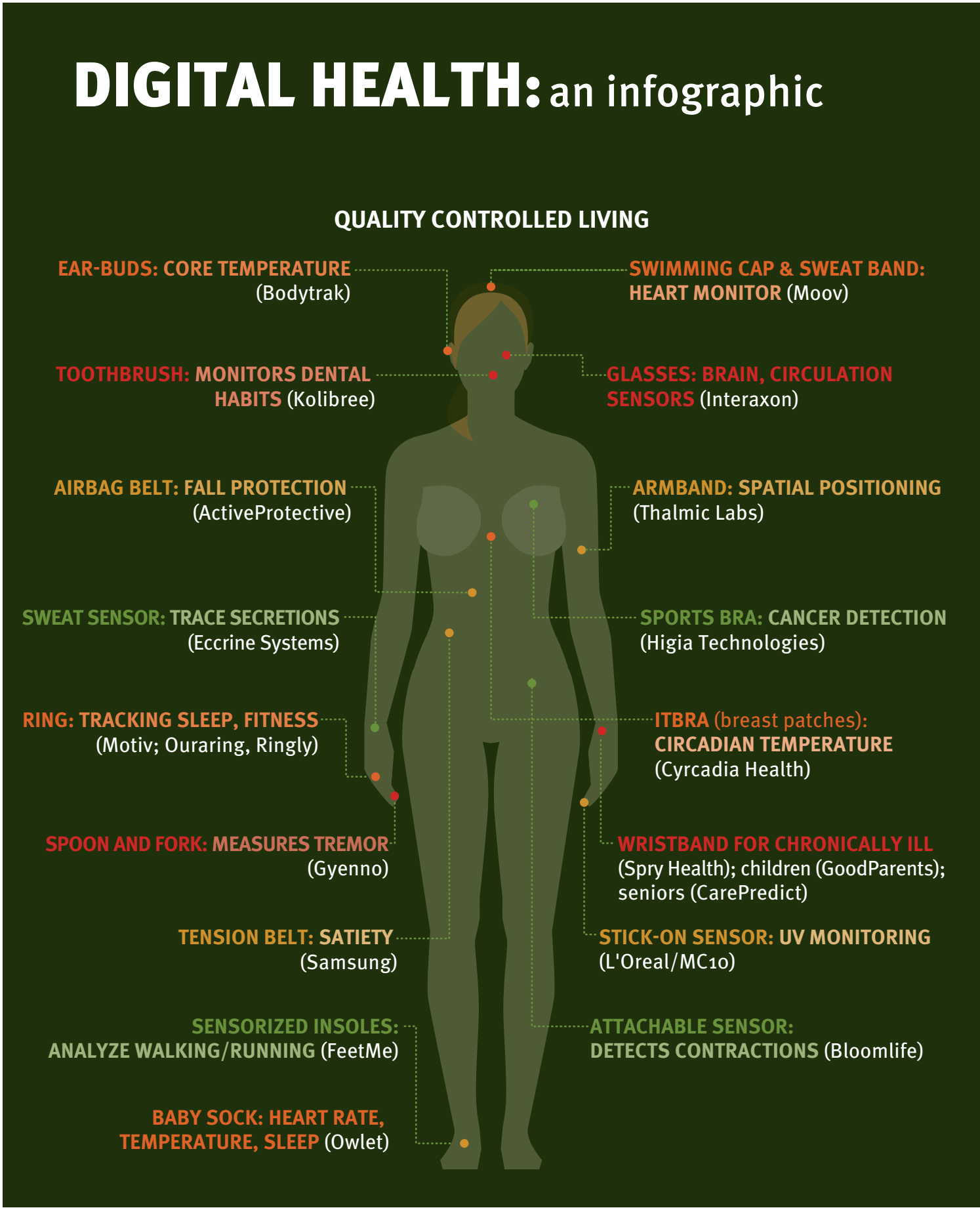
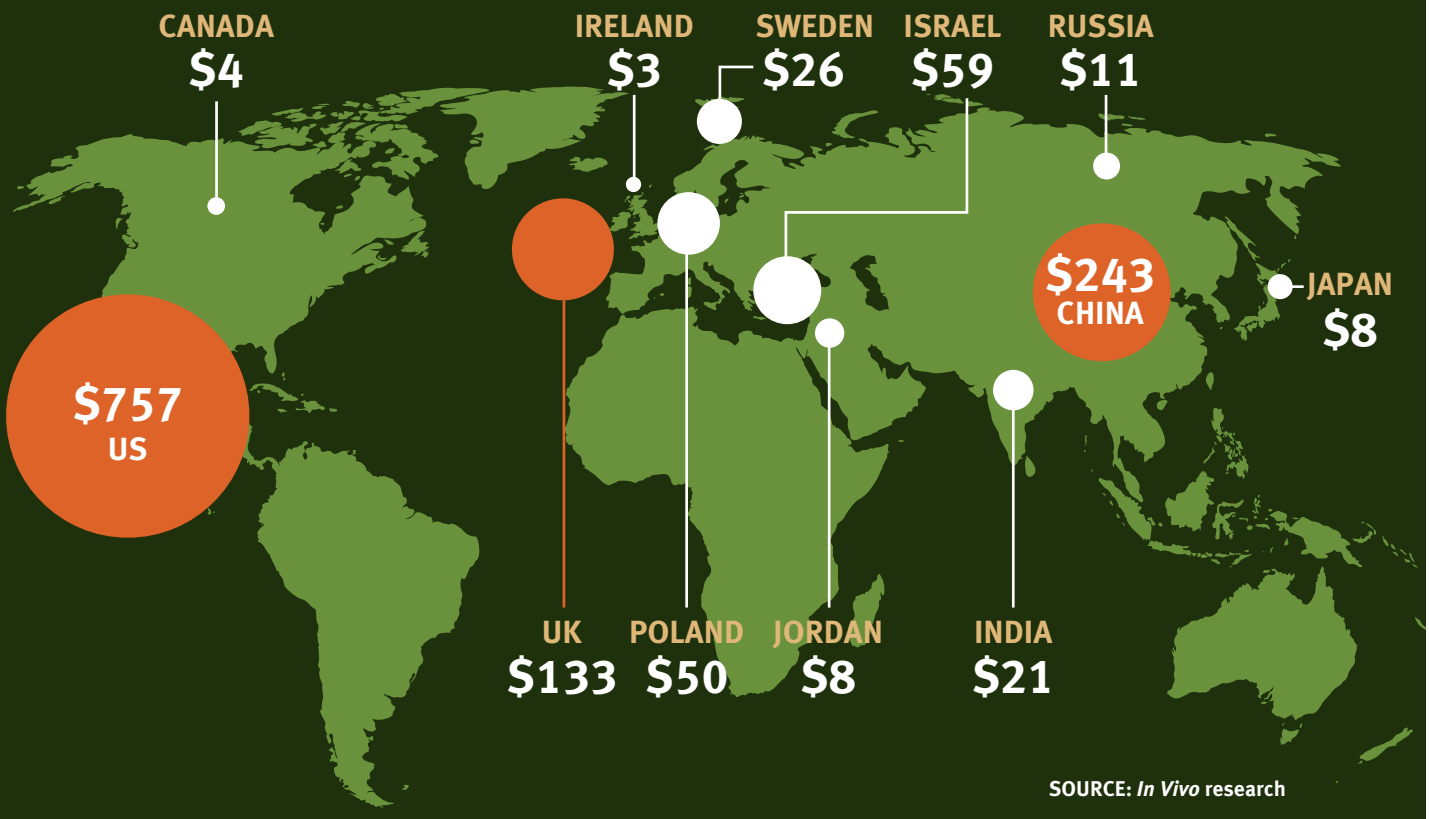
DIGITAL HEALTH: an infographic



15 CONNECTED DEVICES

- **Blister pack** - Janssen R&D
- **Blood pressure cuff** - iHealth Lab
- **Cardiac monitor** - Abbott Laboratories
- **ECG/stethoscope** - Eko Devices
- **Electrocardiogram** - AliveCor
- **Electronic muscle stimulation** - Powerdot
- **Fetal monitor** - Bloomlife
- **Glucose meter** - DarioHealth
- **Infectious disease** via microfluidic chip
- **Peak flow meter** - AsthmaMD
- **Spectrometer** - Hainan University, China
- **Spirometer** - Pond Healthcare Innovation
- **Stethoscope** - Eko Devices
- **Thermometer** - Kinsa
- **Toothbrush** - Kolibree

VC RAISED (MILLIONS, 2016-2017) BY COMPANIES CONNECTING PATIENTS TO DOCTORS



SOURCE: *In Vivo* research

Gayle Rembold Furbert

Will Advanced Technology Simulations Lead To More And Better Drugs? **Start-Up Schrodinger Says It Can**

Shutterstock: Egorov Artem

Schrodinger LLC is a leading player in the emerging high-stakes field of computational chemical simulation software to boost the quality and productivity of drug discovery and lead generation. Its business model relies heavily on validating theoretical concepts of science and engineering in real-world settings through partnerships with a blue-chip list of pharma and biotech companies.

BY WILLIAM LOONEY

Today, the company's software is used in more than 70 countries by more than 400 businesses, including the top 30 big pharma, as well as 1,500 academic and public institutions. A major growth segment is the equity stakes Schrodinger has taken in successful start-up biotechs.

So what? The saga of this 28-year-old company highlights key strategic issues vital to the future of biopharma: maximizing learnings from diverse scientific disciplines; tapping into the "force multiplying" value of foundational research, especially from academia; and innovating around advanced, complex technologies to solve one of the hardest – and most fundamental – problems of science: how does nature use physics to make biology?

One of the big mysteries of modern science is how molecules and proteins interact to establish the biological origins of health and disease. Rearranging this complex repetitive cycle of molecular binds and lapses to yield a positive change in the topography of illness is – unfortunately – an exercise in statistical improvisation. The possible combinations to yield a single molecule with drug-like properties against a pathogenic target is estimated at 10 to the 50th power, a number so large it comes close to what mathematics defines as infinity. Yet, to date, drug discovery in biopharma relies on a grain-in-the-sand calculus of potential, with the average new drug emerging from a screening process involving a little more than 5,000 molecular/protein targets. Industry's prevailing discovery protocol is one of trial and error within an absurdly small field of possibilities, resulting in wide variations in pharmacological effect among individual patients and often quite modest therapeutic improvements overall.

It is no surprise that key stakeholders in biopharma – academia, regulators, patients and industry itself – are united in asking the question: can't we do better?

Like much of what happens in the disconnected worlds of health care, the answer to the question may lie in technology applications that have been percolating outside the scientific mainstream for decades. It took two leading academics from different disciplines – Richard Friesner, a chemistry PhD and professor at Columbia University and William (Bill) Goddard, a physicist and materials scientist PhD from Cal Tech – to identify how advances in structural biology and insights on the physical properties of living matter could be combined with the growth in computing power to make drug

discovery more productive and efficient. The premise was simple: to apply *in silico* simulations to investigate and model millions of combinations of disease-linked molecules and proteins that have been difficult to target with traditional chemistry.

In spite of their backgrounds in basic research, Friesner and Goddard saw the commercial potential in an automated virtual alternative to trial-and-error experimentation in the lab, using computer processing to impose some rigor on a constrained, costly and time-consuming slog. In 1990, the two decided to form a private company to develop and market computer software technology on chemical simulation, drug modeling and design, and materials management, with an emphasis on lead discovery and optimization. To emphasize their commitment to the physical sciences and basic research, the two named their company after the Austrian physicist Erwin Schrodinger, who won a Nobel Prize in 1933 for his work on quantum mechanics. It was the basis for the company's first marketed product, *Jaguar*, a computing software tool that integrates the physicist's landmark work in quantum equations to boost processing power for *in silico* simulations.

Nearly 30 years later, **Schrodinger LLC** has surfed the wave of progress in computational methods for drug discovery to become a leading global producer of software that helps drug investigators simulate and predict the optimal pathways to a new drug – one with a higher statistical probability of working against the specific disease it was designed for. Schrodinger software is used by researchers in 70 countries, with a customer base of more than 400 commercial enterprises, including the 30 largest big pharma, as well as 1,500 government and academic institutions. From only 30 employees as recently as 2002, Schrodinger today employs nearly 400 scientists, material engineers and other PhDs, including 30 in Europe, 30 in India, eight in Japan and a few more in several other countries outside the US home base.

Still privately held, the company received its initial funding from two highly motivated billionaires: David E. Shaw, a PhD polymath in computer science and biology, who in the 1980s launched a hedge fund focused on the then-emerging field of computational finance and now leads an independent research enterprise devoted to solving problems in drug design and lead optimization; and Microsoft founder Bill Gates, who has invested $50 million in Schrodinger through his personal investment company, Cascade Investments LLC. To facilitate closer ties to customers, Schrodinger is partnering with a diverse range of enterprises: blue-chip drug companies like Johnson & Johnson's **Janssen Pharmaceutical Cos., Sanofi, Pfizer Inc., Merck & Co., AbbVie Inc., GlaxoSmithKline PLC, Takeda Pharmaceutical Co. Ltd.** and **Ono Pharmaceutical Co. Ltd.**; technology leaders, including Amazon Web Services and Cycle Computing; academic institutions, of which Shanghai Tech University is a most recent example; and more than a dozen early-stage VC investors such as Canada's MaRS Innovation, which also happens to be a non-profit.

"There is a very significant basic research component to this business. We are not a big data informatics enterprise. Nor do we inhabit the over-hyped world of artificial intelligence and its possibilities in large-scale pattern recognition."

– CEO Ramy Farid

Schrodinger is rooted in the personalities and vision of its two founders – contrarians motivated mainly by a desire to address a big but simple question that has preoccupied science for the last century: how does nature use physics to make biology? The company is not afraid to stress its prevailing interest in what some commercial observers consider to be an overtly academic inquiry. Considerable financial risks have been taken in tackling a conceptual question for which there was no ready answer.

In an interview with *In Vivo*, Schrodinger CEO Ramy Farid, who joined the company in 2002, described a distinctive business culture centered on three pillars: (1) to tackle the hard problems in drug design by focusing on the physics of how things work in the human body – basic, "first principles" research, not necessarily driven by data, on the underlying biological determinants of disease; (2) to invest human and financial capital across disciplines, and for the long term; and (3) to build products that first have to work for Schrodinger, the inventor, before being sold as a solution for the end user, the customer. He continued, "A lesson we learned early is that a theoretical understanding of how our software performed did not survive the pressure test that

comes when exposed to the actual conditions of drug discovery. We realized the starting point for a viable business was getting the software to work in our own projects. It ended up making us a better software developer because we had to test that pressure prospectively, rather than after launching to the market, when a poor response would have doomed the novel technology behind it."

First, however, the company had to tackle the fundamentals. Says Farid, "There is a very significant basic research component to this business. We are not a big data informatics enterprise. Nor do we inhabit the over-hyped world of artificial intelligence and its possibilities in large-scale pattern recognition – a concept of little practical use in drug discovery, where every complex composition of atoms, proteins and molecular binds in its own way. Finding patterns isn't relevant; compound screening with traditional chemistry shows us that – it's wrong more than 90% of the time. What's needed instead is an understanding of how the laws of physics energize and drive these interactions and then to apply those first principles to model different ways these interactions might play out. Software-based simulations programmed to incorporate these first principles of energetics and run them through amped-up computer processing systems can pare down the complexity – and establish leads that might eventually produce a drug, at a lower cost.

Farid also sees no daylight between basic science and profit. "The scientific method – the theory, if you will – can, when we understand it, unlock enormous business potential against what is obviously a real unmet medical need." Surprisingly, for a commercial business, Schrodinger has sought credibility in research by encouraging professional staff to publish in peer-reviewed academic journals. Some 40 patents have been awarded or are pending to Schrodinger scientists.

"Time equals cost" is a driver of Schrodinger's software value proposition, where computer power allows for run-throughs in a matter of hours, as opposed to weeks or even months. Another, even more important attribute is the ability to probe deeper into the spaces where proteins and molecules merge and diverge, providing in turn potentially useful insights into the robustness of their chemical properties. It means the molecules that come out of this process represent improvements over molecules developed with the most advanced contemporary techniques like high-throughput screening.

"You can argue that every drug on the market today is by sheer force of numbers not the best agent against its targeted condition," Farid asserts. "When you take that molecular structure and its component parts of carbon, nitrogen, oxygen and hydrogen, then the possible combinations against a single disease target run close to infinity. Given that a current drug emerges from a surveyed average of only 5,000 different candidate molecules, then it's guaranteed there is something out there more efficacious and less toxic. We have models right now that can sift through billions, even trillions of molecular targets, with higher numbers still to come. The potential for more and better drugs that really work for patients is inherent in these new tools."

One thing Farid and Schrodinger strive to make clear is the company's technology is far more complex than current, hot-button tools like AI. "AI relies heavily on algorithms – which are relatively simple, ubiquitous and open-sourced. That emphatically is not what we do."

However, all this hard-won learning has added years to the point where advocates of *in silico* discovery and lead optimization were ready to deliver on what had been promised. Getting the physics right – to simulate accurately the binding of a molecule to a protein – took some 25 years of debate and controversy to achieve. And there were numerous false starts, especially after management realized that there was no other choice but to make the leap from theory to practice, by applying the company's simulation technology to prove it would increase discovery and lead optimization targets against real-live disease states. Once it did that, the plan was to double down on investing in start-up commercial companies, where Schrodinger products would drive the pipeline and create that essential tie-in to later-stage clinical and market success.

"When you don't know the answers in advance, you can't cheat," is how Farid describes the company's dilemma during its formative years. "A lot of good people concluded that simulating accurately the binding of a molecule to a protein was just too hard and left the field." As the proponent of a new and disruptive technology, Schrodinger also has had to confront opposition from biopharma's R&D establishment, representing multiple generations of chemists used to doing drug discovery the traditional way. Resistance has faded as the Schrodinger model has proved its mettle, but it still exists. "It's very difficult for a software company to convince a big pharmaceutical company to abandon the institutional status quo in drug discovery. We had to create a track record. To start by doing it ourselves."

A Series Of Product Breakthroughs

Schrodinger's first breakthrough product was a modeling tool to predict how the thermodynamics of water molecules can influence how strongly drug candidates bind to their intended target – a key quality measure, as the less stable the water molecule is, the more likely a drug candidate will be therapeutically effective. This was followed by a major computational advance in docking and scoring, where Schrodinger scientist developed a mathematically based processing tool to "dock" and then "score" millions of potential binds between a receptor molecule and a complementing ligand against a particular target. It proved a landmark in establishing a narrowly focused, structure-based approach to lead generation – a departure from hit-or-miss screening, with a positive impact on both time and money spent.

But the most important product breakthrough occurred in the application of physics-based free energy methods as an enhancement against current states of practice like high-throughput screening, and to provide useful, high-volume simulated comparisons against *in vivo* experimental testing. Schrodinger developed a new free energy perturbation (FEP) platform (the company calls it FEP+) with direct application to a key challenge in computational approaches in lead optimization: the relatively slow rate at which new molecules with attractive profiles

can be synthesized and ranked for assessment by the lead discovery team. FEP+'s augmented algorithm computing power helped teams accurately identify the fraction of compounds with the necessary potency to meet project goals, reducing the unpredictability that led many drug companies to stay on the fence rather than embracing computational simulations as a decisive play in their optimization programs. Schrodinger's decision to test the technology itself in seven active drug discovery big pharma collaborations, with successful results, helped pave the way for market acceptance.

"It took us two decades to develop, but FEP+ today is Schrodinger's most important technology," says Farid. "We broke with the prevailing scientific consensus that free energy calculations could solve only parts of the binding properties problem: the physics involved in getting it right were just too hard and so the best route was to cut corners and settle for something less than a definitive reading on molecular affinity, one of the most important properties of a drug. We finally did come up with a tool that models every part of the process – we can compute and simulate affinity without reliance on lab-based experimentation. It means our partner companies can progress further with lead programs previously thought to be unfeasible for computational simulations." The company notes the complexity involved in prepping FEP+ required some 200 person-years of effort to get right. The technology is hard for a competitor to easily replicate.

Schrodinger makes its money by packaging these technologies into software that is licensed to more than 1,500 clients in the private sector, academia and government agencies around the world. There are software "suites" for lead generation and modeling in small molecules, biologics and materials science. Schrodinger's revenues – which totaled nearly $60 million last year – also derive from training, consulting and partnering services linked to its technologies. In addition, the company owns the rights to a number of cloud-based computer processing programs, including *LiveDesign* and *GlideScore*, which in its initial test run in 2015 was able to analyze more than 2 million potential compounds in only two hours. These cloud services are continually expanding their calculation range to identify molecular combinations with therapeutic potential.

Furthermore, Schrodinger's growth is being fueled by revenues from equity stakes in its biotech partners, including milestone payments from projects reliant on the company's discovery technologies. For example, when partner **Nimbus Therapeutics** in 2016 sold to **Gilead Sciences Inc.** its clinical-stage program consisting of an ACC inhibitor to treat non-alcoholic steatohepatitis (NASH), Schrodinger, as a Nimbus shareholder, was able to cash in on a portion of the $600 million purchase price. "All of our pharma and biotech collaborations have milestones associated with them. In the long term we expect this to add significantly to our bottom line," Farid notes.

Equity Stakes In Start-Ups Help Company "Operationalize" Its Offerings

In fact, Schrodinger has been an aggressive proponent of taking a formal equity stake in start-up enterprises committed to "operationalize" its product offering through hands-on engagement in drug discovery and lead optimization – with the ultimate objective of bringing a drug forward for commercial use. This is an activity that Schrodinger, at least for now, has opted not to do itself.

To date, five such equity investment deals have been negotiated, beginning in 2009 with Nimbus Therapeutics, which is building on Schrodinger's computational platform technology to advance high unmet need drug targets in the metabolic, immunology and oncology fields; with **Morphic Therapeutic Inc.**, in 2015, jointly with Harvard University biologist Tim Springer, who discovered a class of proteins known as integrins that program cells to attack healthy tissue and thus promote the development of many auto-immune disorders; with **Relay Therapeutics**, in 2016, whose expertise lies in biophysical methodology, where it is evaluating the motion of proteins to create a defense against certain cancers; with **Petra Pharma Corp.**, which is dedicated to the discovery and development of novel therapies that modulate a key enzyme, PIP4K2, associated with cellular mutations that lead to cancer and other life-threatening diseases, in 2017; and with **Bright Angel Therapeutics**, which Schrodinger co-founded jointly with MaRS Innovation in December last year, to apply the company's simulation software to help drive development of therapies for drug-resistant fungal infections (*see sidebar, "Cross-Country Collaboration: With Schrodinger Technology at the Core"*).

> *"You can argue that every drug on the market today is by sheer force of numbers not the best agent against its targeted condition."*

A shared characteristic of these investments is their contractual access to the full range of Schrodinger's computational and molecular biology modeling assets. The companies are all privately held, with Schrodinger holding a material equity stake, usually about 25% or less , along with financial support from many of big pharma's own in-house VC shops. Each also follows a flexible business model allowing for experimentation in the structuring of multiple alliances and partnerships of their own. For example, Nimbus, still the largest of Schrodinger's equity stakes, divides its therapy programs among separate subsidiaries to allow the option of a quick sell-off early in the post-discovery development phase.

CROSS-COUNTRY COLLABORATION: WITH SCHRODINGER TECHNOLOGY AT THE CORE

A most recent example of **Schrodinger LLC**'s collaborations with the start-up investor community is its December 2017 pact with Toronto-based MaRS Innovation, a non-profit, full-service commercialization accelerator funded in part by the Canadian government as well as 14 major Canadian universities and research institutes. Together, the two are backing a new private company, **Bright Angel Therapeutics**, with a mandate to tackle one of the most persistent – and underfunded – challenges in infectious disease: anti-fungal resistance.

The underlying condition is a heavy hitter. The US Centers for Disease Control & Prevention (CDC) describes invasive fungal disease as an increasingly common cause of health-related bloodstream infections in the US; worldwide, it is a cause of death on par with TB or malaria. In an interview with In Vivo, Bright Angel's new CEO, Dominic Jaikaran, PhD, a biological chemist and former venture capitalist, contends the incidence of fungal disease is spiking as more immuno-compromised patients with chronic conditions flood hospitals and clinics. "If we can conclusively identify the therapeutic Achilles' heel of this disease, an area where significant progress has already been made, then we are in a prime position to develop new drug combinations that will prevent the emergence of resistance," he says.

Like other Schrodinger investments, Bright Angel stands out for its unabashed commitment to the basic research insights found in the academic setting. The company's third co-founder is Leah Cowen, PhD, chair of the University of Toronto's Department of Molecular Genetics and leader of the department's inter-disciplinary Anti-Fungal Research Group. As a post-doctoral associate in the lab of the late Susan Lindquist, Cowen identified specific proteins that help enable resistance to anti-fungal drugs. Another close associate of Lindquist, Luke Whitesell, MD, is Bright Angel's fourth cofounder. He has left Whitehead to join Bright Angel to leverage this research, and, with Schrodinger's advanced computational and modeling technologies, hopes to identify next-generation drug candidates to treat invasive fungal disease.

The immediate strategy for the new company is to use Schrodinger's *in silico* simulations technology to build a drug – or, more likely, a combination of drugs, including those drawn from the existing standard of care – that inhibits the Hsp90 "chaperone" protein. As an essential component of the protein-folding machinery in cells, this target plays a key role in regulating the structure and function of multiple other proteins involved in the development of clinical drug resistance in fungal disease.

According to Jaikaran, Bright Angel will tap resources at both the University of Toronto and Schrodinger to advance the Hsp90 program and identify additional programs that can be in-licensed to the company. "We expect the better part of this year will be focused on generating novel leads utilizing virtual screening and *in silico* drug design tools we now have due to the relationship with Schrodinger. These are a game changer for us as they will keep the costs associated with lead generation down and assist in generating a novel molecule with fungal selectivity. Looking forward, we intend to leverage the data generated from our virtual screening to raise additional financing for later-stage candidate development from non-profits as well as traditional life sciences." Bright Angel's current investors include, in addition to MaRS Innovation and Schrodinger, the University of Toronto and Ontario Genomics.

These equity relationships and other candidate-based partnerships with global big pharma companies like Sanofi and Takeda are the centerpiece of Schrodinger's long-term growth strategy. (*Also see "Deals Shaping the Medical Industry, August 2017" - In Vivo, August 2017.*) In many ways, its leading position in discovery modeling and lead optimization is a means to an end – to become the partner of choice in helping biopharma companies large and small – not to mention new entrants in drug development from the NGO, non-profit and academic fields – to better achieve the transition from discovery to commercialization in key areas of unmet medical need.

Currently, Schrodinger has six projects underway in lead optimization for oncology, autoimmune disorders, and fibrosis, with another 12 in pre-clinical discovery for metabolic diseases, oncology, cardiovascular disease, Alzheimers, schizophrenia, and fungal infections. David Weitz, head of Takeda's Global Research Externalization unit, tells *In Vivo* that its July 2017 deal with Schrodinger focuses on research, with the latter taking the lead in discovery, while Takeda leverages its therapeutic expertise in core pipeline programs on GI, neuroscience and oncology. "Our goal is to envision previously unidentified chemical space to guide the design of new drug candidates in these three areas of importance to us."

What's Next For Schrodinger?

Now that Schrodinger has established its bona fides with both the scientific establishment and the investment community, what's next? One priority is to maintain its edge in technology, which continues to be ripe for disruption – no one in the software business can presume it will own the field indefinitely given that barriers to entry are lower as more of the science is open source. Cryogenic electron microscopy (cryo-EM) is an example of an emerging tool that improves on current practice by facilitating the rapid mapping of protein structures without the added step of crystallization. According to CEO Farid, big money is moving into

the cryo-EM space, mainly because it vastly increases the number of protein structures that can be analyzed. "Within the next two years, drug companies are going to see major benefits as cryo-EM pares down the time, cost and quantity of discovery work." Schrodinger now has a fully serviced application in this area. It suggests that the company has the internal resources to keep up with the pace of technology change, especially as its partnering business with drug developers begins to build. Of course, nothing is ever guaranteed in the high-risk world of drug research.

Another decision facing Schrodinger is common to all private companies as the business matures: to opt for an IPO. "It's a logical question," says Farid, "if only because we are in a hotly competitive business with a complex set of conditions in creating value for our customers." Then there is Schrodinger's cultural DNA centered on an early and enduring commitment to basic research, which is often anathema to the more prosaic concerns of Wall Street. "Schrodinger would not be here today had we not had the vision of our two entrepreneurial founders, the freedom and flexibility we gained as a private company, and the incredibly patient support of independent, deep-pocketed investors Bill Gates and David Shaw. Bill Gates decided to commit millions to us after learning informally about our ambitions after becoming one of our founder Rich Friesner's bridge-playing partners – where else can that happen?" It's certainly a bit idiosyncratic, and one that will have to be weighed seriously in considering a future shift in ownership.

Farid tells *In Vivo* there are no short-term plans to go public or seek an acquisition, for two reasons. First, at least for the near term, the company is adequately resourced to execute around its current operational plan. Second, there is a valid concern about the disruptive effect such moves might have on client relationships, particularly if a change results in Schrodinger entering the drug development business itself. All those partnerships would suddenly raise issues of trust due to the potential for Schrodinger being seen as a competitive threat. However, Schrodinger's ambitious growth objectives mean that it will eventually require more capital – in talking to investors, "no" for the near term does not mean "never." And all of these other issues are resolvable.

Hence the script going forward is to leverage the strengths of Schrodinger's current business model. Concludes Farid, "We will continue our present course of licensing software to biotech and pharma companies while enabling them to use it more effectively and at larger scale. We will grow the drug discovery partnerships, and at the same time reinforce our software technology capabilities by ensuring we are focusing on the right problems, in a real-world setting. Equally important, these partnerships further monetize our technology as the milestones we negotiate give us a piece of the action on a real drug as it moves toward eventual commercialization. That's only fair, given the impact we expect to have in uncovering new therapies of a higher standard of efficacy and quality compared to previous methods."

Les Funtleyder, health care portfolio lead for E Squared Capital Management, who follows Schrodinger, believes the company has a sound proposition in a key emerging business for biopharma – complex, technology-aided drug discovery. "Its business model is powered by some diversely powerful minds and is fairly unique – both factors give it protection against the disruptive forces shaping the industry and technology in general," he observes. "Overall, this expertise in virtual, computer-led discovery and lead simulations is representative of a true scientific advance that will likely bring a bigger number of interesting compounds into the clinic in the medium term. It's a good trend for investors."

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Digital And Connected Care Are Pushing On An Open Door – But Is Medtech Ready?

Digital health care will one day simply be "health care" in the same way that genomic medicine will simply become "medicine." But between then and now, there is much distance to cover – a lot of it in the minds of stakeholders who, maybe reluctantly, see it as a risky strategy. But the emerging consensus is that it represents opportunity.

BY ASHLEY YEO

The digital revolution has been slow to take hold in health care, but forward-thinking medtechs are already maximizing the insights from patient data collection and embracing the patient care possibilities offered by the cloud.

Digital, AI, machine learning and apps offer the chance to provide broader, faster, better-quality care to more patients, possibly with long-term consequences on the markets exploited by those medtechs that have long roots in the pre-digital age.

So what? The rewards might not be there yet, but companies must decide soon if their digital strategy is "either/or" or "when" – if they are not to be disintermediated by the digital revolution.

It is the future direction, a tool for delivery of better quality health to meet rising demand. There is no stopping it, no turning back the clock, should anybody but want to. Whether it's an opportunity or a threat – for it is both depending on where you sit – it is changing the way health care is delivered and accessed, and where it can be delivered, for good.

Digital health and connected care might mean wholescale reinterpretation of stakeholders' traditional roles in the chain of health care delivery. It will mean winners and losers as momentum picks up further, and it will alter the complexion of the medtech industry. Just how far and how fast depends on the readiness of medtech players to adapt, meet the challenge and own the space. And crucially about where the money is.

But no one in this fast-moving sector can take their eye off the ball for a second. It is what Daniel Ruppar, global program director at Frost & Sullivan Global Digital Health, calls "one of the hottest areas of interest in health care right now." Using data collected in the right way represents what ZS principal Pete Masloski sees as "one of the biggest untapped opportunities out there". (*Also see "Winners Are Beginning To Emerge In Digital Health – But Without Planning Medtechs Risk Missing The Boat" - In Vivo, March 2018.*) And AdvaMed Chairman Nadim Yared says that the industry is only just "scratching the surface" on the possibilities for digital and connected care. (*Also see "Digital's Big Moment Has Arrived Say CEOs At Medtech Europe Panel" - In Vivo, March 2018.*)

But what does it extend to and what are the possibilities? Ruppar describes the Global Digital Health Opportunity as being compartmentalized into four overlapping subdivi-

sions: remote monitoring, telemedicine, mhealth, and healthcare IT; and then a single-discipline fifth, representing wearables alone. (*See Exhibit 1.*)

The opportunities for medtechs in this evolving landscape are substantial, but Frost & Sullivan warns that no one company can or should go it alone, depending on what kind of digital health strategy it is trying to build. This is a story about convergence, and about what Stanford University Medical School's Peter J Fitzgerald called "the collision digital and health care" as he addressed the MedTech Europe's recent 2018 MedTech Forum in Brussels, Belgium.

Industry partnerships in the digital ecosystem are intended to do more than score immediate commercial success; they will also enhance the partners' respective understanding of the opportunities. This is the view of Microsoft's Elena Bonfiglioli, who thinks the cloud has rich potential for medtechs willing to enter partnerships to exploit it. The recent deal between **Medtronic PLC** and American Well, which seeks to bridge the remote patient monitoring space in telehealth services, is a prime example.

The convergence story also attracts and embraces providers and payers, and draws in digital health in the connected home, which is a central element in the shift to remote care concepts. In future, care will be delivered via a mix of in-person and digital health solutions, and the balance will likely alter as the shift from fee-for-service (FFS) to fee-for-value (FFV) accelerates. There will be a progressively decentralized approach to health and wellness, with a growing reliance on centers of care other than the inpatient hospital setting.

Confronting The Technology Challenge

Integrating digital requires investment and is often framed as a mindset- and culture-change issue. But it is, still, also a technology challenge, as **Philips Healthcare** explained during the ehi Live 2017 event in Birmingham, UK, last fall.

UK&I Solutions Lead Stephen McMillan told *In Vivo* that while industry is doing a very good job of digitizing particular modalities, in imaging, say, and is "at the forefront of something enormous with digital genomics and pathology," it is not yet doing a very good job of connecting these digitized diagnostics, by joining up information and getting meaningful use out of it, he said. "Using AI and presenting the results back to clinicians in such a way that they can make decisions from it remains a technology challenge at the end of the day."

Philips, a leader in digital integration, is also keenly aware of the nervousness that change management can bring about in health care systems, even if the need for strategic change may be clear and compelling. Industry is pressing ever harder to convey solutions-focused visions that revolve around measuring outcomes, not inputs. But in the UK, there is the long shadow of the costly failure of the 2002 National Programme for IT (NPfIT); it was dismantled in fall 2011, and there is still the legacy of a change program that didn't deliver. It is widely believed that it failed precisely because the NHS treated it as an IT project, not a change management program. But some health service Trusts are still scarred by that, in spite of some successes, such as the PACs and Choose and Book programs, and there is both a residual fear of large programs still, and lessons to learn.

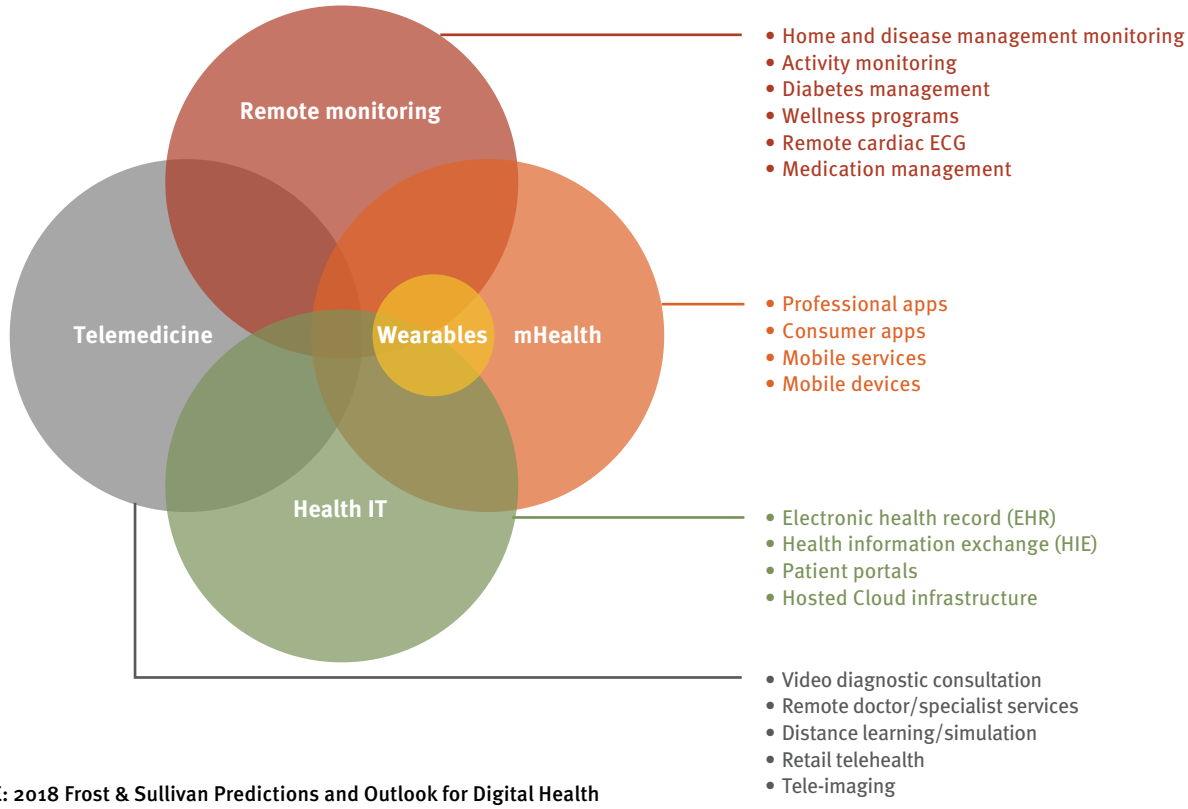
Nevertheless, system transformation is "almost around the corner," says Philips Senior Strategic Business Architect David Pickering. "We are now getting close to it, globally and not just in the NHS," he says.

TOP DIGITAL LOOKOUTS FOR 2018

Frost & Sullivan's 2018 Predictions and Outlook For Digital Health include the following key areas that are primed for fast development, change or greater attention this year:

- Cybersecurity – a dangerous new reality for the health care industry
- ICT leaders go deeper into health care arena – what are the strategies of Amazon, Google, and Apple? This is a top question among tier 1 medtechs, and all the more so after the recent JP Morgan, Berkshire Hathaway, Amazon joint venture. (*Also see "In Vivo's Deals Of The Month, January 2018" - In Vivo, February 2018.*)
- Telehealth expands presence in the mass market media, with more exposure on US prime time TV, for instance, and correspondingly more uptake.
- AI-powered machine learning – more than half of US-based providers will embrace these technologies in 2018. It paves the way for more partnerships in the model of Roche's $1.9bn acquisition of clinical cancer data collection company Flatiron Health (*Also see "Roche To Improve Real-World Cancer Data Extraction With Flatiron Buy" - Medtech Insight, February 21, 2018.*); and between large vendors such as IBM and boutique start-ups.
- Digital "deconfusion" – greater informed awareness of digital terms and concepts will: allow clinical staff, patients and payers to communicate in a more straightforward manner; enhance outreach; and improve policy-making.
- Providers will modernize financial and accounting IT systems.
- Improvements to EHRs, allowing process optimization and time-saving for clinicians.
- mHealth grows, and spawns "Digital Therapeutics," following the success of Pear Therapeutics in securing FDA approval for reSET the first digital therapeutic, in fall 2017, for substance abuse disorder (with claims of therapeutic benefit).
- Patient engagement/patient experience become more central considerations, with mobile apps and patient portals set for strong growth in 2018.

Exhibit 1:
The Global Digital Health Opportunity



SOURCE: 2018 Frost & Sullivan Predictions and Outlook for Digital Health

The next, hard, step is for stakeholders to fully to embrace the shared outcomes challenge, but there is evidence that both suppliers and the NHS are now prepared to take some risk, McMillan believes.

"It's different to former days when suppliers or health care organizations would simply fund something: now it is shared aims, shared outcomes, and shared reward even." With these deeper partnerships, the financial structures are also changing to more long-term models which, if done well, can make health care provision more affordable, especially when delivered at scale. So already finance structures are providing opportunities to turn industry innovation into meaningful ROI, McMillan adds. He is talking about the NHS, but the comments apply globally.

At the same time, while the technology is there to help make the shift, industry still needs to see more desire from the customer base. In turn, it has a major role in demystifying the market space for customers, who are often bewildered by the regular emergence of digital heath concepts and the adjustments needed, from the cloud to cybersecurity, body-worn sensors, brain-implantable chips, data security, Blockchain, the Internet of Things, the Internet of the Patient...and so on. It requires the digital"deconfusion" that Frost & Sullivan predicts will happen in 2018.

The Limitless Potential Of AI And Digital

It is easy to see why the confusion arises, given the range of possibilities, timescales and sheer pace of technology advancements in the world of health care. Addressing ehi Live delegates in a keynote, Philips chief commercial officer for healthcare informatics Jacob Durgan said that by 2030 digitally-enabled health systems will be transitioning from sick care to "well care." They will also be prioritizing better-quality patient experiences. Individuals will be taking greater ownership of their care, and will likely adopt proactive approaches to updating their data. There will be more use of virtual reality and AI, and a major focus on networked care, "where big data will really come into its own." Providers must plan to adjust, and crucially don't want to make mistakes.

The world will get more "sci-fi," said Durgan. At the same time there will be more of an entitlement sentiment among individuals that "health is for all." The benefits of engaging technology with the human body will be better understood, and solutions like electronic tattoos that can control connected apps, and using mind power to give individuals greater control to treat sickness ("neurosculpting") could become valid options. For ease of consumer access, the public will see diagnostic centers housed in convenience stores, the Walmarts, CVSs and Walgreens, which will be assuming some of the work done in hospitals. The potential seems almost limitless, even if the pace of technology adoption seems slow.

AI, Machine Learning And Health Care's Inflexion Point

Peter J. FitzGerald agrees. Fitzgerald, who is director of the Center for Cardiovascular Technology and of the Cardiovascular Core Analysis Laboratory (CCAL) at Stanford University Medical School, describes a "collision of digital and health care" in which big data and the smart device revo-

lution will "bleed over" into health care. Health care, a unique commodity and service, has been behind the curve in the rush to embrace digital and data-driven opportunities. But Fitzgerald foresees the coming of a revolution of the "four Ps" in health care (personalized, predictive, preventive and participatory), mostly achieved with Big Data insights, smart devices, data security, and AI.

AI is the tool that allows an agent or operator to look at data and reinforce the system. It is both confusing and exciting. It prompts stochastic learning that leads to the decision analytic algorithms that assist providers to be more efficient. But AI is very narrow, and domain-specific, says Fitzgerald: it requires very large computing power that serves to assist or "augment" the clinician's decision-making. "It's not artificial intelligence for doctors," he stresses. But it can help with diagnosis, therapy, surgical procedures, triage efficiency and ICU patient selection, as well as in gene editing, radiology, pathology, and dermatology.

Machine learning and AI will help standardize the quality care and address hospital system inefficiencies – an important tool to have given the huge budgets allocated to supply chain goods, diagnostics and treatments. It will narrow variation in diagnostics or, say, show correct stent positioning in a particular patient. This capability naturally extends to robotics used in the remote treatment of patients. "You're going to hear a lot about that this year, not just in cardiovascular but also in stroke patients," he told the large MTF audience in Brussels. "We'll be able to bring the catheters to the stroke patients – this will be happening in the next three to five years."

"This wave of digital data will change the way we think and the way we practice health care," he continued. Patients may even be treated in virtual hospitals – hospitals without beds. The Mercy Virtual Care Center in California ("the world's first facility dedicated to telehealth") is just one example, housing nurses and doctors, and driven by AI and remote images. This virtualization of hospitals will grow exponentially in the next few years.

But you cannot teach a computer to have compassion, caring and empathy; they can determine actionable items which the doctor can act on, he stresses. So there will remain separate roles for both in the care delivery of the future.

> *"AI is very narrow, domain-specific, and requires very large computing power that serves to assist – augment – clinician decision-making."*
>
> *Peter J. Fitzgerald, Stanford University*

Why Stop The Advance of Digital?

This strikes the right chord, according to Dr Ali Parsa, CEO of Babylon Health. "Allow doctors to be 'more human' by allowing machines to be 'more machine'," says Parsa, whose company is behind a primary care app-based service being offered by the NHS in London. He believes that the predictive and diagnostic power of AI offers a complementary service to that of physicians.

The "health for all" plan is what Babylon Health's primary care app is all about – rapid access to doctors, either NHS-provided or on an out-of-pocket basis. In 2017, Babylon Health partnered with the NHS on its *GP at Hand* tool, which made the NHS the first health service in the world to offer free, 24/7 health care via mobile phone. In just two months, 2-3% of millennials in London signed up to Babylon's GP at Hand. The service is at present offered only in London in the UK, but also to the entire nation of Rwanda.

Speaking to *In Vivo*, Parsa said machines would not make the usually understandable (if rare) diagnostic errors that often make the lead in the tabloid press. Health care rarely wins properly in the mainstream dailies, as even the best stories often include exaggerated claims, especially in the IVDs field. (*Also see "UK Outlook 2018: IVDs Faces Up To Digital, Pathology Consolidation And IVDR Challenges" - Medtech Insight, February 28, 2018.*)

Doctors are not used to rare disease symptoms; for instance, bowel cancer is a one-in-3,000 patient occurrence, and to a time-pressured GP may look like something more benign. Doctors have so much more information available to them than is available in their minds, yet many don't use it, Parsa notes. AI takes away the risk, but medicine is a very hierarchical profession, he observes, which can have implications on the speed of adopting new techniques.

Medtech companies operating in this new era have two choices: to remain rooted in the industry's traditional methods of operation and risk being overhauled by the new technologies; or buy up/partner with digitally-expert technology compa-

nies. Some medtechs are already adjusting, but some won't. Often their failure to act is not down to over-conservative CEOs, but to the complex structures and decision-making channels further down the organization. "The construct is really tough for them," says Parsa.

That is not really Parsa's concern, who sees Babylon Health's job as to deliver its promise of making health care accessible, affordable and available to everyone. The results will speak for themselves, he says, pointing how Google rapidly became mainstream after the early fears and negative reactions.

Where Forward-Thinking Medtechs Belong – The Cloud

Medtechs need to be on their toes given the speed at which the industry is evolving, says Elena Bonfiglioli, senior director health industry, EMEA, Microsoft. Speaking to *In Vivo* at the Global MedTech Compliance Conference (GMTCC) 2017 in Amsterdam, the Netherlands, she said that the cloud, the paradigm through which services and solutions from the medtech community can be brought to market, either represents the biggest opportunity for medtechs to transform, or the biggest threat to their business growth.

Last year, Microsoft and GE turned heads when they signed a deal allowing GE's North American customers of the *Predix* software platform for the Industrial Internet to build apps on *Azure*, Microsoft's cloud for businesses. The deal will have potential for GE's health care and other group customers.

On a smaller, but no less important scale, remote patient monitoring solutions start-up LindaCare is a good example of how the digital opportunity can be successfully exploited. The Belgian company, specializing in chronic disease management, was born in the cloud after forward-thinking entrepreneurs acted on the experiences of nursing staff who were having management issues with patients' implanted heart devices from multiple vendors. The company developed a dashboard that organizes remote monitoring data from all cardiac implantable vendors in one program. It also helps triage alerts.

This gives an added-value service to the nurse, and leverages what Bonfiglioli descibes as the cloud's "always-on/anytime/anywhere" approach to give the best insights to professionals. It will also help reduce the cost of delivery of care. (LindaCare recently announced a series B investment, featuring new investors including Philips Healthcare, as well as existing investors Capricorn ICT Arkiv, Connecticut Innovations and others.)

> *"Do we worry about the rules of the past, or do we focus on the new rules that are needed now to bring about the much-needed change?"*
>
> *Elena Bonfiglioli, Microsoft*

She advises that instead of looking at the cloud as a threat, medtechs should view it as a tool to rejuvenate the solutions of today and improve the way they can address the scale of health care needs tomorrow, especially in the area of chronic conditions. They should really be asking themselves, "how do we rethink the model using the cloud an intelligence system to help us?"

The new health care paradigm is more than a handful of big companies, the Microsofts, Googles, and IBMs, owning the big intelligence AI solutions. That is now viewed as the old model. The consensus now is that the winners will be those who can diffuse AI tools from the basics, in say, how to use a mobile phone as a digital assistant, or how health care professionals can access chatbots that meet all the protocols and give the best advice.

The aim of these changes is not to replace medical staff, but to extend their capabilities and allow them to see more patients as demand grows. It is a world in which a machine can, say, medically image a tumor and delineate it in less than a minute, making productivity gains and saving time which can be fed back into the system.

Is The System Ready?

The future is alluring, but the present structures for delivery are not all keeping pace. Bonfiglioli sees a good level of *technical* readiness. She believes that, at the current pace of developments, there will be a substantial consolidation of digital expertise in health care within four to five years. But as to acceptance of the *concept*, that is further away. "We have not even started there," she told *In Vivo* at the 2017 GMTCC. Supposing that we are at the right levels of awareness now, it could be as much as another decade before the new skills, behaviors and culture are in place to make the changes happen, she predicted.

And regarding regulation and market incentives for digital health care, we are still further away. In many countries, telemedicine consultations are still not reimbursed, literally decades after the technology first emerged. It is no surprise then that we don't know how to pay for, say, chatbot services that are more effective than current operator-run services. But the dilemma, as Bonfiglioli expresses it, is: Do we worry about the rules of the past, or do we focus on the new rules that are needed now to bring about the much-needed change? This could take time: she fears that it might be as much as 25 years until the rules and regulations are in place to facilitate the changes fully.

But that won't stop innovative organizations from finding ways to make it hap-

pen. The pace of change will depend on levels of industry leadership. Bonfiglioli also cautions that, "however much work is done, 'it' won't happen if you don't have your CEO and C-suite behind you." It might just be a lot of effort for a little impact. On the brighter side, "the opportunity has never been bigger for smaller companies." They are often driven by a younger set of people who see things with a different mindset, having also been "born in the cloud," and not afraid of devices, mobility, sharing data...

SMEs, right in the middle of two operating models, need to think hard about which way to go and their own business model, asking themselves if they can see a return on investment. It will be difficult for SMEs to make the full jump, as they are not resource-heavy. But they can do an analysis to see what a digital business model might bring to their bottom line.

Probably one of the biggest blocks to progress is payment reforms remaining unaddressed. Analyst research and insight groups like Gartner, IDC and Forrester Research, and major accounting firms, like KPMG and PwC, can help by making a point of clearly defining the opportunity for medtechs. In addition, "we need to educate politicians about how this could happen; this is perhaps a job for the medtech community," Bonfiglioli considers. (*See box: Priorities In The Next 1-2 Years.*)

PRIORITIES IN THE NEXT 1-2 YEARS

There are some building blocks that need to be put in place in the short-term to increase the pace of uptake of digital technologies, says Microsoft's Elena Bonfiglioli.

- The first is to address the skilling of future generations of health care professionals and teaching people what the future workplace will look like.
- The second is to integrate both innovation and economic development more purposefully into the health care agenda. Investing in start-ups and in the innovation capabilities of SMEs would come under this umbrella. There is evidently a role for government health ministries, but they tend not to have innovation responsibilities. In any case, this activity needs to be more joined up.
- The third is to help regulators understand both the opportunity cost and the benefits of embracing new technology, amd make them accountable for "cloud-first innovation-first patient-first policies."

Risks And Benefits In The Digital Future

There is a "dark side" to confront too, says Fitzgerald. EMRs are hackable and patients have been affected in the millions already. It may be easy to stop a pacemaker or an LVAD, as they are not protected, but "we have to be focused on preventing these attacks." Cybersecurity is one of Frost & Sullivan's Top Digital Lookouts For 2018.

Looking beyond these understandable fears, the exponential move into data, analysis and manipulation is what we are going to take advantage of in health care, he adds. "Innovation is thriving more than I've ever seen – it's just different in this digital world. Medtech and IT are being integrated at a very fast pace, and the whole health care world is going to look completely different in three years."

Philips' David Pickering agrees: "We are starting to see some real shape to what the future will look like – it can and does deliver things. But we are still only seeing the tip of the iceberg."

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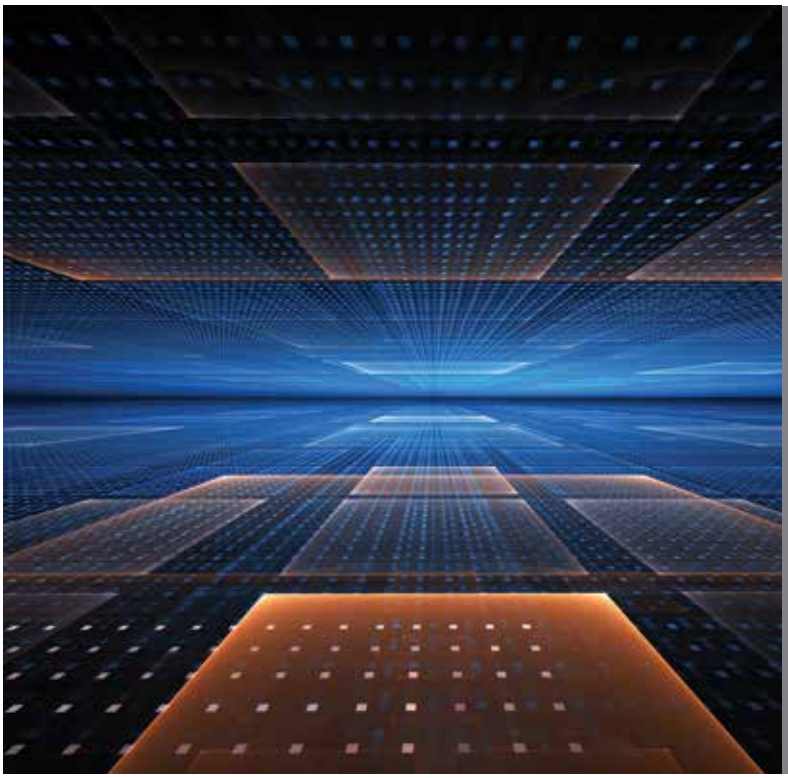
Data And The Digital Horizon: Perspective From The Agency C-Suite



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While digital health applications represent a major opportunity for biopharma, acting on the premise – and realizing its promise – depends on quantum-level shifts in organizational design and cultural resilience to disruptive change. In an *In Vivo* interview, Omnicom Health Group's SVP for Data Solutions Christina Kim says industry progress toward a digitized future varies, but the necessity to act is clear.

BY WILLIAM LOONEY

"Going digital" is not a strategy, nor is its adoption possible just by introducing the right technologies. There is a transcendent human factor: people won't buy into digital unless they understand and endorse the larger purpose behind it.

Voice activation technology is emerging as the most significant – and disruptive – long-term trend in digital, with the potential to impact everything from brand placement and positioning to patient empowerment and well-being.

So what? Digital is already delivering significant insights on customer motivations. A recent joint Omnicom and Cap Gemini Consulting survey to track where physicians actually get their information on managing diseases found that RWE data – still seen as an unsourced outlier by many – trumped clinical trial results by far.

In the following excerpted Q&A, *In Vivo* speaks with Christina Kim, SVP for Data Solutions at Omnicom Health Group Inc., the world's largest health care marketing and communications group spanning a network of organizations and specialists in 55 countries. Kim is responsible for helping biopharma and other health industry clients apply data and the latest digital technologies to address issues including building brand awareness, stakeholder advocacy and managing strategic and operational challenges from the development phase through post-marketing engagement with payers, providers and patients.

***In Vivo*: What's the current state of play in digital health – how far along are we in the "transition" to a fully digitized systems and service model that industry analysts have been predicting for years?**

Christina Kim: As Omnicom Health's lead sponsor of digital solutions for our clients in biopharma, I grapple with this question every day. The volume and reach of data is expanding at breakneck speed. With it comes the ability to use technology-derived analytics to deliver fresh insights and guide decisions at virtually every point of the industry product cycle, ultimately enabling personalized medicine. Yet while the options in digital continue to grow, their application in the real world clinical setting remains uneven. Some of the biggest successes for personalization of therapy are at the physician practice level, where digital technology is being applied to educate around patient care, especially in managing chronic conditions like diabetes and hypertension. The major, continuing obstacle to the potential of digital is the absence of a way to document the entire patient journey with a single, standardized and shareable electronic health record (EHR). Every time you visit a new physician it is necessary to fill out

another medical history form; it is virtually inevitable that the information supplied by the patient will have omissions, discrepancies or outright errors. Hence the ability for a provider or payer to look at the patient as a distinct person with a unique medical history is still in its infancy. There is little possibility to manage an episode of care in a holistic way. The lack of interoperability of EHR deprives us from achieving more system-wide efficiencies and raising quality, satisfaction – and a better outcome for the individual patient.

It's that "last mile" to the patient you are talking about – persuading the patient to act in a way that results in an improvement in his or her health status.

Yes. Our experience finds that patients are increasingly motivated to track their health status. They are comfortable with registering vast amounts of data on their individual lifestyle habits, such as tracking the number of steps throughout the work day, calories consumed, hours of sleep, heartbeats per minute or for metabolic indices like blood sugar. That digital portrait is becoming embedded in the health consumers' DNA. But the big, unresolved question that we hear constantly from patients is what do I do with all this information? Who should I work with to accomplish that? Answering it in a way that keeps people motivated over time is the big challenge for providers and biopharma.

Isn't the problem one of the technology itself? A digital tool won't be used by patients as health consumers unless it is simple, accessible and convenient. The demographics may be changing, but the majority of patients today are not digital "natives."

Some segments of the patient population use digital tools more than others. There is an equally prominent divide between companies that commit and take advantage of digital opportunities and companies that are slow adopters. But I don't share the view that such differences are obvious or predictable. The notion that the older generation is phobic about digital while young people embrace it is overstated. Everyone recognizes that we now live in a digital age; the concept is now ingrained – it's part of the conversation. People and providers want that simplicity, accessibility and convenience because these attributes are prized in the hectic, distracting, multi-tasked environment that we live in today. The economic expression of this sentiment is value. It is especially prominent in health care, where information is opaque and asymmetric and costs for payers – and the patient – are going up. Accessibility and convenience are seen as a given. What's top of mind are issues like what do I do with it? What meaning does it have for me – how will it change my life? These are the pivotal questions. It is a patient's right to expect the answers to be clear and simple.

"The big, unresolved question we hear from patients is what do I do with all this information? Who should I work with to accomplish that? Answering it in a way that keeps people motivated is the big challenge for providers and biopharma."

Omnicom SVP Data Solutions Christina Kim

Building on your comment on adoption rates in digital, does company culture play a role in determining which organizations choose to be proactive about adopting these new technologies?

Culture is a broad concept. It's also very fluid, particularly for us in the advertising space. Traditional ways of defining a target population by ethnicity or income or age is less relevant in determining attitudes toward new technologies in the workplace. What is relevant is if your company management has a history of seeking to innovate by encouraging risk-taking behaviors, not penalizing failure, and testing new ideas through pilots, "skunk works" and other novel organizational arrangements. If there is a culture of experimentation, then it is likely you will have a digital agenda with a management committed to moving it forward.

How does Omnicom define "digital?" What do you focus on in managing that space? What are the most prominent current needs of your biopharma clients in relation to digital health? Where is the growth taking place?

We are always working internally to ensure the ideas we promote are fresh and responsive to market needs. We also focus on partnering with different types of digital technology organizations. Our perspective is that digital represents a big opportunity for biopharma. This influences in turn our investments in the infrastructure around strategic advice and services support at a level commensurate to client needs. For me, I "think digital" every day. I don't define it as a channel, but as the way we live. Honestly, who do you know today who is not on a

> *"The key area of client need is advancing the breadth and quality of cross-channel communications."*

cell phone, installing and using apps, and accessing the internet? Digital is too pervasive to be characterized as a marketing channel. It's a living tool. One of the key arguments we make to biopharma clients is that digital can help them overcome the barriers that exist between patients and the pill in a highly regulated industry. Many companies are adopting novel ways to expand patient communications with their doctors, applying AI to uncover patterns and variations in what patients do with the information they obtain from the physician – and vice versa.

Digital carries additional value as a driver of product support, making it easier for patients and providers to adhere to treatment and secure the best outcome. You have the chat bot, which represents another information delivery and retrieval option among patients and providers. We are also seeing these digital tools applied to enhance of-the-moment communications from one biopharma company to another. The key area of client need is advancing the breadth and quality of cross channel communications. It entails creative strategy development around digital; the design and evaluation of data retrieval, assessment and analytics tools; and execution on strategy and technology to secure outcomes identified by the client. For us, the successful interface between the creative and the technical to raise the scope and quality of communications is fundamental. We work to screen out the data density and "noise" factors, distilling the data down to what really matters for the business, its brands and its audience. We focus heavily on facilitation, execution and optimization of the messages drawn from the data.

Does this represent an expansion of the traditional role of a company like Omnicom, where data analytics is an end itself rather than a tool for marketing, advocacy and communications?

Omnicom is still a communications company at its core. The difference is that with digital we are able to tailor a communications and engagement strategy to each client on the basis of knowing rather than guessing. The historic essence of a company like Omnicom is the creative ideas we put on the table for our clients. Now we can add an additional dimension, which is insights drawn from rich, impactful data that adds to what we know and has worked in other cases – or hasn't.

Our analysis of the digital space suggests there are four key dimensions where these technologies can drive that "patient journey" in health. These are (1) wellness/prevention; (2) symptom detailing; (3) diagnosis; and (4) treatment with real-time information. Is this an accurate depiction of where we are today with digital – or are we missing something?

Yes. In my view, the most relevant aspect for digital relates to the progression to diagnosis. A great example is how the Boston Children's Hospital has built an entire diagnostic reporting system using the Amazon.com Inc. Alexa platform. Parents can access the Hospital's Alexa link with questions on their child's symptoms and get an immediate answer that helps clarify the situation and suggest what to look for regarding symptoms. It's a convenient and non-threatening triaging system for parents. What happens next is the part where we need to work at, largely due to some regulatory issues. For example, only a physician – not Alexa – can render that formal diagnosis. That's appropriate, but how can we extend that digital input a little further, in a way that enhances speed and efficiency without impacting patient safety or influencing a diagnosis based on an underlying commercial interest? We grapple with this dilemma a lot.

In that regard, is the FDA poised to assist by establishing clearer ground rules on biopharma industry engagement on digital?

The FDA has made guidance on the application of digital to drug development and commercialization a priority. The direction is clearly one of allowing more discretion for biopharma companies in taking information that is already certified and deploying it in non-traditional channels like digital. It's the push factor: the appropriate safety and messaging criteria will remain in place, but digital allows for new, expanded ways to get useful information out to providers and patients. Thus, we don't see the FDA as a retrograde actor here. There is a willingness to engage.

Are you optimistic about the impact of digital on the momentum for personalized medicine?

Digital is almost tailor made for a world where medicine is personalized. Progress is being made but realizing its full potential is a slow process. The data from wearable aps is extensive and significant but still it has to be synthesized to the point where it can be applied as "marketing to the one" – by which I mean a specific, targeted audience like the provider or a patient. The challenge is to take the masses of data and make it relevant, from a communications perspective as well as driving the right diagnosis or treatment measure.

How does Omnicom respond to the typical request for help from a biopharma client with a mandate from senior management to "go digital?" From your experience, what are the main pitfalls or stumbling blocks that companies encounter in trying to fulfill that kind of overarching goal?

We tell new clients never to address their needs in the context of a "digital solution." Digital is only a tool – a means to an end. The

client needs to identify that end in advance: what do you want to achieve? The wrong approach is to throw a lot of technology out there and hope it will cover all the options, as was often the case when the Enterprise Resource Planning (ERP) software solutions platform was in vogue. The mistake with digital is to obsess on the technology and say "we need this, this and that." The right approach is to start at the other end and focus on fixing a business objective, establishing the value around what you are seeking to build – and only then look at whether and how a digital application will help you move it forward. Put simply, digital alone is not a strategy. Nor is adoption of digital possible just by introducing the right technologies. Your people won't buy into digital unless they understand and endorse the larger purpose behind it.

What about that human factor? Is it important to create a culture of inclusion to ensure that digital has the requisite support in large organizations like big pharma?

Biopharma companies are not only big, they are highly regulated. Unanticipated risks around new ways of doing things is a concern – and rightly so. Hence involving key parts of the business is always a wise decision. What's vital is to designate an internal champion able to set objectives and who carries the authority necessary to persuade teams to experiment and try new things. One of our learnings is to make sure that regulatory and medical staff are brought into the picture early rather than risk blindsiding them at the end of the process, in a fait accompli.

From a purely organization perspective, how should the C-suite differentiate between a Chief Information Officer (CIO) and a Chief Digital Officer (CDO)?

A good question. As we see it, the CIO handles the nuts and bolts of a company's entire IT infrastructure and the programming and support networks required to function on a daily basis. The CDO addresses narrower elements that relate to the strategic and business applications of information, with an emphasis on the external commercial and customer base. The roles are complementary rather than competitive.

Value is the catchword of the moment in biopharma relations with the payer. How does digital health advance the industry position on the value of medicines?

Digital provides both the real-world anecdotal and quantitative evidence to back the value proposition with payers. It's a tool with the flexibility to chart "long tail" insights and solutions that don't carry immediate results as well as experiments to test out solutions that could be realized quickly, rather than months or years down the line.

Patients are the critical end point in the drug supply chain. They are a necessary but ambiguous target for biopharma because regulation and practice make controlling the patient experience very difficult. How do you help clients put the finger on the patient?

Omnicom has acquired several agencies that specialize in helping biopharma companies communicate with patients. Patients & Purpose is one example. We conduct extensive field research on what this diverse constituency really needs, through KOL analysis, patient surveys, and focus groups. We also rely on our in-house teams responsible for business development and M&A activities to keep track of trends in this sector. It's important to our business model and our clients that we be able to articulate the patient point of view.

Can't big pharma companies do this kind of work on their own?

Yes, and we can augment big pharma's work in this area by bringing our broader perspective about the diversity and range of interests among the overall patient community – across multiple indications, disease states and geographic, gender and demographic orientations. We also have an Omnicom patient network that strives to evaluate the patient as a consumer, which gives us insights into the wellness and prevention areas. Biopharma companies are taking a closer look at prevention strategies as a way to cement the relationship with patients, and we obviously support that because preventive health has been shown to be an excellent community-building exercise.

Omnicom is a holding company – a serial acquirer of expertise in agency communications. Are there examples from your recent M&A that should be of particular interest to biopharma companies?

A couple of years ago, we acquired Biopharm Communications Inc. It's a multi-channel agency focused across the digital and non-digital space. Biopharm allowed us to establish a much stronger base in leveraging data to understand particular audiences and frame communications and messaging platforms around it. We also recently acquired the Snow Companies, focused on direct- to-patient communications, reinforcing Omnicom's commitment to patient empowerment and engagement. Another of our agency partners, GMR Inc., has extensive exposure to digital technologies, especially around the latest software innovations.

> *"As for a similarly revolutionary invention in health care, I'd choose voice activation technology for the potential it has in managing the enormous burden of disability."*

Can you identify areas of digital health that have the greatest growth potential for biopharma in the next five years?

There are growth prospects in many areas. What I find interesting is the potential human and physical opportunities beyond the narrow technology or product implications. For example, I think digital promises a decoupling from the current high levels of concentration of tech talent in urban areas. Digital health is going to unleash a range of virtual applications that will accelerate the ability of people to work and interact remotely, in almost any physical setting. I see proliferating opportunities in telehealth and telemedicine; their potential is only at the beginning of what is possible in terms of access to care and services covering all elements of the health continuum, regardless of where people live. Another paradigm-shifting trend is taking place in clinical trials. It's still a largely untapped space that is arranged into unproductive procedural silos that rarely connect to each other. Consider the impact of a seamless, multi-touch reporting process that will drive down the error and omission rates that slow the timely evaluation of trial data. And there is the growing importance of the post-trial, post registration process, where real-world evidence compiled from, among other things, wearable patient aps and "smart" devices driven by sensor-based software, will finally give regulators the verifiable data they require to establish compliance and drive better patient outcomes.

Artificial intelligence (AI) is today's cool concept – the big word that everyone lays claim to. In fact, however, AI and "machine learning" has been a fixture of next-wave tech innovation for some 50 years. It's a frontier technology. Making it ubiquitous as a decision tool depends on us in the data community to get our houses in order, securing the interoperability of data sets so that we have a better idea of what useful information is actually out there, ready to be retrieved and mined for insights. I think the promise of AI won't be realized until we find a way to render some structure to all these disconnected data sets – that's the foundation for moving forward. AI enables better interpretation of data, but if you don't understand that data to begin with, the practical value of AI as a decision tool will be moot.

Are you concerned about the impact of high-tech disrupters like Amazon or Google/Alphabet's Verily health business? Will they dominate health care in the future through their commanding strength in data retrieval and analytics?

The implications here are huge. The very presence of these companies is forcing other health care verticals to sit up and take notice. In addition to Google's Verily, Amazon has a separate dedicated unit called Amazon Health. IBM has described its entry into health care as the equivalent of the moonshot. Hence PBMs, retail pharmacy, and drug distributors have little choice to rethink how they might do things differently. The logical course for biopharma is to seek partnership opportunities with these tech giants; our strategy at Omnicom is to do the same, where it makes sense and also as a complement to our ongoing interest in smaller start-up firms. While some see these new players as a threat, I am more optimistic. The tech pie is big and there is enough room for everyone. It's equally true that companies like Amazon and IBM are not natives when it comes to the health sector. There is a learning curve – as I have said before, just having great technology and abundant resources is not sufficient. You have to know and understand the data in order to interpret it to solve a business problem.

You cite the lack of interoperability in data sets as a key barrier to realizing the full promise of digital health. In five years, will this problem be diffused?

It's still going to be a problem because there are so many legacy IT systems that need to be phased out. This is a time-consuming and expensive transition. It is not well understood how long it can take to "normalize" data flows – to structure and scrub the data and make it ready for analysis. That task is going to be magnified as more information ends up on line. Nevertheless, I am optimistic about digital in health care because the financial industry has overcome similar impediments. It has succeeded by winning consumer trust and confidence in the way it handles financial data. People have wide access to information that makes life more secure and convenient. It's personalized and accessible. You have the 401(k) account as an ingrained element of normal consumer behavior. In our business, we don't yet have that universal equivalent – the 401(k) for health. At some point, however, I am sure we will. There are emerging systems like blockchain that combine high levels of data security with transparency.

Are you equally optimistic about the acceptance of real world evidence (RWE) in the drug approval process?

Omnicom conducted a study recently with Cap Gemini Consulting where we surveyed large number of physicians on their sources of information on disease management. Surprisingly, far more of the survey group were looking at RWE more than clinical trial results. The conclusion of our study that the system really needs both: evidence from a controlled source is important in setting the parameters of what is effective, but RWE makes the connection to value; it completes the equation. Digital is excellent in facilitating the combination of both streams into a coherent decision metric for providers, payers and the patient. It will happen because it makes sense to everyone.

In the financial sector, the transcendent technology that sealed the relationship between banks and the consumer was the ATM. Do you see any similar product that will prove equally transcendent in health care?

Finance is ahead of health care in making information technology friendly to the consumer. But even the ATM now faces pressure from Venmo and those digital currencies. As for a similarly revolutionary invention in health care, I'd choose voice activation technology for the potential it has in managing the enormous burden of disability. The tool might be simple in execution, but the impact on a disabled person – and the care giver – could be life-changing.

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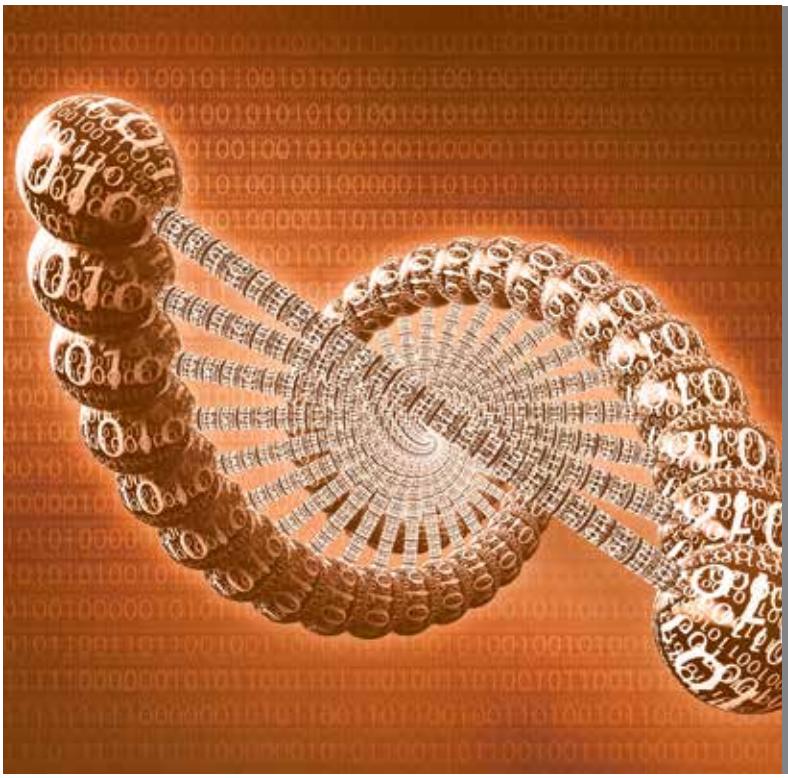

A once-in-a-generation opportunity has opened to digitally redesign a core part of the biopharma business. Capturing the opportunity requires vision and leadership; it's not about the technology.

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BY SAM MARWAHA, MICHAEL RUHL AND PAUL SHORKEY

In many ways, the "digital revolution" has complicated things for pharma, not made them easier, because current operating models aren't designed to accommodate digital innovation.

The authors propose a five-part end-to-end redesign, from product development through to market access, designed to enable pharmas to more readily translate ongoing digital and analytics experimentation into bottom-line impact.

So what? Companies that seize the opportunity will see accelerated competitive differentiation and create broad value for customers and patients. The impact of decisions made in the next few years will shape the pharma industry for decades.

The digital era is revolutionizing the health care industry, but pharma's approach to product development and market access has remained relatively unchanged. Pharma companies have been experimenting with digital technologies and analytics-driven pilots, but instead of seeing meaningful impact on productivity and access, they're watching cost and complexity go up. As one pharma executive put it, "It's like lasagna. We just keep adding ever more layers of cost and taking nothing out."

The reality is that digital technologies won't transform a business if its operating model isn't designed to accommodate digital innovation. To thrive in the era of value-based health care and personalization, companies can't just make incremental changes within their existing operating model. They need an end-to-end redesign.

The disruption of the technology industry by the *iPhone* provides an illustrative analogy to what's possible in pharma today. First, Apple assembled proven technologies (such as touch screens and GPS) into an end-to-end redesign of the customer experience. While existing competitors were optimizing locally within the constraints of the legacy model (by introducing new product features, for instance), Apple was breaking through the constraints of that model entirely. Then Apple opened up the iPhone to an ecosystem of third-party app developers, creating platform economics. Each new app increased the value of the entire platform not only for Apple, but for its development partners and customers, fueling a virtuous cycle that attracted ever more developers and customers and accelerated strategic differentiation.

We see a similar opportunity for pharma companies to assemble proven digital and analytics innovations into an *end-to-end redesign*, from product development through to market access. And by opening up the data science platform at the heart of the re-

design to *customers* (payers and provider institutions) and external innovators, pharma can create its own *platform economics*. Such a redesign has the potential to double the economic value of a pharma company's assets.

A New Model For Pharma

A shift is required from the current functionally divided approach to product development and market access to an agile, data science-enabled model that takes advantage of continuing digital innovation and regulatory flexibility. The end-to-end redesign includes identifying and prioritizing the evidence valued by payers early in the process, shifting the burden of evidence generation from randomized controlled trials to new approaches that apply predictive analytics and real-world evidence, automating patient matching (i.e., the pairing of the right patient with the right trial or treatment), and engaging customers more proactively throughout the life cycle of a product. It requires breaking down functional silos and adopting agile ways of working. Taken together, these changes will quite dramatically reduce costs and accelerate the time to access and peak sales, while reducing risk and increasing value (net price and access).

At the heart of the redesign is a data science-enabled business platform that provides personalized evidence that matters to customers across the product life cycle. (*See Exhibit 1.*) Let's say the product team finds that patients A and B are at the highest risk for disease progression and are unresponsive to existing treatments, representing an unmet need. With the platform in place, clinical-trial recruiters will know that these two types of patients are good candidates for the trial of their company's new medication. Once evidence from the trial is available, customers will know about patients A and B, who represent the cohort that will benefit most from the medication. Physicians will know how to find patients A and B and match them to the medication. Finally, providers will be able to share what they learn in the real world with the pharma company's product team, further enriching the platform and fueling a virtuous cycle.

Although pharmaceutical companies already have access to lots of data on populations and patients (through vendors, collaborative research with customers, registries, informed consent and other mechanisms), these data are used narrowly within individual functions for specific purposes like trial design, patient recruitment, pricing and marketing. Companies are falling short when it comes to building the fundamental capabilities needed to thrive in an era of value and personalization.

> *"Companies with a powerful data science platform will be viewed as partners of choice by innovative start-ups that lack late-stage development and commercialization capabilities."*

To get the most from data within the existing regulatory framework, pharma companies need to work with major customers (as a complement to aggregator relationships) to collaboratively run analytics behind their firewalls ("analytics travels to the data"). This win-win approach drives the platform economics. Customers value access to analytics that solve their big problems, such as finding patients at the highest risk for disease progression or identifying patients who are receiving suboptimal care. Meanwhile, pharma companies gain access to customer data (directly via strategic partnerships or indirectly via intermediaries), tapping into ever-richer insights about patients in the real world and creating smarter analytics to unlock even greater value for customers. Companies with a powerful data science platform will be viewed as partners of choice by innovative start-ups that lack late-stage development and commercialization capabilities.

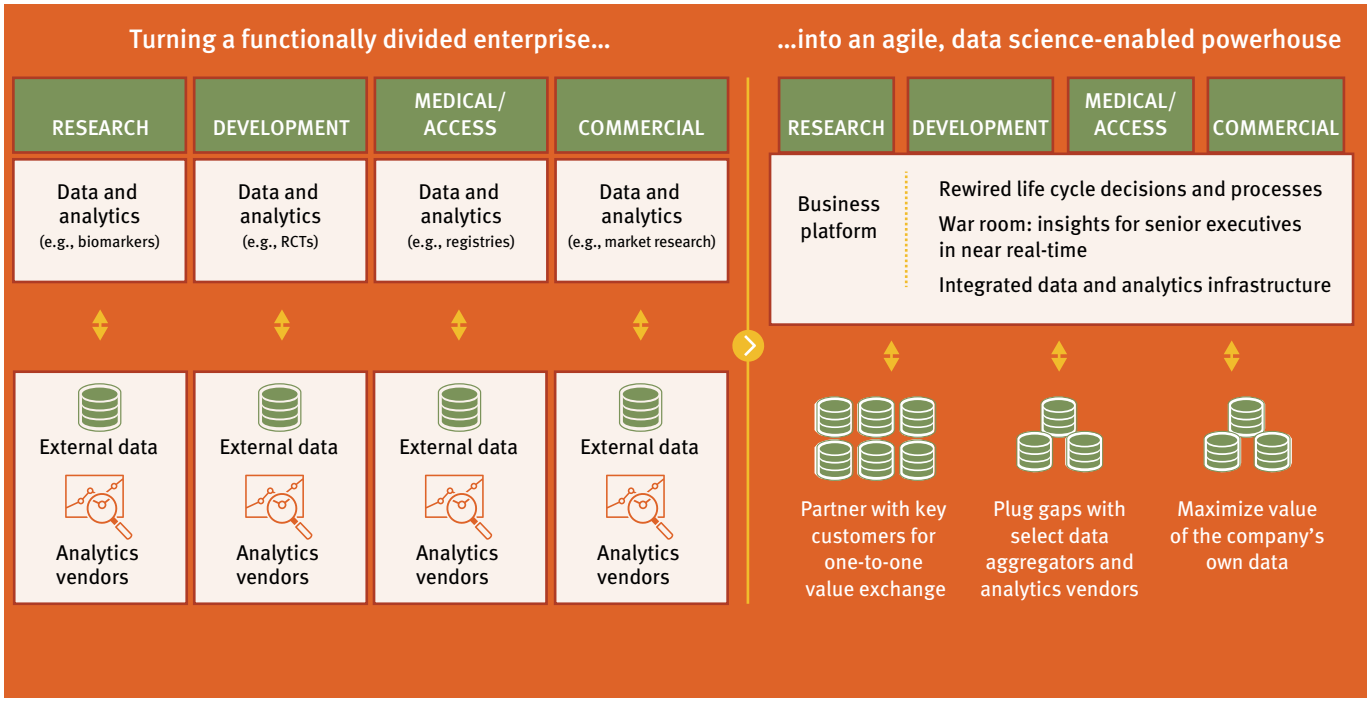
We haven't seen an opportunity of this magnitude in the pharmaceutical industry for a very long time. In the 1990s, **Pfizer Inc.** created a closed-loop field force platform that totally overhauled its commercial performance. By leveraging external data on point-of-sale prescriptions along with formulary data and local customer information, the company redesigned its approach to territory management, call planning and sales incentives in a way that was "personalized" at the local level. The platform, along with other developments in Pfizer's business, resulted in a fivefold increase in revenue from 1995 to 2005. A similar window of opportunity now exists for innovation in product development and market access.

Why Now?

A confluence of factors is forcing the reinvention of pharma's product development and market access models. Payers are pushing back against the economics of

Exhibit 1

The Data Science Platform At The Heart Of The End-To-End Redesign



SOURCE: Boston Consulting Group

blockbusters and mass markets, demanding to see evidence of real-world value by population segment. Under the existing model, this adds cost and delays and narrows pharma's market access, pushing the economics to the breaking point. At the same time, new technological possibilities – such as data and analytics, digital, and next-generation sequencing – are providing an opening to break through the constraints of that model. Regulators are actively encouraging this reinvention, opening up new regulatory frameworks for agile product development.

Four trends are contributing to this opportunity:

1. Explosion in real-world data science. The gold standard for evidence has traditionally been clinical trials – the first generation of data-driven evidence. The second generation has come from the digitization of health care over the past two decades – electronic claims, electronic medical records (EMRs), lab automation and next-generation sequencing – and making these data ready for evidence generation. Wearables, ingestibles and other Internet of Things devices will drive the third generation of personalized population health insights. Advances in analytical technologies, particularly artificial intelligence and machine learning, are now allowing companies to translate massive and growing amounts of data into actionable insights, at a personalized level, on disease progression and treatment. The scores of new ventures are attracting tremendous interest from pharma and VCs. Most recently, Roche made a big bet on data science with its acquisition of Flatiron Health Inc.

2. Regulatory innovation everywhere. In the US, the passage of the 21st Century Cures Act opened the door for the use of real-world evidence (RWE) to satisfy requirements for label expansion, while the Prescription Drug User Fee Act has enhanced the Food and Drug Administration's ability to consider RWE when evaluating a drug's safety and efficacy. And a new European Medicines Agency program, PRIME, has laid the foundation for RWE to be increasingly substituted for randomized controlled trials (RCTs) in Europe. We believe this trend will persist as regulators continue to encourage digital innovation.

3. Customers demanding patient-level value. Information asymmetry has flipped in the past few years; customers have 80% of the data on the performance of a pharma company's products. Customers are digging into these data to segment patient populations, identifying those at the highest risk for disease progression and modifying the deployment of care management resources and programs accordingly. For payers, this is the next step beyond managing unit costs and utilization. They are demanding a similar commitment from pharma, asking to see "de-averaged" evidence at the subgroup level that can be tracked in their claims or EMR data – particularly in the disease areas targeted by high-priced specialty drugs. In this way, customers can track key outcomes (such as a reduction in the total cost of care vs. the projected baseline) in the patient subpopulations of greatest interest to them. The imperative for pharma is to seize the opportunity to engage more strategically with customers on their biggest problems – or else be left on the sidelines.

4. An industry model increasingly under strain. The industry's cost structure

has become unsustainable. It takes over $2.5 billion to bring a new product to market. Rebates continue to increase, rising on average from 28% to 41% over the five-year period between 2012 and 2017. Compounding all of this, the window between launch and loss of exclusivity has shortened from 180 months to 145 months. The demand from customers for additional evidence, combined with the attendant costs and delays to best access (the point at which the maximum number of patients who need the medication have affordable and convenient access to it), are only worsening the economics of the existing model.

Five Elements Of The End-To-End Redesign

Five specific changes in the operating model – all predicated on working across functional boundaries, including the voice of the customer in life-cycle decisions, and adopting agile approaches broadly – define the end-to-end redesign.

1. Design evidence generation for customer value at the outset. Under the new model, pharma companies would collaborate with customers up front, identifying the most relevant endpoints from a customer perspective, and prioritizing evidence generation around value to the customer. This would allow them to model the customer economics well in advance of launch and thereby prepare customers for the impact of any cost savings. They could also discuss win-win pricing options earlier in the process. Finally, it should be possible to eliminate much of the back-and-forth with payers on getting access post-launch, reducing waste in the evidence generation process.

2. Use predictive analytics and RWE wherever possible, rather than RCTs. The majority of a company's postmarketing commitments and evidence generation can be fulfilled using RWE. Some of the evidence valued by payers can be generated using predictive analytics. As the regulatory window widens, a portion of the evidence generated in Phase II and Phase III RCTs can be replaced with alternative approaches. Recent examples indicate that doing so reduces cost and time significantly. One pharma company used rapid-cycle analytics on top of a network of payer databases to satisfy its postmarketing commitments, accomplishing this at 95% lower cost and reducing the time required for evidence generation from 60 months to 6 months. Another firm expanded its oncology label through RWE, taking advantage of the regulatory opening made available by the 21st Century Cures Act.

> *"The majority of a company's postmarketing commitments and evidence generation can be fulfilled using real-world evidence."*

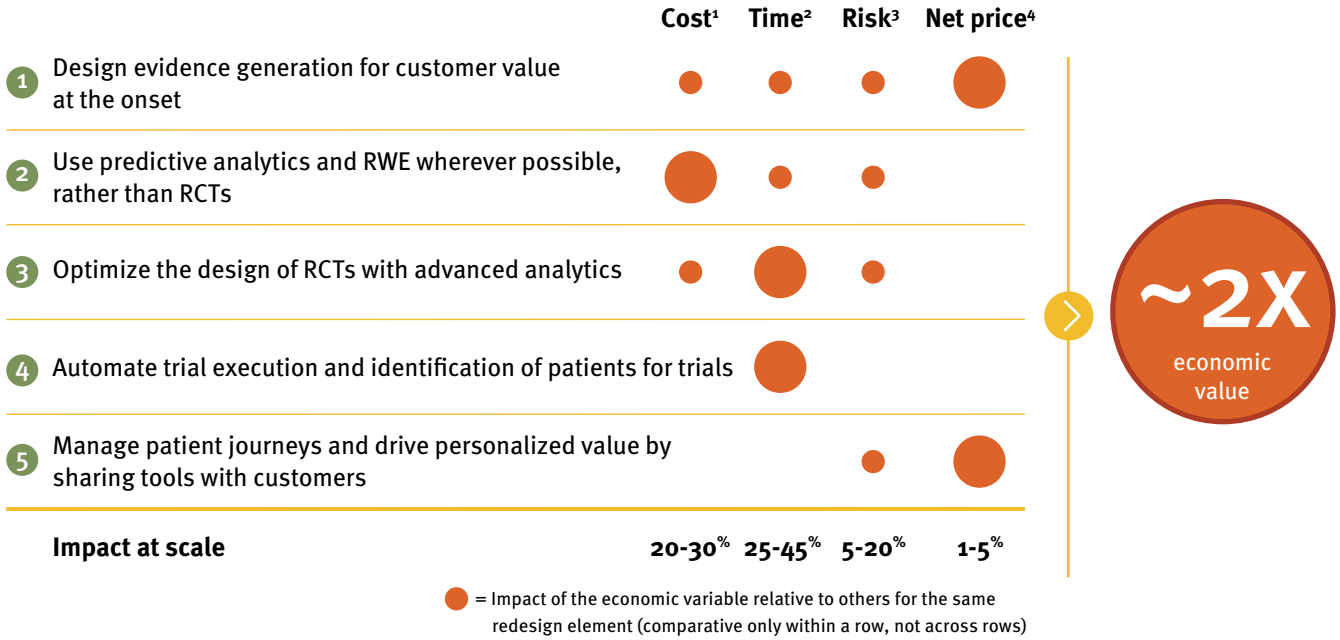
3. Optimize the design of RCTs with advanced analytics. Using real-world data science and predictive tools, pharma companies should design clinical endpoints to demonstrate the largest drug effect in high-payer-value patient subpopulations. Optimizing RCT design can dramatically reduce the risk inherent in trials by increasing their likelihood of success, yielding more valuable evidence. Existing experiments include the many partnerships in which third parties use EMR data to optimize trial inclusion and exclusion criteria.

4. Automate trial execution and identification of patients for trials. Pharma companies should analyze customer data to identify patients who meet specific inclusion criteria for trial enrollment and then automate enrollment and data management. By automating trial execution and accelerating patient recruitment, companies can significantly shorten clinical trials and increase the consistency and integrity of their trial data. One analytics company is already using new biomarker-based analytics to automate the matching of patients to clinical trials and treatments.

5. Manage patient journeys and drive personalized value collaboratively with customers. The value of a pharma company's analytic toolkit can (and should) accrue directly to its partnering customers. The toolkit can be used to help payers identify high-value patients and enable physicians to get the right patients on the right therapy at the right time, resulting in more personalized formularies. Pharma companies should collaboratively demonstrate value to customers and share in the risk by means of value-based contracts where appropriate. This post-launch collaboration with

Exhibit 2

Redesign Doubles The Economic Value Of Products



Economic impacts based on real-world revenue curves, which may vary from long-range plans. 1) Total development cost, inclusive of Phase IV trial costs; 2) Time from beginning of preclinical to best access; 3) Total likelihood of program success (probability of technical success); 4) Weighted (across different levels of access) net price of the drug.

SOURCE: Boston Consulting Group

customers can significantly improve patient outcomes and customers' total costs. For example, to accelerate uptake and demonstrate a new medication's real-world value compared with that of a product that was soon to go off-patent, one pharma company provided a payer with the RWE-based analytics needed to target the new drug to the right patient subpopulation.

The Payoff

Proof points already exist for each of the five elements of the redesign. Implementing them together at scale will *double* the economic value of a pharmaceutical company's products. (*See Exhibit 2.*) This is owing to a combination of four factors: lower cost of evidence generation, lower risk, faster time to best access (increasing the launch-to-loss-of-exclusivity window) and better net price (inclusive of rebates, copay assistance, and access). The redesign ultimately puts companies on a new curve, allowing them to more readily translate ongoing digital and analytics experimentation into bottom-line impact (as opposed to just adding new costs, as is often the case with such investments today).

By being faster, cheaper and better at product development and market access, companies also gain a huge advantage in external sourcing and business development, becoming the partner of choice for external innovators. As better owners of products, they can take the lead in M&A and unlock much greater synergies from those transactions.

How To Make It Happen

The biggest perceived barriers to embracing this new model are regulatory and compliance issues: ensuring that collaboration with customers doesn't run afoul of fraud and abuse statutes and fair-market-value considerations, accessing data without triggering privacy violations, and avoiding off-label-marketing compliance issues. Although these are very valid concerns, our experience suggests that significant value can be unlocked within the existing regulatory framework. Regulators are encouraging digital innovation and many concerns are addressable.

The real hurdle to capturing value stems from a reluctance to make changes to core business processes, cultural resistance to using new data in decision-making and a disinclination to stop doing things the old way. But any digital reinvention implemented within the constraints of the existing operating model will fall flat, delivering at best 20% of the total value. The key is not to make changes *within* existing siloed functions but to implement operating model changes across all key functions.

We suggest four steps to capture the full value of the end-to-end operating model redesign.

Set a bold top-down agenda. The organization's leaders should communicate the vision, in the form of stories, to clarify how the company will create value for stakeholders and gain an edge on competitors. They should set goals that cannot be achieved under the existing model and deputize a subset of the top team to lead the charge. They'll also need to create incentives to get the new

model up and running while still supporting continued performance under the existing model as the transition proceeds.

Make asset life-cycle decisions based on data science. It's time for pharma to shift away from its traditional functionally divided model for decision-making with its bias for asset progression and regulatory caution toward an agile, data science-enabled model that proactively uses integrated insights (around patient, practice and disease) to frame the major decision along the product life cycle through an end-to-end lens. Specifically, this includes: pervasive availability of integrated insights on populations, treatment patterns and assets in near real time; premium on Silicon Valley-style "minimum viable products (MVPs)" and other mechanisms for fast reduction of uncertainty; every decision optimized for end-to-end impact; explicit tracking against customer endpoints and risk factors; red teams to challenge decisions; and democratization of decision-making with AI and machine learning to continuously improve human decision-making. Companies should establish *war rooms* for each category or disease area to promote this culture of data science decision-making and embed it into core business processes through habit-forming user interfaces: develop an easy-to-use dashboard that provides continuously updated evidence and insight on critical development and access questions to support executive decision-making; and establish cross-functional *value teams* that collaborate with decision-makers to ensure end-to-end optimization of decisions.

Elevate data science into a business platform. Companies must pivot away from siloed data and analytics and embrace a cross-functional business platform for making asset decisions. This requires several changes to the existing model:

- Partner directly with leading customers to build a collaborative approach to evidence generation and patient finding/matching/tracking throughout the asset life cycle.

- Prioritize collaboration with data aggregators and analytics vendors that provides distinctive value above and beyond existing partnerships and enables a view of patients and populations that cuts across functions.

- Pursue two-sided value creation so that the platform provides end-to-end integrated insight and improves decision-making by both the company and its strategic partners.

Create a mechanism (Pharma 4.0 Lab) to drive operating model change and asset value acceleration. It is very hard to drive the required end-to-end redesign of the operating model within the existing structure. A proven way to achieve such change is to create a distinct entity – a safe space – for building the new model, operating it to critical scale (in parallel to the existing model), and then transferring it back into the core organization. There is significant value in embarking on this build-operate-transfer with a "friendly" payer/provider customer. The overarching objective of this approach, which we call *Pharma 4.0 Lab*, is to progress select assets throughout the major life-cycle stages up to peak access within a redesigned operating model:

- Leadership team made up of senior representatives of the company, partnering customer(s) and third-party accelerators.

- Fully deployed pharma company resources, including data science talent and assets, complemented with customer and third-party resources; carefully chosen to drive an agile data-science culture.

- Agile operating model built on an open-architecture data science platform that allows for plug-and-play with third-party innovators.

- Injection of new resources (50+% of the total) that include: design thinking, agile experts, data scientists and innovators from other industries.

- Explicit legal and regulatory support to take advantage of new openings, finding how to make happen vs. putting up roadblocks.

- Select assets accelerated through to access using the new operating model, to double economic value (in comparison to progressing assets within the existing model).

There are a couple of options for the endgame as end-to-end value is demonstrated: either transfer the new operating model back into existing operations or funnel additional assets into the Pharma 4.0 Lab. There is also the option to spin off (with participant ownership) a data-science toolkit company. These models have shown value in other industries like financial services, retail and automotive.

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MEETING GROWTH CHALLENGES ROUNDTABLE PANEL PART 1:

Laying The Foundation For A Sustainable Business

BY MIKE WARD

Developing products that are clinically meaningful requires more than a novel approach to an unmet medical need. A panel of biotech executives and venture investors discuss how to meet the challenges of building a sustainable business from day one.

Credit: studiovin

Starting up life science companies has probably never been easier. Our understanding of disease biology continues to grow, the pool of experienced biotech executives with the battle scars of entrepreneurship has never been deeper, and the cash pile to bankroll their development continues to grow. The challenge these days is what do company executives have to do to ensure they can translate their ground breaking ideas into sustainable businesses that develop products that make a meaningful difference to patients.

In Vivo spoke with Gil Van Bokkelen, chairman and CEO of Athersys, Inc., Daniel R. Orlando, chief operating officer of Vericel Corporation, Robert McNeil, general partner and managing director of Sanderling Ventures and CEO of Dalcor Therapeutics, Ali Fattaey president and CEO of Curis, Inc., Mei Mei Hu, co-founder and CEO of United Neuroscience, Inc., Gregory Hanson, CFO of MabVax Therapeutics Holdings, Inc., and Dennis Podlesak, COO at Domain Associates LLC, in a roundtable interview about the challenges company executives face as they try to build their business. Sponsored by Freyeur & Trogue, Impactiv and rbb Communications, the roundtable took place during the J.P. Morgan Healthcare Conference in San Francisco.

Focus on clinically meaningful outcomes

One of the strongest foundation stones life science entrepreneurs can lay when starting to build a company around an idea they have is a thorough understanding of the indication they are targeting and develop a way to dramatically change the treatment paradigm.

"Until 10 years ago, if a drug was approved, the general sense was it could have an important role in treating patients and that would be seen as a success. If you look at how the landscape has changed over time, no entrepreneurs or business leaders would invest either time or money unless the treatment has the potential to be truly differentiated," warned Domain's Podlesak.

"Venture firms and companies both look at how the to grow the business. Unless they can dramatically change the treatment paradigm they tend not to be able to attract capital," he added.

An example of a paradigm-shifting approach in the Domain portfolio is Adynxx, a San Francisco-based biotech that is testing brivoligide, a molecule that inhibits EGR1, a transcription factor that plays a critical role in establishing and maintaining pain following injury or trauma, as a potential non-opioid, disease-modifying therapeutic for post-operative pain. The drug is in a second Phase II trial. If it works it would be the first drug to actively prevent chronic pain.

"Given the prevalence and severity of chronic pain following surgery, combined with the lack of safe, effective and non-addictive treatment options, we believe it can fundamentally transform the treatment paradigm for post-surgical pain. It is an example of how the bar can be raised," added Podlesak.

The challenge comes when the indication has historically been intractable or the endpoints for the clinical trial is not obvious.

"Stroke is a perfect example. Everyone is aware that it is one of those areas where there has been a lot of disappointments – outright failures. Current practice is to either give the patient a thrombolytic like tissue plasminogen activator or take one of the recently developed surgical procedures. Both require treating the patient in the first few hours of the stroke and the clinical reality of that is only a small percentage of patients – roughly 8% – will benefit," noted Athersys' Van Bokkelen.

Athersys is developing an approach that will buy clinicians and patients more time testing MultiStem, a proprietary stem cell product manufactured from human stem cells obtained from adult bone marrow or other non-embryonic tissue sources, in the treatment of multiple distinct diseases. The company is currently evaluating in a Phase II study the administration of MultiStem therapy to patients who have suffered a heart attack, or acute myocardial infarction.

"Our clinical data show that we can effectively treat patients up to 36 hours after a stroke has occurred. It's a very simple procedure that involves an intravenous drip. We believe it will dramatically improve clinical outcomes," added Van Bokkelen.

A lack of meaningful endpoints has been a major stumbling block for companies in the neuroscience space. "That is what has been holding back neuroscience for so long – it's a chicken and egg situation – we needed to figure out the outcomes that we could measure against. It is also a regulatory challenge as the endpoints we have are a bit fuzzy," explained United Neuroscience's Hu. As neurodegeneration takes place over years it is difficult to identify objective and clean endpoints.

United Neuroscience's lead program is UB-311, its novel synthetic peptide vaccine targeting beta amyloid in the treatment of Alzheimer's disease. So far, the company has reported from an ongoing Phase Ii study that UB-311 was able to generate antibodies to specific beta amyloid oligomers and fibrils with no decrease in antibody levels in patients of advanced age. Moreover, amyloid PET imaging and genetic screening for APOE4 status demonstrated an efficient method to identify subjects with mild Alzheimer's for disease modification trials in early-to-mild Alzheimer's.

Predictability as a valuable as clinical outcome

Oncology is one of the areas where the outcomes are more clearly defined and standard clinical trial endpoints are already well established. Emerging oncology companies, however, have to look beyond those endpoints – which normally revolve around durability of the clinical benefit. "It is more important that you can enhance the predictability of choosing the right patients – knowing who may or may not benefit," noted Curis' Fattaey.

Being able to identify the best patients for a particular treatment clearly not on benefits patients, it helps payers, investors and the companies too. "For us, it impacts our way of thinking about how we grow. Do we have enough infrastructure and technologies to be able to tell who is going to benefit or not," Fattaey added.

Curis' lead program, CUDC-907, an orally-available, small molecule inhibitor of HDAC and PI3 kinase enzymes, is currently in a Phase II, open-label, multicenter trial designed to evaluate its efficacy and safety in subjects 18 years and older with relapsed/refractory (RR) MYC-altered diffuse large B-cell lymphoma (DLBCL). Patients with RR DLBCL are eligible for treatment with CUDC-907, as long as they have tumor tissue available that can be tested for MYC-altered disease.

Marrying assets that help improve the predictability of outcome, according to MabVax Therapeutics' Hanson, are probably more important for building a business than the market opportunities or intellectual property.

"We are in pancreatic cancer, an area that many companies have failed when trying to come up with effective treatments. Why would we want to go after it? It just so happens our antibody targets a particular antigen that is expressed on more than 90% of pancreatic tumors and so has a high probability of success," he added.

MabVax Therapeutics' approach was to develop the HuMab-5B1 antibody, which was discovered from the immune response of cancer patients vaccinated

Ali Fattaey
President & CEO, Curis Inc.

Robert McNeil
Managing Director, Sanderling Ventures & CEO, Dalcor Therapeutics

Daniel R. Orlando
COO, Vericel Corporation

Dennis Podlesak
Partner, Domain Associates LLC

Mei Mei Hu
Co-founder & CEO, United Neuroscience Inc.

Gil Van Bokkelen
Chairman & CEO, Athersys Inc.

Gregory Hanson
CFO, MabVax Therapeutics Holdings, Inc.

with an antigen-specific vaccine during a Phase 1 trial at Memorial Sloan Kettering Cancer Center and subsequently in-licensed, as a therapeutic. Moreover, noting that the HuMab-5B1 antibody has excellent tumor targeting capabilities, as well as being internalized by pancreatic cancer cells, the company created a tumor-targeting platform.

The company conjugated the antibody, MVT-5873, with the radiolabel zirconium 89, to create MVT-2163, a PET agent as an important tool to aid in the diagnosis, monitoring and assessment of pancreatic cancer patients as well as an attractive companion diagnostic for the MVT-5873 therapeutic product.

"The problem with pancreatic cancer is by the time it is discovered it's too late. Your life expectancy is such that you would be lucky to get beyond a year. So by being able to identify the metastatic sites you can know whether the patient is suitable for surgery or not. This is a new paradigm because many surgeons find out after that surgery was not a good decision. We feel that we are going to do something that has not been possible before," he added.

MabVax Therapeutics is testing both MVT-5873 as a monotherapy or in combination with the current standard of care chemotherapy regimen in subjects with metastatic pancreatic cancer and MVT-2163 in the diagnosis, monitoring and assessment of pancreatic cancer patients and as a potential companion diagnostic for the MVT-5873.

Investors are particularly keen on sifting out the probable from possible. "One way of thinking about it – a lot of our job becomes sorting out what is more probable. You are looking for things that are disproportionately more likely to succeed," noted Podlesak.

"Until 10 years ago, if a drug was approved, the general sense was it could have an important role in treating patients and that would be seen as a success. If you look at how the landscape has changed over time, no entrepreneurs or business leaders would invest either time or money unless the treatment has the potential to be truly differentiated," warned Domain's Podlesak.

One way of increasing the probability of success is to take under-appreciated and underperforming assets and revive them. In 2014, Vericel, created when Ann Arbor, Mich.-based Aastrom Biosciences bought Sanofi's cell therapy and regenerative medicine business, a holdover from Sanofi's 2011 acquisition of Genzyme Corp. Vericel paid $4m in cash plus a $2.5m promissory note to get access to Carticel and MACI cell therapy products for the treatment of cartilage defects in the knee and Epicel (cultured epidermal autografts) a permanent skin replacement for the treatment of patients with severe deep-dermal or full-thickness burns, a business with about $44m in annual revenue. In the first nine months of the current year, these products posted net revenues of just under $41m.

At the time Aastrom was a struggling company but the acquisition of the cell therapy portfolio, the name change the shift of its headquarters to Cambridge were, according to Vericel's Orlando crucial steps in the transformation of the business from a clinical-stage company to a fully integrated, commercial-stage specialty biologics company. "We believed with the right attention we could get leverage more of the potential of the products we had acquired," he added.

This is the first installment of a multi-part coverage of the Meeting Growth Challenges Roundtable, sponsored by Freyeur & Trogue, Impactiv and rbb Communications, conducted during the J.P. Morgan Healthcare Conference in San Francisco.

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On the Move

Recent executive appointments in the life sciences industry

COMPANY CHANGES

ALBIZATI, Kim F., PhD
To: Molecular Assemblies Inc., VP, Chemistry & Biochemistry (Feb)
From: Dart Neuroscience, Senior Dir., Chemistry, Mfg. & Controls
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BEDROSIAN, Camille L., MD, PhD
To: Ultragenyx Pharmaceutical Inc., EVP, CMO (Jan)
From: Alexion Pharmaceuticals Inc., SVP, CMO
Phone: 415-483-8800

BIGAL, Marcelo, MD, PhD
To: Purdue Pharma LP, CMO (Mar)
From: Teva Pharmaceutical Industries Ltd., CSO
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DAVIS, John, MD
To: Magenta Therapeutics Inc., CMO (Feb)
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ANTHONY POLVERINO
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DOUGLAS SWIRSKY
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Deal-Making

Covering deals made February 2018

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

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

For information about access please contact Customer Care at 800-332-2181 or ibislsales@informa.com

IN VITRO DIAGNOSTICS

Financings

Chembio Diagnostics nets $11.2mm via FOPO

OpGen nets $11.1mm via FOPO of units

MEDICAL DEVICES

Mergers & Acquisitions

Allergan acquires **Elastagen** for $95mm plus up to $165mm in earn-outs

Aesculap buys **Dextera** for $17.3mm

J&J pays undisclosed amount for **Orthotaxy**

LivaNova buys **TandemLife**

Roche acquires health care tech company **Flatiron Health**

Alliances

Abbott gets rights to **SurModics'** PAD device

Merit acquires needle biopsy products from **BD**

Financings

Avinger nets $16.5mm via FOPO of convertible preferred stock

LivaNova enters loan agreement with BoA Merrill Lynch to support **TandemLife** acquisition

Motus GI nets $16.1mm in IPO

Novocure enters $150mm loan financing; pays off existing debt

Tandem Diabetes Care nets $64.9mm via FOPO

ViewRay gets $59mm investment through private placement with **Fosun**

Viveve brings in $32.4mm through FOPO

Xtant Medical grosses $6.8mm in PIPE

PHARMACEUTICALS

Mergers & Acquisitions

Astellas pays $102.5mm for **Universal Cells**

Kolmar Korea acquires **CJ CheilJedang**'s CJ Healthcare

Merck acquires immuno-oncology partner **Viralytics**

Mundipharma acquires **Tolmar Australia**

Alliances

AbbVie, **Voyager** sign agreement for anti-tau antibodies aimed at CNS diseases

Aldeyra, **Janssen R&D** ally in inflammatory diseases

AnaBios licenses atrial fibrillation candidates from **Sanofi**

Kowa, **Nissan** settle patent litigation with **Apotex** related to generic *Livalo*

ArQule grants **Roivant**/**Sinovant** exclusive derazantinib rights in China

Bavarian Nordic and **AZ** investigate immunotherapy combo

Syndax and **AZ** perform solid tumor combo trial

Cerecor licenses several programs from **Avadel**

Avid Bioservices sells off PS-targeting program to **Oncologie**; completes transition to CDMO

BioDelivery Sciences settles patent litigation; licenses US *Belbuca* rights to **Teva**

Biohaven applies **Catalent**'s *Zydis* technology to rimegepant migraine candidate

Bioverativ gets rights to **Oxford BioMedica**'s *LentiVector* tech for hemophilia therapies

BMS, **Nektar** build off of 2016 trial collaboration, sign official immuno-oncology deal

CANbridge pays $30mm up front for rights to **Puma**'s *Nerlynx*

Dare licenses exclusive rights to **SST**'s FSAD candidate SST6007

ElsaLys grants **Thea** exclusive option to ELB011

Everest Medicines gets exclusive Asian rights to **Tetraphase**'s eravacycline

Kite gets rights to **Sangamo**'s zinc finger nuclease platform; could pay $3bn

Sam Chun Dang grants **Glenmark** rights to ophthalmic portfolio in North America

Servier and **ImmunoQure** develop interferon-alpha human autoantibody for rare diseases

Theravance partners IBD program with **Janssen Biotech**

PharmAbcine and **Merck** evaluate TTAC0001/*Keytruda* combination

Advanced Accelerator licenses **CTT**'s F-18-labeled CTT1057 as a prostate cancer diagnostic

Partner Therapeutics acquires **Sanofi**'s immunostimulant *Leukine*

Seattle Genetics licenses ADC payloads from **PharmaMar**

Pieris and **Seattle Genetics** partner for immuno-oncology projects

Santhera gets exclusive worldwide rights to **Polyphor**'s POL6014

Roivant gets rights to **Poxel**'s imeglimin worldwide except in certain Asian countries

Teva licenses rights to **ProBioGen**'s *HuALN* platform technology

Takeda enters CNS collaboration with **Wave Life Sciences**

Financings

Addex Therapeutics plans to gross CHF40mm in private placement

Advaxis nets $18.8mm through public offering

Adverum nets $64.9mm via FOPO

Affimed gets $24.9mm in public stock sale

Public offering nets $165mm for **Aimmune**

Dermatology-focused **Evolus** nets $55.8mm in Nasdaq IPO

FOPO nets $282mm for **Amicus**

Ascendis nets $211.5mm via follow-on offering of ADSs

Athersys enters into $100mm new equity facility with Aspire Capital; $1mm initial investment

Avadel nets $119.6mm in senior notes offering

Avid Bioservices nets $21.8mm in FOPO

Public offering nets $107mm for **Catalyst Biosciences**

Cellular Biomedicine gets $30.5mm through private investment from Sailing Capital

CTI BioPharma closes $65mm public offering

Dare nets $9.5mm in FOPO to support concurrent licensing deal with **SST**

Dova nets $75.2mm via FOPO

Dynavax enters $175mm loan agreement; gets $100mm up front

Gemphire nets $20.5mm through public stock offering

Immunovaccine nets $Cdn13.5mm through bought deal offering

MediciNova nets $37.6mm in FOPO

Private placement grosses $55.8mm for **Merus NV**

MiRagen Therapeutics nets $36.2mm in FOPO

Moleculin nets $8.4mm through registered direct offering

NovaBay gets $6mm via PIPE

Onconova sells shares and pre-funded warrants; nets $9.3mm

Public offering nets $21.3mm for **OncoSec**

Public offering nets $47.6mm for **Pieris**

DDT company **PolyPid Ltd.** files for IPO; later withdraws; re-files nearly three years later

Ra Pharmaceuticals nets $47.4mm in FOPO

CNS therapeutics firm **Sage** nets $549mm in FOPO

Seattle Genetics public offering nets $659mm to fund **Cascadian** purchase

Veloxis gets $60mm through debt financing

Viking Therapeutics nets $58.8mm via FOPO

IN VITRO DIAGNOSTICS

Financings

CHEMBIO DIAGNOSTICS INC.

Chembio Diagnostics Inc. (point-of-care tests for infectious diseases) netted $11.2mm through the public offering of 1.78mm common shares at $6.75 each. The company will use the funds for development and sales and marketing activities, and to update its equipment and facilities. (Feb.)

Investment Banks/Advisors: Craig-Hallum Inc.

OPGEN INC.

OpGen Inc. (infectious disease diagnostics) netted $8.5mm through the follow-on public offering of 2.84mm units priced at $3.25 per unit; each unit consists of one common share and one five-year warrant to buy a half of a share at an exercise price of $3.25 per share. The company also realized $2.55mm in net proceeds through the issuance of 851k pre-funded units at $3.24; each consisted of one pre-funded warrant to purchase one common share at an exercise price of $0.01, and one warrant to purchase one-half share of common stock. The company will use the proceeds for R&D activities including development and manufacturing of its *Acuitas* AMR gene panels for detecting antibiotic resistance. (Feb.)

Investment Banks/Advisors: HC Wainwright & Co.

MEDICAL DEVICES

Mergers & Acquisitions

ALLERGAN PLC
ELASTAGEN PTY. LTD.

Allergan PLC has agreed to acquire privately held Australian company **Elastagen Pty. Ltd.** (biomaterials and surgical sealants). (Feb.)

Elastagen will receive $95mm in cash up front and is also eligible for future earn-outs of up to $165mm based on the achievement of certain commercial goals (according to Hogan Lovells, Elastagen's legal advisor on the deal). The company's recombinant human tropoelastin is a 60kDa extracellular matrix protein and

a precursor to elastin--a key component in the skin, arteries, bladder, and lungs--which gives tissue its elasticity and also has a critical role in cell regulation. Due to the progressive loss of the elastin protein that occurs with aging, skin elasticity deteriorates. Tropoelastin forms the basis of Elastagen's *Elastatherapy* advanced tissue repair platform, which was licensed from the **University of Sydney**, where it was invented in the lab of professor Anthony Weiss. The *Elastatherapy* technology has potential applications in aesthetics, including scar remodeling and plastic surgery. Tropoelastin's advantages include its physical elastic properties and its ability to support cell growth and tissue repair. As a recombinant human biomaterial, its polymers are biocompatible and without immune rejection issues. Recently reported results of a feasibility study of injectable tropoelastin for stretch marks demonstrated positive safety outcomes and an 80% reduction in stretch mark depression volume. In addition to aesthetic indications, tropoelastin is being studied in surgical applications, particularly as a surgical wound sealant, to repair and close elastic tissues such as lungs and blood vessels. Founded in 2008, Elastagen venture backers include ATP Innovations, Brandon Capital, GBS Ventures, Korea Investment Partners, Cell Innovation Partners, AmorePacific Ventures, and the Wellcome Trust. Tropoelastin will be a complementary addition to Allergan's existing facial aesthetics portfolio, which is headed by blockbusters *Botox* cosmetic and the *Juvederm* (hyaluronic acid) collection of dermal fillers. Last year Allergan also supplemented its plastic surgery and facial aesthetics offerings through the $2.5bn acquisition of contouring device company **Zeltiq** and its *CoolSculpting* controlled-cooling fat reduction technology used in aesthetic procedures.

B. BRAUN MELSUNGEN AG
Aesculap Inc.
DEXTERA SURGICAL INC.

B. Braun Melsungen AG's **Aesculap Inc.** finalized the acquisition of cardio-thoracic device maker **Dextera Surgical Inc.** (formerly Cardica) for $17.3mm. (Feb.)

Dextera had filed for Chapter 11 bankruptcy protection back in December. Soon thereafter Aesculap reached an agreement to buy the firm with a $17.3mm stalking-horse bid in a court-supervised auction. No other buyers submitted bids by the mid-January deadline so the auction was canceled and Aesculap was allowed to buy Dextera. Dextera develops, manufactures, and sells various surgical devices such as staplers and products for use in coronary artery bypass graft surgery. Specific offerings include the *MicroCutter 5/80* stapler and *PAS-Port* proximal and distal anastomosis systems. Under a previous 2016 tie-up, **B. Braun Surgical** became the exclusive marketer and distributor of Dextera's *MicroCutter 5/80* surgical stapler in Spain.

JOHNSON & JOHNSON
ORTHOTAXY SAS

Johnson & Johnson, through its Apsis SAS subsidiary, has acquired closely held French surgical device maker **Orthotaxy SAS** for an undisclosed sum. (Feb.)

Orthotaxy offers software-enabled technologies for use in surgical procedures. The company is initially developing devices for total and partial knee replacement. With the Orthotaxy IP, J&J hopes to create a next-generation comprehensive robotic-assisted solution for a range of orthopedic applications. The acquired firm's 16 employees will stay on and continue their work at its headquarters in France. According to a recent report from *Meddevicetracker*, the worldwide market for robot-assisted surgical devices is expected to increase from $3bn in 2016 to $5.3bn by 2021. The current market leader in the space is **Intuitive Surgical**.

LIVANOVA PLC
TANDEMLIFE

To expand its cardiac surgery portfolio, **LivaNova PLC** is paying $200mm to acquire private cardiopulmonary device maker **TandemLife** (formerly known as CardiacAssist). LivaNova could also hand over up to $50mm in regulatory-based earn-outs. (Feb.)

The acquired company was founded as CardiacAssist in 1996 and twenty years later it announced a rebranding effort and changed its name to TandemLife to focus on making advanced cardiac and respiratory devices available to more patients. The firm has developed systems for extracorporeal life support (ECLS) and percutaneous mechanical circulatory support (pMCS). TandemLife's specific brands are *TandemLife* (cardiopulmonary support through veno-arterial ECLS), *TandemLung* (pulmonary support through veno-venous ECLS), *TandemHeart* (left heart support via pMCS), and *ProtekDuo* (right heart support via pMCS). In connection with the agreement, LivaNova entered into a $170mm term loan facility with Bank of America Merrill Lynch International Limited. Two months ago LivaNova acquired sleep apnea device maker **ImThera Medical** for $78mm up front and up to $147mm in regulatory and sales milestones.

ROCHE
FLATIRON HEALTH INC.

Roche agreed to acquire all outstanding shares of **Flatiron Health Inc.** (e-health) for $1.9bn in cash (enterprise value of $2.17bn; Flatiron was previously valued at $1.2bn in 2016). (Feb.)

The acquisition stems from an existing partnership that the two companies already have, with Roche previously holding a 12.6% equity interest in Flatiron. Flatiron Health operates as a technology platform providing oncology-specific electronic health record software and a suite of software products for advancing real-world evidence of cancer research. Founded by ex-Google employees Nat Turner and Zach Weinberg, Flatiron has raised more than $300mm (including its most recent $175mm round back in 2016) from investors including Roche and Alphabet's venture arm, GV. Post-closing, Flatiron is expected to continue its current business model and network of partnerships. The company partners with over 265 community cancer clinics, six major academic research centers and 14 out of the top 15 oncology companies. Industry sources say that large distributor **McKesson** had also shown interest in possibly acquiring Flatiron. The transaction comes at a time when digital health is heating up and partnerships are blurring the lines from more traditional therapeutic company acquisitions. The addition of Flatiron comes after Roche's partnership with **23andMe** and will provide Roche with the technology and data analytics infrastructure to be a global player in the "new" health care model. Investment Banks/Advisors: Allen & Co. (Flatiron Health Inc.)

Alliances

ABBOTT LABORATORIES INC.
SURMODICS INC.

SurModics Inc. granted **Abbott Laboratories Inc.** exclusive worldwide rights to commercialize its *SurVeil* drug-coated balloon to treat the superficial femoral artery. (Feb.)

In addition, Abbott has options to negotiate for SurModics' below-the-knee and arteriovenous fistula drug-coated balloon products currently in pre-clinical development. SurModics receives $25mm up front plus up to $67mm in development milestones. *SurVeil* is in a US pivotal clinical trial in comparison with the Medtronic's market-leading *Admiral* drug-coated balloon in patients PAD in the legs. Both firms will collaborate on development and regulatory activities required for US and European approvals. Should *SurVeil* be approved, SurModics will manufacture and supply Abbott with the product, realize revenue from initial product sales to Abbott, and share in profits from third-party sales. The deal adds to Abbott's extensive portfolio of PAD products such as stents and vessel closure devices.

BECTON DICKINSON & CO.
MERIT MEDICAL SYSTEMS INC.

As part of **Becton Dickinson & Co.**'s purchase of **CR Bard Inc.**, the company divested various soft tissue needle biopsy de-

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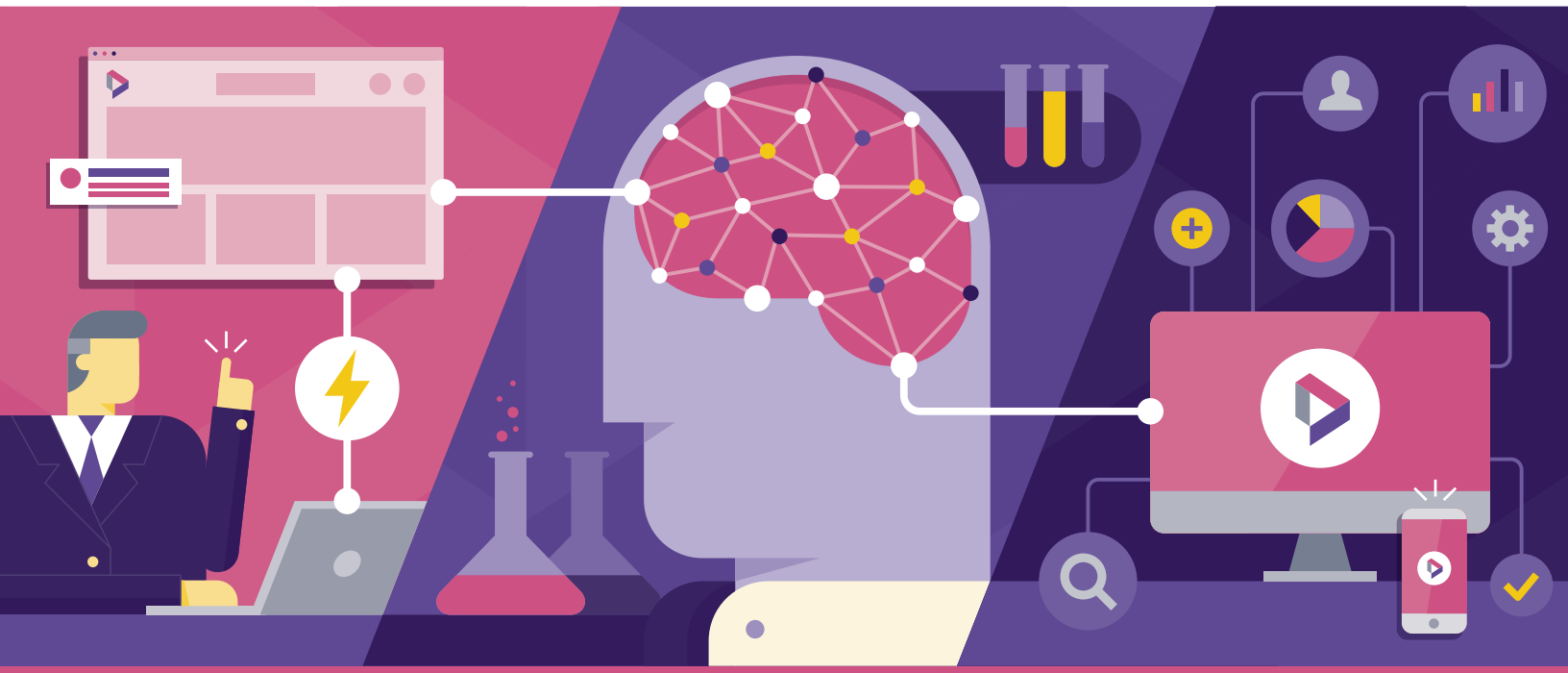

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vices to **Merit Medical Systems Inc.** (Feb.)

The divested products include: *Achieve* programmable automatic biopsy system, *Temno* biopsy system, *Tru-Cut* biopsy needles and *Aspira* pleural effusion drainage kits, and the *Aspira* peritoneal drainage System. In exchange for the assets, Merit has agreed to pay $100mm in cash to BD. The products will be sold by Merit's direct salesforce and distribution partners and will complement Merit's *Corvocet* full core biopsy system and *Laurane* bone biopsy products. Investment Banks/Advisors: Piper Jaffray & Co. (Merit Medical Systems Inc.)

Financings

AVINGER INC.

Avinger Inc. (therapies for peripheral artery disease) netted $16.5mm through the public offering of 18k Series B convertible preferred shares priced at $1k each. The company also issued 18mm seven-year warrants to buy one common share at an exercise price of $2. In the offering, a total of 18k shares of Series B preferred stock, convertible into approximately 9mm shares of common stock, and warrants to purchase approximately 18mm shares of common stock will be issued. Avinger will use some of the proceeds for ongoing development of products (such as the *Pantheris* atherectomy devices) based on its *Lumivascular* intravascular image-guided technology and for commercialization activities. In conjunction with financing, CRG and affiliates will convert $38mm of debt into Avinger Series A convertible preferred stock under a previous term loan agreement. (Feb.)

Investment Banks/Advisors: Ladenburg Thalmann & Co. Inc.

LIVANOVA PLC

In connection with its acquisition of cardiopulmonary device firm **TandemLife**, **LivaNova PLC** entered into a $170mm term loan facility with Bank of America Merrill Lynch International Ltd. The facility will terminate on August 14, 2018, but can be extended to February 13, 2019 under certain circumstances. The loan bears interest at a variable annual rate based on LIBOR plus an applicable margin of 0.75% per annum for the first six months, 1% for the following three months, and 1.25% after that time. For TandemLife, LivaNova is paying $200mm up front and up to $50mm in regulatory milestones. (Feb.)

MOTUS GI HOLDINGS INC.

Medical device firm **Motus GI Holdings Inc.** (bowel cleaning) netted $16.1mm in its initial public offering of 3.5mm common shares priced at $5, the lower end of its intended $5-7 price range. (Feb.)

Investment Banks/Advisors: Oppenheimer & Co. Inc.; Piper Jaffray & Co.

NOVOCURE LTD.

Novocure Ltd. (developed the Tumor Treating Fields alternating electrical field technology to treat cancer) entered into a $150mm non-dilutive term loan with BioPharma Credit PLC (managed by Pharmakon Advisors). The company drew down the loan in full immediately, and will use the proceeds to repay obligations under a 2015 $100mm loan agreement with Pharmakon's BioPharma Secured Investments (Feb.)

Investment Banks/Advisors: Armentum Partners

TANDEM DIABETES CARE INC.

Tandem Diabetes Care Inc. (developer of insulin pumps and continuous glucose monitoring systems) netted $64.9mm in a follow-on public offering of 34.5mm common shares (including full exercise of the overallotment) at $2 each. (Feb.)

Investment Banks/Advisors: National Securities Corp.; Oppenheimer & Co. Inc.

VIEWRAY INC.

ViewRay Inc. (MRI-guided radiation therapy for cancer) grossed $59mm through a direct registered offering of 7.1mm common shares at $8.31 (a slight premium) to existing investor **Fosun International**. Through the transaction, Fosun increases its ownership of ViewRay to 18.4%; it previously held a 9.9% stake following an investment it made in the company's $50mm RDO late last year. (Feb.)

VIVEVE MEDICAL INC.

Women's health device maker **Viveve Medical Inc.** netted $32.4mm through a follow-on public offering of 11.5mm shares (including the overallotment) at $3. The company will put the funds toward R&D, clinical and regulatory, and sales and marketing expenses. Viveve's noninvasive *Geneveve* treatment (which incorporates its cryogen-cooled, monopolar radiofrequency (CMRF) technology) is approved for marketing in 60 countries for indications in vaginal laxity and/or improvement in sexual function. The company recently announced plans to expand its CMRF platform into the stress urinary incontinence (SUI) market following positive results from a recently completed pilot study in female SUI patients, and will proceed with two additional safety and efficacy trials. (Feb.)

Investment Banks/Advisors: Cowen & Co. LLC; Ladenburg Thalmann & Co. Inc.; Maxim Group LLC; Raymond James & Associates Inc.

XTANT MEDICAL HOLDINGS INC.

Xtant Medical Holdings Inc. (orthopedic-focused regenerative medicine products) grossed $6.8mm in a private placement financing of 945.8k common shares at $7.20 (41% premium to prior 10-day market trading average) to investors OrbiMed and ROS Acquisition Offshore LP. Simultaneously the company also exchanged $70.2mm of convertible notes into 10.4mm common shares at the same price per share. Xtant just completed a 1:12 reverse stock split prior to the financing. (Feb.)

PHARMACEUTICALS

Mergers & Acquisitions

ASTELLAS PHARMA INC.
UNIVERSAL CELLS INC.

Astellas Pharma Inc. is paying $102.5mm to acquire private stem cell therapeutics developer **Universal Cells Inc.** The agreement also includes potential earn-outs based on pre-determined clinical milestones. (Feb.)

Post-acquisition, Universal Cells becomes a wholly-owned Astellas subsidiary. Astellas was particularly attracted to Universal Cells' Universal Donor Cell platform which can create cell therapeutics by manipulating human leukocyte antigen (HLA) expression instead of requiring HLA matching, thus reducing the risk for immunological rejection. Astellas had already been familiar with the technology; in October 2017, its **Institute for Regenerative Medicine** received exclusive rights to use Universal Donor Cell in a single indication. Astellas now plans to explore the platform for a variety of indications including those with limited or no treatment options. Universal Cells' pipeline includes preclinical programs for undisclosed therapy areas and the firm has partnerships with **Adaptimmune** and **Healios**.

KOLMAR KOREA CO.
CJ CORP.
CJ CheilJedang Corp.

CRO **Kolmar Korea Co.** agreed to acquire **CJ CheilJedang Corp.**'s CJ Healthcare for KRW1.31tn ($1.22bn). (Feb.)

CJ Healthcare manufactures over-the-counter drugs and health foods and had 2017 revenues of approximately KRW500bn (2.62x enterprise value to sales multiple). Its pipeline focuses on digestive disorders, cancer, and immune diseases. The company is developing CJ12420 (tegoprazan), a next generation potassium-competitive acid blocker currently in Phase III trials for GERD. CJ also has a NASH candidate in preclinical (CJ14199) and a preclinical rheumatoid arthritis therapy, as well as research-stage liver and immune-oncology candidates. The two companies have very little product overlap and expect to see significant synergies (Kolmar is strong in ointments while CJ is known for eye drops and injections). Kolmar reportedly outbid private

equity firms Carlyle and MBK Partners for the company. CJ CheilJedang decided to put the healthcare business on the selling block back in 2017 (had originally been looking to do an IPO) to focus on its core grocery business (also out-licensed second-generation erythropoietin biosimilar rights in China back in January). The acquisition represents the first major pharma transaction in Korea in the past few years as companies have been reluctant to spend money and stay focused on generics for stable revenues. Investment Banks/Advisors: Morgan Stanley & Co. (CJ CheilJedang Corp.); Deutsche Bank AG (Kolmar Korea Co.)

MERCK & CO. INC.
VIRALYTICS LTD.

Merck & Co. Inc. will pay $A1.75 ($1.38; a 165% premium) or $A502mm to acquire oncolytic immunotherapy developer **Viralytics Ltd.** (Feb.)

Post-acquisition, Viralytics will become a subsidiary of Merck. The pair have been working together since entering a trial collaboration agreement in 2015. Through that tie-up, they are evaluating the combination of Viralytics' *Cavatak* oncolytic immunotherapy (a proprietary formulation of the Coxsackievirus Type A21 that preferentially infects and kills cancer cells) together with Merck's PD-1 antagonist *Keytruda* (pembrolizumab) as a potential treatment for advanced non-small cell lung cancer and metastatic bladder cancer as well as prostate cancer and melanoma. Merck now gains full control of *Cavatak* (Viralytics' sole candidate), expanding the Big Pharma's immuno-oncology pipeline. Viralytics' shareholders voted in favor of the acquisition, pending no further superior offers. Investment Banks/Advisors: Credit Suisse Group (Merck & Co. Inc.); Lazard LLC (Viralytics Ltd.)

MUNDIPHARMA INTERNATIONAL CORP. LTD.
Mundipharma Pty. Ltd.
TOLMAR HOLDING INC.
Tolmar Australia Pty. Ltd.

Mundipharma Pty. Ltd. acquired **Tolmar Australia Pty. Ltd.**, a division of **Tolmar Holding** with offerings for prostate cancer. The purchase price was not disclosed. (Feb.)

Through the deal, Mundipharma gains control in New Zealand and Australia of Tolmar's two marketed therapies *Eligard* (leuprolin acetate) and *Bi Eligard* cp, a combination product comprised of subcutaneous *Eligard* and oral bicalumatide tablets. Both are indicated for the treatment and management of advanced prostate cancer. The acquisition expands Mundipharma's cancer portfolio beyond the existing products *Aloxi* (palonosetron) and *Akynzeo* (netupitant/palonosetron) for chemotherapy-induced nausea and vomiting, and *Folotyn* (pralatrexate), which is indicated for relapsed/refractory peripheral T-cell lymphoma.

Alliances

ABBVIE INC.
VOYAGER THERAPEUTICS INC.

AbbVie Inc. and **Voyager Therapeutics Inc.** are teaming up in the development of vectorized tau antibodies for treating neurodegenerative conditions including Alzheimer's disease, progressive supranuclear palsy, and frontotemporal dementia. (Feb.)

Voyager will conduct research and preclinical development activities, after which point AbbVie can choose one or more vectorized antibodies to move into IND-enabling studies. Each company agreed to identify up to five antibodies for inclusion in the collaboration; they will then select up to three antibodies as candidates, with AbbVie having the right to select two of the antibodies. Voyager is in charge of conducting and funding the IND-enabling and Phase I trials. Following Phase I, AbbVie has an option to license the candidates and would take over further clinical development and commercialization activities.

ALDEYRA THERAPEUTICS INC.
JOHNSON & JOHNSON
Janssen R&D LLC

Aldeyra Therapeutics Inc. is teaming up with **Janssen R&D LLC** in the development of drugs targeting aldehydes. (Feb.)

Aldehydes can activate certain pro-inflammatory factors to fight inflammation. Aldeyra's platform can be used to create therapies that sequester pro-inflammatory aldehyde mediators. The company's lead candidate arising from the technology is Phase III reproxalap for dry eye disease, allergic conjunctivitis, uveitis, and Sjögren-Larsson syndrome. Under the agreement, Aldeyra and Janssen seek to advance existing analogs of reproxalap for systemic inflammatory diseases. The parties will together conduct research activities to be overseen by a joint scientific review committee. For a limited period and subject to certain conditions, Janssen has the option to negotiate an exclusive license to any compounds. Aldeyra chose to partner with Janssen because of its commitment to the inflammatory space.

ANABIOS CORP.
SANOFI

AnaBios Corp. licensed development and commercialization rights to an undisclosed family of atrial fibrillation compounds from **Sanofi**. Financial details were not revealed. (Feb.)

AnaBios uses its suites of translational technologies to evaluate in-house and partnered drug programs. With the Sanofi compounds, the company will utilize its *CardioPRIME* ex vivo platform to assess the safety and efficacy of the in-licensed candidates, which are in development to modulate a novel cardiac ion channel target. *CardioPRIME* is a human cardiomyocyte-based assay that assesses both pro-arrhythmia and inotropic risk of drug compounds. The system has been validated with a set of 38 molecules with previously known clinical outcomes, and exhibited 96% sensitivity and 100% specificity.

APOTEX INC.
KOWA CO. LTD.
Kowa Pharmaceuticals America Inc.
NISSAN CHEMICAL INDUSTRIES LTD.

Kowa Pharmaceuticals America Inc. and **Nissan Chemical Industries Ltd.** have settled patent litigation with **Apotex Inc.** surrounding generic *Livalo* (pitavastatin). Kowa and Nissan had filed for patent infringement following Apotex's ANDA filing for 1, 2, and 4mg pitavastatin tablets. Kowa and Nissan had already sued other generics firms for filing ANDAs for pitavastatin. Under all the settlements, including the current agreement with Apotex, the defendants will market generic *Livalo* starting on May 2, 2023 or earlier under certain circumstances. *Livalo* is sold worldwide for the treatment of hyperlipidemia and hypercholesterolemia. (Feb.)

ARQULE INC.
ROIVANT SCIENCES GMBH
Sinovant Sciences Ltd.

ArQule Inc. granted **Roivant Sciences GMBH** and its **Sinovant Sciences Ltd.** division exclusive rights to develop, manufacture, and sell in China, Hong Kong, Macau, and Taiwan the investigational cancer candidate derazantinib. (Feb.)

Derazantinib, a fibroblast growth factor receptor antagonist, is in Phase III trials for intrahepatic cholangiocarcinoma (biliary tract cancer). Roivant paid $3mm up front and committed to a $2.5mm development milestone within the next year; $82mm in regulatory and commercialization milestones; and royalties in the low-teens. The company plans to continue studying the candidate in its current indications, but also intends to study it for other FGFR-driven tumors.

ASTRAZENECA PLC
BAVARIAN NORDIC AS

Bavarian Nordic AS and **AstraZeneca PLC** will conduct trials to explore the combination of Bavarian's CV301 with AZ's *Imfinzi* (durvalumab) and chemotherapy to treat metastatic colorectal or pancreatic cancers. (Feb.)

Bavarian is studying CV301, a CEA/MUC-1 inhibitor, in a Phase Ib/II trial in combination with *Keytruda* (pembrolizumab) for non-small cell lung cancer, and in Phase II

with *Tecentriq* (atezolizumab) for bladder cancer. *Imfinzi*, a PD-L1 immunotherapy, is marketed for bladder and non-small cell lung cancers, and in trials for a number of other solid and blood cancers. Bavarian and AZ will contribute clinical trial material and funding for a Phase I/II trial, to be conducted at **Georgetown University**, with a primary endpoint of progression-free survival and secondary endpoints including overall survival, objective response rate, and disease control rate.

ASTRAZENECA PLC
SYNDAX PHARMACEUTICALS INC.

Syndax Pharmaceuticals Inc. agreed to pair its monoclonal antibody SNDX6352 with **AstraZeneca PLC**'s anti-PD-L1 antibody durvalumab in Phase Ib/II trials for solid tumors. (Feb.)

Through the trial collaboration, safety and efficacy studies will be conducted on the combination; safety and dosing will be established in Phase Ib, with Phase II trials designed to study effectiveness across a variety of tumors. Syndax licensed SNDX6352, a colony stimulating factor 1 receptor inhibitor, from **UCB** in 2016 and currently has the candidate in Phase I. AZ's durvalumab is marketed as *Imfinzi* for bladder cancer, awaiting approval for non-small cell lung cancer, and is in over two dozen trials for solid and blood cancers.

AVADEL PHARMACEUTICALS PLC
CERECOR INC.

Cerecor Inc. is acquiring four of **Avadel Pharmaceuticals PLC**'s marketed pediatric products. (Feb.)

Included in the deal are the antihistamine *Karbinal* ER for seasonal and perennial allergic rhinitis; *AcipHex Sprinkle* delayed-release capsules for gastroesophageal reflux disease; cefaclor, an antibiotic for otitis media, lower respiratory infections, pharyngitis and tonsillitis, urinary tract infections, and skin and skin structure infections; and the *Flexichamber* device for administering aerosolized medication from most pressurized metered dose inhalers. The four products generated a combined $8mm over the last 12 months. Cerecor will assume Avadel's remaining payment obligations to Deerfield, including a $15mm note due January 2021 plus related interest payments, and a 15% annual royalty on sales of the four acquired products. Avadel is divesting the programs to focus on its urology, sleep, and hospital-based offerings, while Cerecor strives to become a leading pediatric pharma company in the US.

AVID BIOSERVICES INC.
ONCOLOGIE INC.

Avid Bioservices Inc. (formerly Peregrine Pharmaceuticals) divested its phosphatidylserine (PS)-targeting program for cancer to **Oncologie Inc.**. The deal includes late-stage candidate bavituximab, as well as other antibodies and intellectual property. (Feb.)

Oncologie pays $8mm up front; up to $95mm in development, regulatory, and commercialization milestones; and mid-teens royalties. Avid had bavituximab in Phase III trials for non-small cell lung cancer and in earlier trials for breast, pancreatic, liver, prostate, and colorectal cancers, as well as melanoma. The candidate is also partnered with **AstraZeneca** in a trial collaboration to evaluate it in combination with AZ's durvalumab for solid tumors (including NSCLC).

BIODELIVERY SCIENCES INTERNATIONAL INC.
TEVA PHARMACEUTICAL INDUSTRIES LTD.

As a result of a patent litigation settlement agreement, **BioDelivery Sciences International Inc.** agreed to license Teva Pharmaceutical Industries Ltd./B-/ non-exclusive US rights to its *Belbuca* (buprenorphine) buccal film. Per the terms Teva will be able to begin selling the generic *Belbuca* (on the market for non-nociceptive pain) in the US beginning on January 23, 2027. (Feb.)

BIOHAVEN PHARMACEUTICALS HOLDING CO. LTD.
CATALENT INC.

Biohaven Pharmaceuticals Holding Co. Ltd. gained exclusive worldwide rights to use **Catalent Inc**'s *Zydis* orally disintegrating tablet (ODT) technology in the development of Biohaven's rimegepant (BHV3000). (Feb.)

Originally in-licensed from **Bristol-Myers Squibb** under a 2016 deal, rimegepant is Biohaven's lead calcitonin gene-related peptide (CGRP) receptor antagonist candidate, currently in multiple Phase III studies (initiated last year) for acute migraine. Phase III trial topline data is expected by the end of Q1 2018. In addition, Biohaven's CGRP antagonist pipeline includes preclinical BHV3500, also for migraine, expected to enter the clinic during 1H 2018. Under the current deal, Biohaven's exclusive rights to use the *Zydis* technology extend to the development of other small-molecule CGRP receptor antagonists (in addition to rimegepant).

BIOVERATIV INC.
OXFORD BIOMEDICA PLC

Bioverativ Inc. licensed rights to use **Oxford BioMedica PLC**'s *LentiVector* gene delivery technology in the development of therapies for hemophilia. (Feb.)

Oxford gets $5mm up front and could receive up to $100mm in milestones, plus royalties on sales of successfully launched products incorporating the licensed technology. Bioverativ also agreed to fund process development and scale-up, and signed a separate clinical supply agreement for GMP manufacturing of the products at Oxford. *LentiVector* allows for the stable and efficient delivery of genes into target cells using a vector that provides long duration of gene expression. It was not made clear which specific candidate or candidates at Bioverativ would benefit from *LentiVector*, but the company's pipeline currently shows potential treatments for hemophilia A and B in preclinical and Phase I studies. Bioverativ joins a growing list of partners using the technology in their drug development efforts, including **GSK**, **Immune Design**, and **Novartis**. (Novartis' *Kymriah* (tisagenlecleucel) is manufactured with *LentiVector*, and was the first CART-T cell therapy approved by the FDA (in August 2017) to treat B-cell precursor acute lymphoblastic leukemia.)

BRISTOL-MYERS SQUIBB CO.
NEKTAR THERAPEUTICS

Stemming from a September 2016 clinical trial collaboration testing the combination of **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) and **Nektar Therapeutics'** NKTR214, the companies have now signed an agreement that lays out an official deal with cost and profit splits, as well as commercialization rights. (Feb.)

The partners first teamed up in 2016 to study the *Opdivo*/NKTR214 combination in five tumor types. The current deal (which supersedes their original and now terminated agreement) lays out an official joint development and commercialization plan for the combination of both *Opdivo* and NKTR214, as well as *Opdivo+Yervoy* (ipilimumab) and NKTR214 in more than 20 indications across nine tumor types, including melanoma, renal cell carcinoma, non-small cell lung cancer, bladder cancer, triple negative breast cancer, small cell lung cancer, colorectal cancer, gastric cancer, and sarcoma (these could be expanded). These will be registration-enabling clinical trials, and the ones in renal cell carcinoma and melanoma are expected to begin in mid-2018. The development costs of the trials will be split based on the company's ownership interest in the therapies used in the trials. And a CD122-biased immunocytokine therapy targeting the interleukin 2 receptor, and works to expand cancer-fighting T-cells and natural killer cells in the tumor microenvironment. Nektar is also studying NKTR214 in combination with **Merck & Co.**'s *Keytruda* and **Roche**'s *Tecentriq*.

CANBRIDGE LIFE SCIENCES LTD.
PUMA BIOTECHNOLOGY INC.

Puma Biotechnology Inc. granted **CANbridge Life Sciences Ltd.** exclusive rights to develop and sell its breast cancer therapy *Nerlynx* (nerlatinib) in mainland China, Taiwan, Hong Kong, and Macau. (Feb.)

Puma gets $30mm up front, up to $40mm in regulatory milestones, and sales milestones that could hit $185mm, plus dou-

ble-digit royalties. *Nerlynx* was approved in the US for HER2-positive breast cancer, but has not yet been cleared for marketing in any other countries. CANbridge hopes to have it in the market in the Greater China region by mid-2019. CANbridge's cancer pipeline already has several projects in-licensed for the Chinese market, including **EUSA Pharma**'s oral mucositis rinse and investigational treatments for glioblastoma (from **Apogenix**) and squamous cell esophageal cancer (from **Aveo**). The current deal is the second signed by Puma since the beginning of year. In January, it granted **Medison Pharma** rights to sell *Nerlynx* in Israel.

DARE BIOSCIENCE INC.
STRATEGIC SCIENCE & TECHNOLOGIES LLC

Dare Bioscience Inc. licensed exclusive worldwide rights to **Strategic Science & Technologies LLC**'s female sexual arousal disorder (FSAD) candidate SST6007 (sildenafil citrate) in all women's health indications. (Feb.)

SST is eligible to receive clinical development, regulatory, and commercial milestones ranging from $500k up to $150mm, plus tiered royalties in the single digits to the mid double-digits (*Strategic Transactions* estimates 1-50%). Dare concurrently closed a $9.5mm public offering to help fund this deal and a funding requirement for it to secure the exclusive worldwide license. Phase II SST6007, a topical cream containing the phosphodiesterase 5 (PDE-5) inhibitor sildenafil citrate, is designed to treat both pre- and post-menopausal women suffering from FSAD--the inability to attain or maintain sexual arousal--by increasing blood flow to the vulvar-vaginal tissue, potentially enhancing genital arousal response and overall sexual satisfaction. SST6007 uses SST's *KNOSIS* technology, which delivers active pharmaceutical ingredients transdermally through a platform that enables the API to be driven from the delivery vehicle and to permeate into the targeted tissue.

ELSALYS BIOTECH SAS
LABORATOIRES THEA

ElsaLys Biotech SAS granted **Laboratoires Thea** an exclusive option for development and commercial rights to its ELB011 antibody in ophthalmology. (Feb.)

Though specific financial terms were not disclosed, the agreement includes an up-front payment to ElsaLys if Thea exercises the option (possibly by end of 2018), milestone payments, and sales royalties. ELB011 is a CD16 antagonist in preclinical studies for wet age-related macular degeneration and other retinal vascular pathologies. It has potential for use alone or in combination with anti-VEGF agents, which is the current treatment for such conditions. (At least 30% of people with retinal vascular disorders do not respond to anti-VEGF therapies.) ElsaLys will continue preclinical development and produce batches for toxicology studies and clinical trials. Thea would take over all clinical development and commercialization activities. Clinical trials are expected to commence in 2020.

EVEREST MEDICINES LTD.
TETRAPHASE PHARMACEUTICALS INC.

Tetraphase Pharmaceuticals Inc. licensed **Everest Medicines Ltd.** exclusive rights to develop and commercialize eravacycline in China, Taiwan, Hong Kong, Macau, South Korea, and Singapore. (Feb.)

In exchange, Tetraphase will receive $7mm up front, up to $16.5mm in clinical development and regulatory milestones, up to $20mm in sales royalties, and tiered double-digit sales royalties. The partners will create a joint steering committee to oversee Everest's development and commercialization activities. Eravacycline is a fluorocycline antibiotic for multiple infections including complicated intra-abdominal infections (cIAI) and those caused by multidrug-resistant pathogens such as carbapenem-resistant enterobacteriaceae, Escherichia coli, and Acinetobacter baumannii. For the cIAI indication, the drug is under NDA review in the US and has a 98% likelihood of approval (10% above average) according to *Biomedtracker*. In December 2017, Everest licensed exclusive rights to **Arena Pharmaceuticals**' Phase II candidates ralinepag for pulmonary arterial hypertension and etrasimod for various autoimmune diseases.

GILEAD SCIENCES INC.
Kite Pharma Inc.
SANGAMO THERAPEUTICS INC.

Gilead Sciences Inc. division **Kite Pharma Inc.** licensed exclusive rights to use **Sangamo Therapeutics Inc.**'s zinc finger nuclease (ZFN) technology for the development of new cell therapies for cancer. (Feb.)

Kite pays $150mm up front; up to $1.26bn in development, regulatory, and first-sale milestones; up to $1.75bn in sales milestones; and tiered escalating single-digit royalties. (Milestones are based on at least ten successfully developed products.) The ZFN gene editing platform allows for targeted gene knock-out or therapeutic gene insertion using zinc finger DNA-binding proteins. Sangamo will design ZFNs and adeno-associated viruses to disrupt and insert genes in T cells and natural killer cells (including inserting genes that encode chimeric antigen receptors, T-cell receptors, and NK cell receptors) directed at targets agreed upon by both partners. Kite will then lead clinical development, regulatory, manufacturing, and commercialization activities for next-generation autologous and allogeneic cell therapies. Kite will also reimburse Sangamo for certain expenses. The deal is the second this year for Sangamo, which also penned an agreement with **Pfizer** in January, utilizing its zinc finger protein transcription factors for the development of neurodegenerative disease therapies.

GLENMARK PHARMACEUTICALS LTD.
SAM CHUN DANG PHARM. CO. LTD.

Sam Chun Dang Pharm. Co. Ltd. licensed **Glenmark Pharmaceuticals Ltd.** exclusive rights to develop, manufacture, and commercialize six generic ophthalmic products in the US and Canada. (Feb.)

Financial terms of the agreement were not disclosed. Glenmark will obtain the necessary marking approvals in the licensed territories; it plans to file six ANDAs in H1 2019. SCD will continue the development and manufacturing of the products in its home country of South Korea. The licensed generics generated an estimated $1.7bn in the US in 2017.

IMMUNOQURE AG
SERVIER SA

Servier SA and **ImmunoQure AG** will work together to develop new therapies for autoimmune diseases including lupus and Sjögren's syndrome. (Feb.)

ImmunoQure's drug development technology uses naturally-derived autoantibodies against drug targets from select patient populations as the basis for engineered antibody therapies for autoimmune and inflammatory diseases. Under the collaboration with Servier, the partners will advance one of ImmunoQure's human interferon-alpha autoantibodies through preclinical studies, after which point Servier gets exclusive global rights to develop and sell the therapy for diseases with elevated interferon-alpha levels. The company will initially focus on lupus and Sjögren's. ImmunoQure gets money up front plus up to €164mm ($203mm) in milestones, as well as sales royalties.

JOHNSON & JOHNSON
Janssen Biotech Inc.
THERAVANCE BIOPHARMA INC.

Theravance Biopharma Inc. is partnering its Phase II-ready inflammatory bowel disease candidate TD1473 (as well as related back-up compounds) with **Janssen Biotech Inc.** (Feb.)

Janssen will pay $100mm up front. Theravance is in charge of conducting a Phase II trial of TD1473 in Crohn's disease and a Phase IIb/III study in ulcerative colitis, both expected to commence in the second half of this year. Once that trial data is available, Janssen can opt to license exclusive global rights and would take over development of the compound in the Crohn's indication; should Janssen opt-in, it would pay $200mm. Theravance Biopharma will finish developing TD1473 in the US through completion of the Phase IIb/III program. If the drug is approved,

Theravance can opt to co-commercialize in the US, while Janssen would handle all ex-US commercialization activities.

MERCK & CO. INC.
PHARMABCINE INC.

PharmAbcine Inc. and **Merck & Co. Inc.** entered into a trial collaboration to study the combination of PharmAbcine's TTAC0001 (tanibirumab) with Merck's *Keytruda* (pembrolizumab) as a potential new therapy for recurrent glioblastoma multiforme and metastatic triple-negative breast cancer. (Feb.)

TTAC0001, an anti-VEGFR2 monoclonal antibody, is in Phase II studies for brain cancer. Anti-PD-1 treatment *Keytruda* is marketed for melanoma, non-small cell lung cancer, Hodgkin's lymphoma, and head and neck, bladder, stomach, and esophageal cancers. It is also approved for colorectal cancer and in preclinical and clinical trials for a variety of other solid and blood tumors. The partners believe that the complementary mechanisms of action between the two therapies could produce a strong combination treatment. PharmAbcine will carry out international Phase I/II trials.

NOVARTIS AG
Advanced Accelerator Applications SA
CANCER TARGETED TECHNOLOGY

Advanced Accelerator Applications SA (recently acquired by **Novartis**) licensed exclusive worldwide rights to **Cancer Targeted Technology LLC**'s CTT1057, a small-molecule positron emission tomography (PET) diagnostic imaging agent. (Feb.)

The agreement calls for CTT to receive an up-front licensing fee, milestones, and royalties. CTT1057 is a ligand of the prostate-specific membrane antigen (PSMA) labeled with the fluorine 18 (F18) radioisotope and used with PET imaging to detect metastatic lesions in prostate cancer. A phosphoramidate-based peptide, CTT1057 specifically binds to PSMA and can be imaged within two hours of administration to detect with great precision cancer that has escaped from the prostate. CTT initiated a Phase I study in late 2016 to evaluate safety, pharmacokinetics, and radiation dosimetry of CTT1057, which AAA plans to further advance and commercialize for prostate cancer. CTT1057 will fit in nicely with AAA's theragnostic portfolio, which includes two approved PET imaging agents for neuroendocrine tumors (NETs), *NETSPOT* (US) and *SomaKit TOC* (EU), both labeled with PET tracer gallium 68 and developed as companion diagnostics to AAA's *Lutathera* (lutetium 177), a nuclear medicine also approved in the US and the EU for NETs.

PARTNER THERAPEUTICS INC.
SANOFI

Recently launched **Partner Therapeutics Inc.** (PTx; oncology) has commenced operations by acquiring the immunostimulant *Leukine* (sargramostim) from **Sanofi** for an undisclosed sum. (Feb.)

PTx also takes on Sanofi's Lynwood, Washington manufacturing facility and associated staff; the plant will serve as main supply center for the therapeutic. *Leukine*, which Sanofi originally got from **Bayer** in 2009, is a bone marrow stimulant that helps the body produce white blood cells following induction chemotherapy in patients with acute myelogenous leukemia. It is also used before and after peripheral blood stem cell transplant and in cases of bone marrow transplant failure or engraftment delay. In addition to its approved indications, PTx plans to continue ongoing development in melanoma and hematopoietic syndrome of acute radiation syndrome (H-ARS). (A supplemental BLA was filed for the H-ARS indication last year, and the compound has a PDUFA date of March 29, 2018.) Concurrent with the licensing announcement, PTx also detailed the closing of its $60mm Series A funding round.

PHARMAMAR SA
SEATTLE GENETICS INC.

PharmaMar SA granted **Seattle Genetics Inc.** exclusive global rights to use certain of its marine-derived payloads in the development of antibody-drug conjugates for cancer. (Feb.)

In return for development, manufacturing, and commercialization rights, Seattle Genetics pays $5mm up front, development, regulatory, and sales milestones, and royalties. The licensed assets stem from PharmaMar's new marine payloads department, through which the company offers synthetic, structurally diverse payload molecules that are highly potent and have sub-nanomolecular cytotoxic activity. Seattle Genetics will incorporate the payloads into its ADC development technology, which combines monoclonal antibodies, linker systems, and cell-killing agents into therapeutics designed to fight cancer.

PIERIS PHARMACEUTICALS INC.
SEATTLE GENETICS INC.

Pieris Pharmaceuticals Inc. and **Seattle Genetics Inc.** are joining resources to develop new bispecific immuno-oncology agents for solid and blood cancers. (Feb.)

Pieris brings to the collaboration its *Anticalin* protein platform. *Anticalins* are engineered lipocalins designed to mimic antibodies by binding to sites on both small and large molecules. Seattle Genetics' expertise lies in the development of antibody-drug conjugates, and the company has a collection of cancer targets and tumor-specific mAbs that will be utilized under the deal, with the ultimate joint goal of designing antibody-*Anticalin* fusion proteins that can enable a patient's immune cells to specifically attack tumors. Seattle Genetics pays Pieris $30mm up front; up to $1.2bn in total milestones based on the progress of up to three candidates; and royalties up to the low-double digits (*Strategic Transactions* estimates 1-29%).

POLYPHOR LTD.
SANTHERA PHARMACEUTICALS AG

Polyphor Ltd. licensed **Santhera Pharmaceuticals AG** exclusive global rights to develop and commercialize Phase I POL6014 for cystic fibrosis and other pulmonary diseases. (Feb.)

Polyphor will receive CHF6.5mm ($7mm) in Santhera equity up front (238,924 shares at CHF27.2053 each; a 19% discount), up to CHF121mm ($130mm) in cash based on development, regulatory, and sales milestones, plus tiered sales milestones. Polyphor could also receive additional milestones and royalties tied to the development and commercialization of POL6014 for non-CF pulmonary indications. POL6014 is a macrocycle elastase inhibitor neutrophilic with potential for treating neutrophilic pulmonary diseases such as non-cystic fibrosis bronchiectasis, alpha-1 antitrypsin deficiency, and primary ciliary dyskinesia. Polyphor had been developing the compound with financial backing from **Cystic Fibrosis Foundation Therapeutics**. Santhera will take over development and plans to conduct a multiple ascending dose tolerability trial in H2 2018, as well as begin talks with the US and EU regulatory agencies. The candidate has been shown to attain high concentrations in the lung when administered via **Pari Pharma**'s *eFlow* nebulizer. POL6014 joins Santhera's pipeline which includes lead program idebenone for respiratory complication in Duchenne muscular dystrophy.

POXEL SA
ROIVANT SCIENCES GMBH

Poxel SA licensed **Roivant Sciences GMBH** rights to develop and commercialize its Type II diabetes compound imeglimin in the US, Europe, and all other countries except certain Asian territories where Poxel's partner **Sumitomo Dainippon Pharma** has rights. (Feb.)

Sumitomo's license extends to Japan, China, South Korea, Taiwan, Indonesia, Vietnam, Thailand, Malaysia, the Philippines, Singapore, Myanmar, Cambodia, and Laos. That deal was penned in October 2017 and could generate up to $299mm for Poxel. Under the current agreement, Roivant paid Poxel $35mm (€28mm) up front and could shell out up to $600mm in development, regulatory, and sales milestones, plus double-digit sales royalties. In addition, Roivant agreed to make a $15mm investment in Poxel through the purchase of 1.43 newly issued ordinary shares at €8.50 ($10.41) each. Poxel will contribute $25mm to imeglimin's development.

PROBIOGEN AG
TEVA PHARMACEUTICAL INDUSTRIES LTD.

ProBioGen AG licensed **Teva Pharmaceutical Industries Ltd.** non-exclusive rights to its *Human Artificial Lymph Node* (*HuALN*) platform technology for use in assessing potential drug candidates. (Feb.)

The 3D matrix-based technology provides for predictive in vitro testing of immune responses triggered by product candidates. *HuALN* mimics in vivo conditions and provides for analysis of immunogenicity, immunofunction and immunotoxicity. The platform is based on a patented, miniaturized perfused bioreactor. Human blood-derived dendritic cells, T & B lymphocytes, and mesenchymal stem cells-derived stromal cells are inoculated into its hydrogel matrix. *HuALN* can test a wide range of substance classes including small molecules, proteins, peptides and nucleic acids, and predicts drug-related effects on the human immune system. The platform overcomes limitations of conventional models and effectively bridges the gap between animal testing and first-in-human studies.

TAKEDA PHARMACEUTICAL CO. LTD.
WAVE LIFE SCIENCES LTD.

Takeda Pharmaceutical Co. Ltd. and **Wave Life Sciences Ltd.** entered into an option and license agreement focused on central nervous system disorders, including Huntington's and Alzheimer's diseases, amyotrophic lateral sclerosis (ALS), and dementia. (Feb.)

Takeda pays $110mm in cash up front and will purchase $60mm of Wave's common stock (1.1mm shares at $54.70 (a 25% premium), for a 4% stake). The agreement, which could be worth over $2bn to Wave, consists of two components. In the first, Takeda has an option to co-develop and co-commercialize four nucleic acid therapies: WVE120101 and WVE120102, gene expression inhibitors that target the mutant allele of the huntingtin gene and are in Phase Ib/IIa for Huntington's disease; WVE397201, which targets the C9ORF72 gene and will enter clinical trials later this year for ALS and frontotemporal dementia; and an undisclosed candidate targeting the ATXN3 gene for spinocerebellar ataxia type 3.

Financings

ADDEX THERAPEUTICS

Addex Therapeutics (small-molecule allosteric modulators for neurological disorders) received commitments of up to CHF40mm ($42.9mm) for a potential private placement of 12.8mm new shares at CHF3.13 (a 3% premium). For each new share, investors will also receive a seven-year warrant to purchase 0.45 of a share at CHF3.43. Committed backers include New Enterprise Associates, New Leaf Venture Partners, CAM Capital, and clients of Herculis Partners and Semper Finance Group (for an aggregate of CHF30mm). The remaining CHF10mm will be placed privately through a book-building process to qualified institutional investors. (Feb.)

Investment Banks/Advisors: MTS Health Partners

ADVAXIS INC.

Advaxis Inc. (Listeria-based immunotherapies for cancer) netted $18.8mm through the public sale of 10mm common shares at $2. Projects that will benefit from the proceeds include axalimogene filolisbac (persistant, recurrent, or metastatic carcinoma of the cervix), ADXS-PSA for prostate cancer, ADXS-NEO, a neoantigen therapeutic for various cancers, and ADXS-HOT, targeting hotspot mutations in prevalent cancers including NSCLC. (Feb.)

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

ADVERUM BIOTECHNOLOGIES INC.

Adverum Biotechnologies Inc. (gene therapies for rare and ocular diseases) netted $64.9mm through the follow-on offering of 10.22mm common shares (including full exercise of the overallotment) at $6.75 each. The company will use some of the funds for ongoing preclinical and clinical development of its pipeline candidates. Its lead candidate is Phase I/II ADVM043 alpha-1 antitrypsin deficiency. (Feb.)

Investment Banks/Advisors: Cowen & Co. LLC; Piper Jaffray & Co.; Raymond James & Associates Inc.

AFFIMED NV

Affimed NV (immunotherapies for cancer and other serious diseases) publicly sold 13.2mm common shares (including the overallotment) at $2 for net proceeds of $24.9mm. The company's next-generation antibody therapeutics development ef-

forts utilize Affimed's platforms focused on tetravalent bifunctional proteins (NK-cell TandAbs and T-cell TandAbs) and trifunctional antibodies for dual targeting of tumor cells. (Feb.)

Investment Banks/Advisors: Jefferies & Co. Inc.; Wells Fargo Securities LLC

AIMMUNE THERAPEUTICS INC.

Aimmune Therapeutics Inc. (food allergy immunotherapies) netted $165mm through a public offering of 5.5mm common shares at $32. Proceeds are earmarked for continued development, regulatory filings, and commercialization of lead candidate AR101 for peanut allergy. Funds will also support ongoing work on additional projects designed with the company's *CODIT* oral immunotherapy platform. (Feb.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Cantor Fitzgerald & Co.; Credit Suisse Group; Piper Jaffray & Co.; RBC Capital Markets; Roth Capital Partners; Wedbush PacGrow Life Sciences

ALPHAEON CORP.

Evolus Inc.

Medical aesthetics company **Evolus Inc.** (neurotoxin development and manufacturing) netted $55.8mm in its initial public offering of 5mm shares at $12, the low end of its anticipated $12-14 range. (Feb.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; JMP Securities LLC; Mizuho Bank Ltd.; SunTrust Banks Inc. (Evolus Inc.)

AMICUS THERAPEUTICS INC.

Amicus Therapeutics Inc. (therapies for rare metabolic conditions) netted $282mm in its follow-on public offering of 19.35mm common shares at $15.50. The company will use some of the proceeds for global commercialization of migalastat for Fabry's disease, to invest in manufacturing capabilities for its Phase II Pompe disease candidate ATB200, and for additional R&D and commercial activities. (Feb.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Cowen & Co. LLC; Goldman Sachs & Co.; JP Morgan & Co.; Leerink Partners LLC

ASCENDIS PHARMA AS

Ascendis Pharma AS (rare diseases) netted $211.5mm through the follow-on public offering of 3.95mm American Depositary Shares priced at $57; each ADS represents one ordinary share. The company will use some of the proceeds for clinical development, regulatory, and commercialization activities for its *TransCon* growth hormone; for development of other rare disease endocrinology programs including *TransCon PTH* and *TransCon CNP*; and for R&D in new therapy areas. (Feb.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Credit Suisse Group; JP Morgan & Co.; Stifel Nicolaus & Co. Inc.; Wedbush PacGrow Life Sciences; Wells Fargo Securities LLC

ATHERSYS INC.

Aspire Capital Fund agreed to invest up to $100mm through a new equity facility in **Athersys Inc.** (developing *MultiStem* off-the-shelf cell therapy). The fund invested $1mm initially at a price of $2 per share (500k shares; 8% premium to prior 10-day trading average) and Athersys can sell the remainder within the next three-year period (up to an additional 23.75mm shares; Athersys also sold 450k shares to Aspire as consideration for entering into the purchase agreement as a commitment fee). The funding is at the company's discretion regarding timing and Aspire is obligated to purchase the common shares based on the agreement (the company, however, is not obligated to sell). The proceeds will be used to advance Athersys' pipeline for ischemic stroke and regenerative medicine. (Feb.)

AVADEL PHARMACEUTICALS PLC

Avadel Pharmaceuticals PLC (specialty pharmaceuticals) netted $119.6mm in proceeds from the pricing of a $125mm senior notes offering. The notes bear an interest rate of 4.5%, with payments required semi-annually in cash in arrears each February 1 and August 1 beginning on August 1, 2018. The debt matures on February 1, 2023 and is exchangeable at the option of the holder at an initial exchange rate of 92.6956 ADSs per $1,000 principal, or approximately $10.79 per ADS (Avadel's ADSs were averaging $7.90 at the time of the transaction.) (Feb.)

Investment Banks/Advisors: Leerink Partners LLC; SunTrust Banks Inc.; TR Winston Capital Inc.

AVID BIOSERVICES INC.

Avid Bioservices Inc. netted $21.8mm in a follow-on public offering of 10.3mm common shares (including 1.3mm overallotment shares) at $2.25. The company plans to use a part of the proceeds from the offering for expansion of its CMO business. Earlier this month, Avid divested its phosphatidylserine (PS)-targeting program for cancer to **Oncologie Inc.**, completing its transition into a CDMO. (Feb.)

Investment Banks/Advisors: HC Wainwright & Co.; Roth Capital Partners; Wells Fargo Securities LLC

CATALYST BIOSCIENCES INC.

Catalyst Biosciences Inc. netted $107mm through the public sale of 3.38mm common shares (including the overallotment) at $34. Some of the proceeds will support continued development and manufacturing activities for CB2679d (Factor IX protease for hemophilia B; Phase I/II) and marzeptacog alfa (next-gen Factor VIIa for hemophilia A or B with inhibitors; Phase II/III). (Feb.)

Investment Banks/Advisors: B. Riley FBR Inc.; Ladenburg Thalmann & Co. Inc.; LifeSci Capital LLC

CELLULAR BIOMEDICINE GROUP INC.

Cellular Biomedicine Group Inc. (immunotherapies mainly for cancer) grossed $30.5mm through a private sale of 1.7mm common shares at $17.80 (a 9% discount) to Sailing Capital Overseas Investment and affiliates. The funding will help the company continue development activities for its clinical projects in the areas of progressive malignant lymphoma, acute B lymphocytic leukemia, and Hodgkin's lymphoma, and will also support research into T-cell redirection using TCR therapies. The PIPE follows a separate $14.5mm private placement that closed at the end of 2017. (Feb.)

CTI BIOPHARMA CORP.

CTI BioPharma Corp. (treatments for blood cancers) netted $65mm through a public offering of 23mm common shares (including the overallotment) at $3. Proceeds will be used to complete the PAC203 clinical trial of pacritinib for patients with primary myelofibrosis who filed prior therapy with ruxolitinib and complete an MAA review of the candidate by the EMA; support development of pacritinib outside of myelobfibrosis; and complete the PIX306 trial, which is studying *Pixuvri* (pixantrone) combined with rituximab in comparison to rituximab combined with gemcitabine in patients with aggressive B-cell non-Hodgkin lymphoma. (Feb.)

Investment Banks/Advisors: JMP Securities LLC; Leerink Partners LLC; Needham & Co. Inc.; Oppenheimer & Co. Inc.

DARE BIOSCIENCE INC.

Dare Bioscience Inc. (focused on women's health) netted $9.5mm in a public offering of 5mm shares at $2.05, plus warrants to purchase up to 3.5mm common shares at an exercise price of $3.00. The financing will help support, and was also a funding requirement for, Dare's concurrent worldwide exclusive license to **Strategic Science & Technologies LLC**'s Phase II female sexual arousal disorder candidate SST6007 (a topical cream formulation of phosphodiesterase 5 inhibitor sildenafil citrate) in a deal worth up to $150mm to SST. (Feb.)

Investment Banks/Advisors: Roth Capital Partners

DOVA PHARMACEUTICALS INC.

Rare disease therapies developer **Dova Pharmaceuticals Inc.** netted $75.2mm through a follow-on public offering of 2.5mm common shares priced at $32

each. The company plans to use most of the proceeds for activities surrounding avatrombopag including initiation of Phase III trials for patients with thrombocytopenia undergoing surgery and chemotherapy-induced thrombocytopenia, the sNDA submission (expected in H2 2018) in immune thrombocytopenic purpura, and commercialization activities. (Feb.)

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

DYNAVAX TECHNOLOGIES CORP.

Dynavax Technologies Corp. (immunotherapies for infectious and autoimmune diseases and cancer) entered into a $175mm non-dilutive term loan agreement with CRG LP, which provided the company with an initial $100mm tranche immediately. The additional $75mm can be funded at Dynavax's option prior to June 30, 2019. (Feb.)

GEMPHIRE THERAPEUTICS INC.

Gemphire Therapeutics Inc. netted $20.5mm through a public sale of 3.14mm common shares at $7. The company is developing therapeutics for cardiometbolic and hepatic diseases and currently has lead candidate gemcabene in Phase II trials for hypercholesterolemia and hypertriglyceridemia, and Phase I for nonalcoholic steatohepatitis (NASH). (Feb.)

Investment Banks/Advisors: Laidlaw & Co.; LifeSci Capital LLC; Piper Jaffray & Co.; Raymond James & Associates Inc.; Roth Capital Partners

IMMUNOVACCINE INC.

Immunovaccine Inc. (immuno-oncology) netted $Cdn13.5mm ($10.9mm) through a bought deal offering of 7.2mm common shares (including the overallotment) at $Cdn2. Proceeds will support continued development of immunotherapies that utilize the company's *DepoVax* depot delivery system, which is designed to help enhance the uptake and exposure of antigens and adjuvants to cells of the immune system, resulting in a rapid and sustained immune response against disease targets. (Feb.)

Investment Banks/Advisors: Bloom Burton & Co.; Echelon Wealth Partners; National Bank Financial Corp.

MEDICINOVA INC.

MediciNova Inc. netted $37.6mm in a follow-on public offering through the sale of 4.4mm common shares at $9.05. The company plans to use the proceeds to fund advancement of MN166 (ibudilast; in development for progressive MS, ALS, glioblastoma, substance dependence, and addiction), including a Phase III trial for progressive MS, and MN001 (tipelukast; a small molecule in Phase II for idiopathic pulmonary fibrosis and NASH). (Feb.)

Investment Banks/Advisors: B. Riley FBR Inc.; Ladenburg Thalmann & Co. Inc.

MERUS NV

Merus NV grossed $55.8mm through the private placement of 3.1mm common shares at $18 (a 4.5% premium) to investors including Biotechnology Value Fund and affiliates, Aquilo Capital Management, Sofinnova Venture Partners, and LSP Life Sciences Fund. The company develops full-length bispecific antibody therapeutics, and will use the proceeds to support preclinical and clinical studies. (Feb.)

MIRAGEN THERAPEUTICS INC.

MiRagen Therapeutics Inc. (RNA-targeted therapies) netted $36.2m in a follow-on public offering of 7mm common shares at $5.50. The company plans to use the offering proceeds to fund clinical development of its pipeline, including lead candidates MRG106 (inhibitor of microRNA-155 for various blood cancers) and MRG201 (replacement for microRNA-29 for pathological fibrosis). (Feb.)

Investment Banks/Advisors: Deutsche Bank AG; Evercore Partners; Jefferies & Co. Inc.; Oppenheimer & Co. Inc.; Wedbush PacGrow Life Sciences

MOLECULIN BIOTECH INC.

Moleculin Biotech Inc. netted $8.4mm through a registered direct offering of 4.3mm common shares at $2.10 (a 15% premium). Roth Capital was the placement agent. Funds will support ongoing preclinical and clinical development of the company's cancer candidates including lead project annamycin for leukemia and additional compounds for glioblastoma, melanoma, and pancreatic cancer. (Feb.)

Investment Banks/Advisors: Roth Capital Partners

NOVABAY PHARMACEUTICALS INC.

NovaBay Pharmaceuticals Inc. (developed *Avenova* for lid and lash hygiene, *NeutroPhase* skin and wound cleanser, and *CelleRx* for aesthetic dermatology) grossed $6mm through the private placement of 1.7mm common shares at $3.52 each (a slight discount) to OP Financial Investments. Funding will help support commercialization activities. China Kington Asset Management was the placement agent. (Feb.)

ONCONOVA THERAPEUTICS INC.

Cancer drug developer **Onconova Therapeutics Inc.** publicly sold 7mm units (including the overallotment) at $1.01 for net proceeds of $6.58mm. The units consisted of one common share and a one-year warrant to buy 0.1 share of Series A preferred stock at $1.01. Onconova also sold to certain shareholders 2.94mm pre-funded units at $1, with each unit containing a warrant to purchase one common share and a warrant for 0.1 share of Series A preferred stock. Net proceeds from the pre-funded warrant sale amounted to $2.76mm. (Feb.)

Investment Banks/Advisors: HC Wainwright & Co.

ONCOSEC MEDICAL INC.

OncoSec Medical Inc. (intra-tumoral immunotherapy) netted $21.3mm through a public offering of 15.3mm common shares (including the overallotment) at $1.50. Funds will support the ongoing Phase II PISCES/KEYNOTE-695 trial of the intra-tumoral electroporation delivery system *ImmunoPulse* IL-12 in combination with an approved chemotherapy for melanoma. (Feb.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Piper Jaffray & Co.

PIERIS PHARMACEUTICALS INC.

Pieris Pharmaceuticals Inc. (developing treatments for cancer, respiratory and infectious diseases, and anemia) netted $47.6mm through a public offering of 6.3mm common shares (including the overallotment) at $8. Proceeds will support continued drug development, including advancement of lead immuno-oncology candidate PRS343. The funding was announced just days after Pieris entered a collaboration with **Seattle Genetics** through which the partners will develop multiple targeted bispecific solid and blood cancer treatments. Pieris received $30mm up front and could get up to $1.2bn in milestones under the deal. (Feb.)

Investment Banks/Advisors: Cowen & Co. LLC; Evercore Partners; Jefferies & Co. Inc.

POLYPID LTD.

Nearly three years after pulling its initial filing for an IPO (filed in Oct 2014 and pulled in early 2015) and two years after raising a $22mm Series D round, drug delivery technology (DDT) company **PolyPid Ltd.** re-filed for it's initial public offering on the Nasdaq with a new underwriting group. (Feb.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Cowen & Co. LLC; Goldman Sachs & Co.; Oppenheimer & Co. Inc.; Raymond James & Associates Inc.

RA PHARMACEUTICALS INC.

Nearly 16 months after going public, **Ra Pharmaceuticals Inc.** (therapeutics for complement-mediated diseases) netted $47.4mm in a follow-on public offering of 8.4mm common shares at $6. The company will use the net proceeds to fund its Phase II clinical trial of RA101495 for Generalized Myasthenia Gravis (gMG) and for other pipeline candidates. (Feb.)

Investment Banks/Advisors: BMO Financial Group; Credit Suisse Group; Jefferies & Co. Inc.; SunTrust Banks Inc.

Andrea Charles, *Editor Custom Content*

SAGE THERAPEUTICS INC.

CNS-focused **Sage Therapeutics Inc.** netted $549mm in a follow-on offering of 3.5mm shares at $164. The company will use the proceeds to support the potential launch of Phase III brexanolone (SAGE547) in postpartum depression (PPD), for which an NDA filing is expected in 2H 2018; to continue development of GABAA receptor modulator SAGE217 in major depressive disorder, PPD, Parkinson's disease, and PPD (Phase II), insomnia (Phase I), bipolar disorder (preclinical), and other CNS indications; and to further other pipeline programs, including SAGE718 (in Phase I for CNS diseases related to NMDA receptor hypofunction) and SAGE324 (in preclinical studies for epileptiform disorders and essential tremor). Sage will also put some of the proceeds toward growing its commercial and manufacturing capabilities. (Feb.)

Investment Banks/Advisors: BMO Financial Group; Cowen & Co. LLC; Goldman Sachs & Co.; JP Morgan & Co.; Morgan Stanley & Co.; RBC Capital Markets

SEATTLE GENETICS INC.

Seattle Genetics Inc. (targeted antibody-based cancer therapies) netted $659mm through a public offering of 13.27mm common shares (including the overallotment) at $52. Proceeds will fund the firm's acquisition of **Cascadian Therapeutics**; on the same day it announced the FOPO, Seattle Genetics offered $10 per share or approximately $614mm to purchase the oncology drug development company. (Feb.)

Investment Banks/Advisors: Barclays Bank PLC; JP Morgan Chase & Co.

VELOXIS PHARMACEUTICALS AS

Veloxis Pharmaceuticals AS (therapies for organ transplant patients) secured a $60mm loan from funds managed by Athyrium Capital. Proceeds from the five-year floating rate interest-only note will be used to refinance existing debt, fund the working capital of the firm's US division **Veloxis Pharmaceuticals Inc.**, and support US commercialization of *Envarsus XR* (tacrolimus) for the prevention of kidney transplant rejection. (Feb.)

VIKING THERAPEUTICS INC.

Viking Therapeutics Inc. (developing therapies for metabolic and endocrine disorders) netted $58.8mm through the follow-on public offering of 12.65mm common shares (including full exercise of the overallotment) at $5 each. The company will use the funds for ongoing development of Phase II VK5211 for hip fracture, Phase II VK2809 for lipid disorders, and preclinical VK0214 for adrenoleukodystrophy. (Feb.)

Investment Banks/Advisors: Maxim Group LLC; Roth Capital Partners; William Blair & Co.

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