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JANUARY 2018

2018 OUTLOOK

By *In Vivo*'s Biopharma, Medtech and Diagnostics Teams

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January 2018

BIOPHARMA

MEDTECH

DIAGNOSTICS

2018 OUTLOOK

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January 2018

DEPARTMENTS

EXCLUSIVE ONLINE CONTENT

From The Editor

NANCY DVORIN

Welcome to our annual outlook issue, chock-full of insight and opinions about what to expect in the coming year.

Bill Looney lays out six strategies for pharma companies struggling to find their footing in a health care world suddenly populated by new players. He observes that in the competition to own the patient experience, biopharma risks being marginalized as medicines access becomes the province of powerful third parties with a different, budget-driven perspective on treating disease.

Ashley Yeo outlines tactics for pursuing innovation in a value-based world, and points out the difficulty that some medtechs report in their transition to full-blown partnership in health care delivery – many providers continue to see them solely as purveyors of devices. On the diagnostics front, Mark Ratner expects continued evolution of regulatory pathways for complex tests in 2018 and advises that artificial intelligence tools are poised to gain traction in patient monitoring.

Also inside these pages: Mike Ward's recap of JP Morgan, Emily Hayes' look at extending immuno-oncology R&D into other therapeutic areas, and a list of things that *In Vivo* Editorial Advisory Board member and ZS partner Brian Chapman says are keeping medtech execs awake at night. Last but not least, our esteemed former colleague Peter Charlish reflects on a 35-year career writing about health care.

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Up-Front

SNAPSHOTS FROM JANUARY'S CONTENT

When it comes to the amount of money put to work in the biotech sector, 2017 saw companies raise close to $73 billion globally, an almost $11 billion shortfall from 2016. Part of the reason was the dearth of major merger and acquisition activity during the year. Page 1

There's always a continual push to find new technologies, but large-cap medtech is always struggling with the balance of innovation and commodities. Even for major groups like Medtronic, 50% or more of what they sell can be classified as "commodities." http://bit.ly/2DviErZ

For big pharma, it's a huge bet to shift direction: from investing in individual drugs to treat a disease to building customized, complex data sets that map the underlying genetic profiles of individual patients, resulting in interventions – not exclusively drug-based – that reverse or prevent the disease itself. Page 12

From Trump's inauguration on January 20 through June, the FDA did not issue one medical device- or IVD-related guidance document. But once new commissioner Scott Gottlieb was settled in, the dynamic changed dramatically. http://bit.ly/2DC8F8k

BCG says that while up to four-fifths of the US market is talking about risk-based/value-based outcomes, less than 15% of current US payments can be classified as value-based or risk-shared – and even those are still largely fee-for-service plus an incentive, as opposed to a true insurance risk, or population-based payment. Page 22

Just three anti-obesity products launched in the past 30 years stand out for having a novel mode of action: Roche's *Xenical*, Novo Nordisk's *Saxenda* and Arena Pharmaceuticals' *Belviq*. But none of them is ideal. Page 36

2017's Top Biopharma Deal-makers

AMANDA MICKLUS

Biopharma deal-making didn't disappoint in 2017, despite the continued friction on drug pricing and the pressure to improve R&D productivity. A co-development and co-commercialization agreement between **AstraZeneca PLC** and **Merck & Co. Inc.** involving the key immuno-oncology drugs *Keytruda* (pembrolizumab) and *Imfinzi* (durvalumab), which are each being combined with the PARP inhibitor *Lynparza* (olaparib), was one of the largest biopharma alliances signed in 2017, and continued the dominance of immuno-oncology in partnerships. Oncology was also again the focus of the largest volume of companies raising funds through venture rounds and IPOs.

There was significant consolidation in the consumer health industry – **Stada Arzneimittel AG** was taken private, **Reckitt Benckiser Group PLC** bought **Mead Johnson Nutrition Co.**, and **Fresenius SE & Co. KGAA**'s **Fresenius Kabi AG** acquired **Akorn Inc.** Overlaying these transactions is the potential to change the way health care is accessed and delivered, with firms outside of the industry, namely Amazon, intent on entering the pharma supply chain. Retain pharmacy player and PBM **CVS Health Corp.** also has plans to better integrate health care delivery, announcing the largest deal of 2017 – the $77 billion acquisition of insurance company **Aetna Inc.** – to do just that.

We focus here on the deal-makers, showing which companies dominated the landscape in terms of deal volume and value, as well as the therapeutic categories that grabbed the most attention.

Exhibit 1

2017's Top Five Most Active Pharmaceutical In-Licensers

*Listed below each company are its top deals by potential deal value ($m)**
Includes deals by parent companies and their subsidiaries

DATE	LICENSER	SUBJECT OF LICENSE	POTENTIAL DEAL VALUE
TAKEDA		2017 DEAL VOLUME: 15 | 2016 DEAL VOLUME: 7 (+114%)	
Oct.	HemoShear	HemoShear's REVEAL-Tx platform to model liver diseases, including NASH	470
Aug.	AstraZeneca	Preclinical MEDI1341 for Parkinson's disease	400
Jul.	Tesaro	Exclusive rights in certain Asian countries to niraparib	340
JOHNSON & JOHNSON		2017 DEAL VOLUME: 13 | 2016 DEAL VOLUME: 7 (+86%)	
Nov.	Zymeworks	Azymetric and EFECT platforms in the research, development, and commercialization of up to six bispecific antibodies	1,452
Apr.	PeptiDream	Peptide Discovery Platform System to identify and optimize macrocyclic/constrained peptides against several metabolic and cardiovascular targets	1,150
May	Protagonist Therapeutics	Preclinical PTG200 plus related interleukin-23 receptor antagonists for all indications including inflammatory bowel diseases such as Crohn's disease and ulcerative colitis	990
NOVARTIS		2017 DEAL VOLUME: 10 | 2016 DEAL VOLUME: 6 (+67%)	
Jan.	Akcea Therapeutics	Options on cardiovascular-related antisense candidates, Phase II AKCEA-APO(a)-LRx and preclinical AKCEA-APOCIII-LRx	1,655
Aug.	Xoma	Phase II anti-IL-1b allosteric monoclonal antibody gevokizumab (XOMA052), plus other IL-1b antibodies for cardiovascular diseases	469
May	Durect	Phase III post-operative pain candidate Posimir (bupivacaine)	293
BOEHRINGER INGELHEIM		2017 DEAL VOLUME: 9 | 2016 DEAL VOLUME: 6 (+50%)	
Dec.	Autifony Therapeutics	Exclusive option to acquire the Kv3.1/3.2 positive modulator platform, including lead compound, Phase I AUT00206 for schizophrenia and Fragile X syndrome	740
Nov.	MiNA Therapeutics	Treatments for fibrotic liver diseases, including those against targets that restore the metabolic functionality of epatocytes and prevent fibrotic tissue formation in patients with NASH	356

DATE	LICENSER	SUBJECT OF LICENSE	POTENTIAL DEAL VALUE
Sept.	Gubra	Novel peptides that regulate food intake	300
MERCK & CO. INC.		2017 DEAL VOLUME: 7 | 2016 DEAL VOLUME: 6 (+17%)	
Jul.	AstraZeneca	Co-commercialization of Lynparza (olaparib) as a monotherapy and in combination with other compounds, including Imfinzi (durvalumab) and Keytruda (pembrolizumab)	8,500
Oct.	KalVista Pharmaceuticals	Plasma kallikrein inhibitors, including Phase I KVD001, for diabetic macular edema	761
Nov.	Cue Biopharma	CUE Biologics platform to develop engineered biologics for autoimmune diseases	374
ROCHE		2017 DEAL VOLUME: 8 | 2016 DEAL VOLUME: 15 (-47%)	
Dec.	Idorsia	Options on preclinical immuno-oncology candidates	467
Oct.	Warp Drive Bio	Options on natural antibiotic compounds to combat multi-drug-resistant Gram-negative bacterial infections	387
Apr.	Bristol-Myers Squibb	Phase II human growth and differentiation factor 8 antagonist BMS986089 for Duchenne muscular dystrophy	375

*Potential Deal Value is the sum of up-front fees plus pre- and post-commercialization money.

SOURCE FOR ALL EXHIBITS: Strategic Transactions | Pharma Intelligence, 2018

Exhibit 2

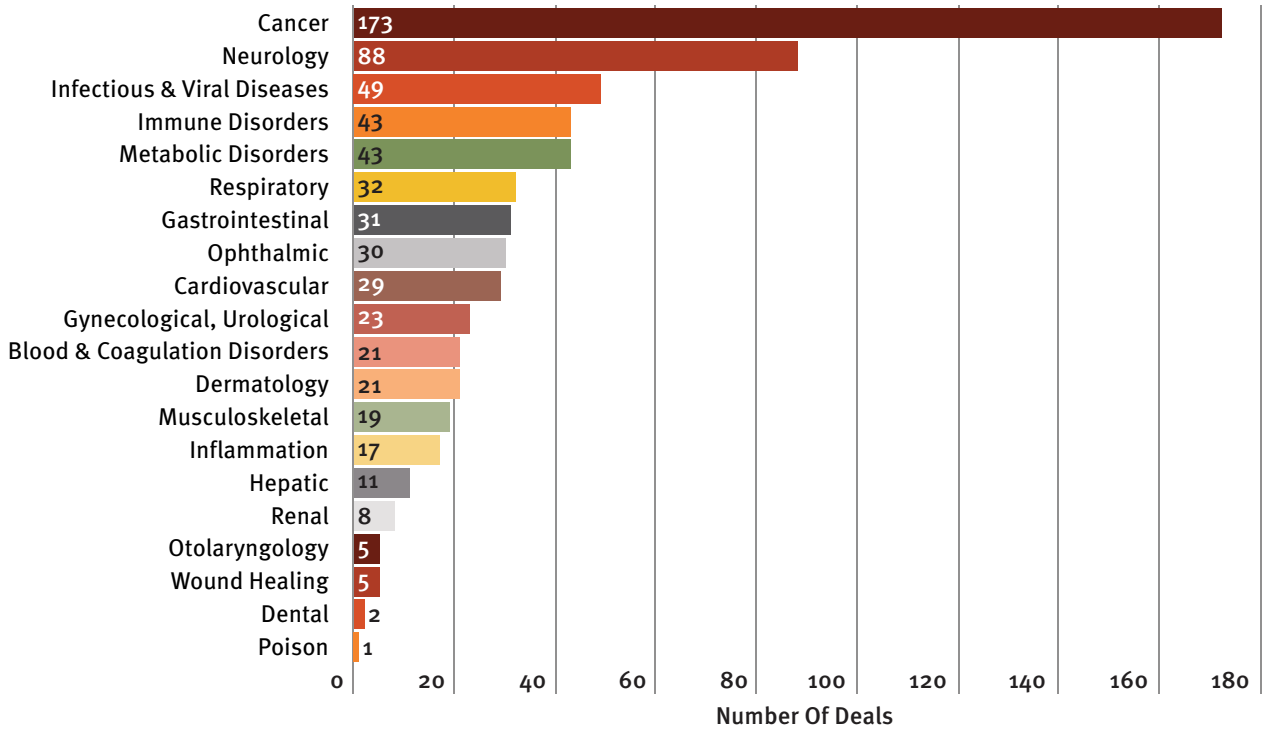
Top 10 Biopharma Acquisitions Of 2017

DATE	ACQUIRER	ACQUIRED	PRIMARY ASSET(S) GAINED THROUGH DEAL	POTENTIAL DEAL VALUE ($M)*
Dec.	CVS Health	Aetna	Integration of health care delivery through combination of retail pharmacy/PBM and insurance provider	77,000
Jan.	Johnson & Johnson	Actelion	Pulmonary arterial hypertension portfolio, including Tracleer (bosentan) and Opsumit (macitentan)	30,173
Feb.	Reckitt Benckiser	Mead Johnson	Pediatric nutrition products	17,689
Aug.	Gilead Sciences	Kite Pharma	Cell and gene therapy platform in oncology, including the CAR-T therapy Yescarta (axicabtagene ciloleucel)	11,900
Oct.	Amneal Pharmaceuticals	Impax Laboratories	Creates the fifth-largest generics company in the US	8,661
May	Thermo Fisher Scientific	Patheon	Contract development and manufacturing capabilities	7,200
Feb.	Bain Capital, Cinven Partners	Stada	Generic and OTC products	5,546
Jan.	Takeda	Ariad Pharmaceuticals	Oncology therapeutics, including kinase inhibitor Iclusig (ponatinib) and brigatinib	5,200
Jun.	Pamplona Capital Management	Parexel	CRO capabilities	4,888
Apr.	Fresenius Kabi	Akorn	Branded, generic, and OTC pharmaceuticals	4,684

*Includes the up-front fee plus any potential earn-out payments.

Exhibit 3
2017's Top Deal-makers: Cancer, Neurology and Infectious Disease

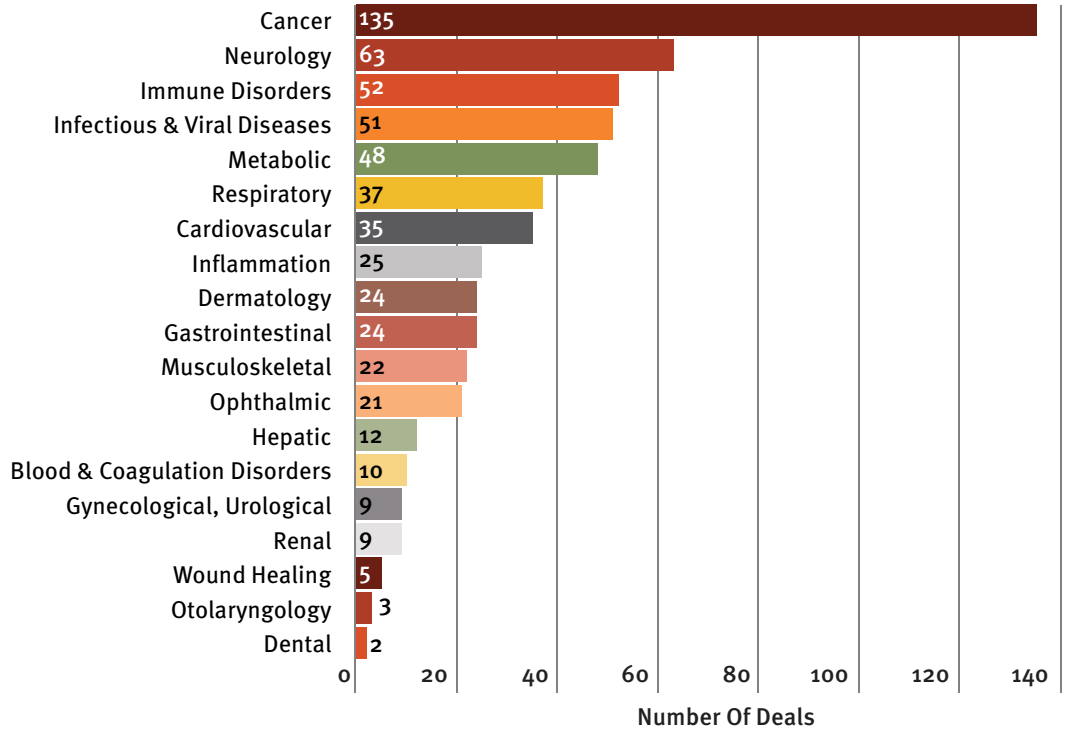
*Alliances By Therapeutic Area**



*Alliances with multiple therapeutic categories were counted more than once, in each of their respective categories.

Exhibit 4
2017's Top Money Grabbers: Cancer, Neurology and Immune Disorders

*IPO And Venture Financing Transaction Volume By Company Therapeutic Area Of Focus**



*Financing deals were counted more than once if the company was involved in more than one therapeutic area.

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Around The Industry

No Seismic Shifts As Torrential Rain Dampens JPM Jamboree

It might have been the torrential rain that fell on the first day of the *JP Morgan Annual Healthcare Conference* that dampened the spirits of the 9,000 plus delegates attending the traditional annual kickoff for life sciences-focused companies, but the dearth of seismic announcements during the meeting cannot have helped. Major topics of discussion included perennial concerns around pricing models, lackluster deal announcements, poor gender and racial diversity, and what US companies might do with the anticipated tax windfall. There was a lot of discussion but not much clarity.

With the FDA approving the largest number of new molecular entities in more than a decade, there was much backslapping about how the industry might now be better at delivering innovation. Approvals of CAR-T drugs and gene therapy products were seen as a sign of a promising future for the sector. The black cloud on that horizon, however, is how society will pay for such products. *(Also see "New Payment And Financing Models For Curative Regenerative Medicines" - In Vivo, July 2017.)*

One of the most anticipated presentations was from **Spark Therapeutics Inc.** – still basking in the glory of having its gene therapy *Luxturna* (voretigene neparvovec-rzyl) approved late in 2017 – which announced it had a new gene therapy program for Pompe disease that it hopes will supplant existing enzyme replacement therapies. The company took the opportunity to discuss some novel payment and distribution models it is thinking about, including direct sales to payers or their specialty pharmacies, outcomes-based rebates and options for payment installments, which it is currently discussing with CMS.

Lack of diversity in the industry, and at the presenting podiums, in particular, was another topic that resonated in the corridors around the meeting rooms. On social media there was a lot of buzz about the fact that there were more presenters at the meeting named Mike than women at the podium. A number of executives did take the opportunity to acknowledge the problem and outline some plans they have to rectify it. Olivier Brandicourt, MD, CEO at **Sanofi**, revealed that the company was working to have a 50:50 gender balance among its senior managers by 2022–23; currently only 20% of its senior managers are women.

One area where the JPM meeting, and the satellite events that take place concurrently, has seen more diversity is the increasing influence of Chinese actors. The number of Chinese delegates descending on San Francisco continues to rise and there were several ancillary events focused on opportunities to either do business in China or with Chinese companies.

One of the sideshows – the *WuXi Global Forum* – managed to get Ruyi He, MD, chief scientist at the Center for Drug Evaluation at the Chinese FDA, to outline how the agency intends to be as efficient at evaluating candidate drugs as the US FDA and the European Medicines Agency (EMA). The Chinese FDA is aggressively hiring reviewers, expanding the staff from just 60 a few years ago to 600 at present, with another 200 to be recruited in the coming months and to double in size by the start of next year's JPM.

Beyond seeking granularity on the progress of the various pipelines, most of the presenting companies faced questions around the potential impact that the US tax reforms might have on their businesses. The usual response was that they were still evaluating the details of the plan and would only be in a position to deliver more nuanced responses in the forthcoming reporting season. While some industry commentators such as EY are predicting a surge in M&A activity as companies enjoy lower tax rates and an opportunity to repatriate cash held outside the US, it was apparent that the windfall is more likely to be used to buy back shares and pay higher dividends, although some of the top-tier biotechs did indicate that they would use some of the money to work in acquisitions or investing in their pipelines. *(Also see "Biopharma 2018: Is There Still A Place For Pharma In The New Health Care Economy?" - this issue.)*

UNDERWHELMING DEAL ANNOUNCEMENTS

On the eve of JP Morgan, there were several announcements that contributed to the glum mood. **Pfizer Inc.**'s not unexpected decision to exit early-stage neuroscience research set the tone, supported by other announcements that failed to excite investors from the likes of **Celgene Corp.** and **Shire PLC**, while Sanofi reworked partnerships it has with **Alnylam Pharmaceuticals Inc.** and **Regeneron Pharmaceuticals Inc.**

Celgene's announcement that it is acquiring **Impact Biomedicines** and its late-stage myelofibrosis JAK2 inhibitor fedratinib drew a muted response. Investors appear to question the value of the deal, worth $1.1 billion up front and potentially an additional $5.9 billion in regulatory and sales-based milestones, as the asset, when managed by Sanofi, threw up some safety concerns. *(Also see "Celgene's $1.1bn Impact Buy Is First Of More Deals To Come In 2018 And Beyond" - Scrip, January 9, 2018.)*

Celgene made the move on Impact to offset its reliance on its multiple myeloma blockbuster *Revlimid* (lenalidomide), which is expected to start losing patent exclusivity in 2022 and has accounted for more than 63% of the company's total revenues since 2010. In 2017, Revlimid sales topped $8.2 billion, up 17.4% compared

with 2017. Celgene has been a consummate deal-maker and CEO Mark Alles told the JPM audience to expect more deals as the company sits on a cash pile of nearly $11 billion. Celgene, which retreated 28% during the last quarter of 2017 following a string of disappointing clinical results, finished the year 9.85% down at $104.36 per share. The stock was up just 1.7% during JPM to close the week at $106.00.

Shire is also aware of the lopsidedness of its business. In an accomplished and confident presentation, CEO Flemming Ornskov, MD, described how the company plans to put clear water between its rare disease and neuroscience activities by creating two distinct divisions during the first half of 2018. Having already hinted previously that such a separation was in the cards, it appeared that the markets were somewhat disappointed that Shire had not been more bullish with its intentions following last year's strategic review. The Dublin, Ireland-domiciled company saw its stock slip 5% to $149.10 per share on the day of the announcement.

One transaction that did move the needle in a positive way for one of the conference participants was the settlement of a patent dispute between **Teva Pharmaceutical Industries Ltd.** and **Alder BioPharmaceuticals Inc.** The biotech saw its shares jump 38% to $17.85 by the end of the week after Teva granted Alder a non-exclusive license to its anti-calcitonin gene-related peptide (CGRP) antibodies and methods. This enables Alder to move forward globally, with the exceptions of Japan and South Korea, with eptinezumab (ALD403), its Phase III migraine-prevention candidate. Removal of the patent overhang is expected to open the door for Alder to find a commercial partner in a competitive marketplace that will include **Eli Lilly & Co.** and **Amgen Inc.**, in addition to Teva.

Other companies that enjoyed a JPM share price bump include **Atara Biotherapeutics Inc.**, up 53% to $28.25 per share, **NanoCarrier Co. Ltd.**, which rose 42% to Yen911.00; and **Global Blood Therapeutics Inc.**, which added $15.10 (36%) to finish the week at $56.60.

The only deal announcement that resulted in a share price moving significantly was that of Belgian biotech **Ablynx NV**, which told delegates that it had rebuffed advances from **Novo Nordisk AS** on two occasions in December. Ablynx revealed that, on December 22, the Danish pharma offered to acquire it for €28 a share in cash plus a CVR with total potential cash payments of up to €2.50 a share, representing a 60% premium at the time and valuing the company at €2.6 billion. Ablynx posted the highest share movement during the week, closing 73% higher at €36.60 on Euronext Brussels.

Highlighting the challenge neuroscience poses for companies big and small, the poorest performing stock during JPM week was **Axovant Sciences Ltd.** Axovant announced that it was discontinuing the development of intepirdine, its 5-HT6 receptor antagonist, which was targeting treatment of Lewy body dementia and Parkinson's disease dementia. The compound missed the primary endpoints of both the Phase IIb HEADWAY and Phase II Gait and Balance studies. This is not new territory for either the company or the candidate drug as Axovant announced in September 2017 that interpirdine had failed in Alzheimer's. The company's stock fell $3.28 (61%) during the week to close at $2.09 per share on January 12.

BEYOND HUMIRA

Among the top-tier pharma businesses, there was a lot of interest in what **AbbVie Inc.**'s management had to say about how it intends to wean itself off its *Humira* (adalimumab) dependency. Although the company expects Humira to face biosimilar competition as early as 2022 in the US, Abbvie still expects the anti-inflammatory biologic to be its main cash generator through 2025 and beyond, with a predicted $21 billion in sales globally in 2020.

Part of Abbvie's post-Humira strategy is the broadening of its immunology pipeline. In particular, the company focused on risankizumab, its anti-IL23 antibody, and upadacitinib, its oral JAK1 inhibitor, which it forecasts could achieve 2025 peak sales of $5 billion and $6.5 billion, respectively. Abbvie expects both these pipeline assets will treat patients who don't respond well to Humira. It also plans to aggressively advance the drugs in multiple immunology indications beyond rheumatoid and psoriatic arthritis.

Abbvie is confident that it will be able to grow its non-Humira business from $9.6 billion in 2017 to more than $35 billion in 2025 – representing a CAGR of 17% a year – on the back of more than 20 new launches by 2020. Short-term drivers include the company's hematologic cancer assets, *Venclexta* (venetoclax) and *Imbruvica* (Ibrutinib), which are being developed for further label expansions and oncology indications.

CAPITAL OPPORTUNITIES

One of the major questions that made the rounds at JPM is whether the capital markets will be more or less supportive of the biotech and medtech sectors. Pharma and biotech stocks made progress during 2017. The top performing index was the NYSE Arca Biotechnology Index, an equal-dollar weighted index that comprises 30 leading companies with at least a $1 billion market capitalization, which although flat in the final quarter advanced some 37% across the year. This performance compared favorably with the NASDAQ Composite, Dow Jones Industrial Average and the S&P 500, which rose during 2017 by 28%, 25% and 19%, respectively. The NASDAQ Biotechnology Index advanced 21%, whereas the NYSE Pharmaceutical Index moved up just 13% during the year.

When it comes to the amount of money put to work in the biotech sector, 2017 saw companies raise close to $73 billion globally, an almost $11 billion shortfall from 2016. Part of the reason was the dearth of major merger and acquisition activity during the year – **Johnson & Johnson**'s acquisition of **Actelion Pharmaceuticals Ltd.**and **Gilead Sciences Inc.**'s purchase of **Kite Pharma Inc.** accounted for 80% of deal values in 2017. However, there was also an outflow of funds from the sector as investors looked for other areas to invest in. According to Informa's *EPFR Global*, fund flow in biotech in 2017 saw some $1.1 billion move out of the sector, although there was a net inflow of about $1.1 billion in the second half of the year.

Nevertheless, companies and investors were fairly confident that the sector will still get capital market support. Indeed, biotechs raised almost $900 million during the first week of January, while the queue for biotech initial public offerings looks robust.

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What Will Keep Medtech Industry Leaders Awake At Night In 2018?

The first concern on the minds of the medtech industry's leaders is that the gains of large-scale transformation are a long time in coming. The industry has talked about commercial transformation for a considerable time. Some companies have consolidated their previously separate business units. Others have invested in strategic account management. Others still have created new business models and value-sharing approaches. While this higher-order commercial evolution is absolutely required, the pace at which customers are preparing is maddeningly slow.

More than a few hospital system customers, for example, are not organized to partner in the way that medtech might like. Traditional purchasing processes used by the customer can make the new, innovative value-sharing programs seem simply too sophisticated or at least out of sync with their needs.

In reality, a high degree of heterogeneity exists within the customer universe, which means that large medtechs are realizing that they have undertaken some of the very difficult work of transformation, without really being rewarded for it yet.

Another worry for stakeholders is that there are cracks in commercial analytics and operations, and these are becoming more and more visible. A history of prioritizing action in the field over measurement has meant that medtechs have skewed investment toward having a well-equipped sales and service team and away from the commercial analytics and operations that support them.

Add that to a rich history of acquisitions and autonomously run business units and we get a clear picture of companies that struggle with commercial discipline. Commercial teams differ substantially across the divisions of a large medtech. These teams struggle to manage prices effectively or to enforce anything but the simplest contracts. Identifying common customers across divisions, enforcing compliance and providing a consolidated view of business performance are becoming increasingly acute challenges at the same time that the industry is recognizing just how important these fundamentals are.

The fragility of the global supply chain is a growing issue. Obviously, the supply chain is always important, but we have seen some very high-profile problems recently that have put leaders under a lot of pressure. They can range from moving too aggressively to shift manufacturing into low-cost areas, to grappling with disaster recovery from hurricanes in the Caribbean, to not sufficiently rationalizing product portfolios after an acquisition. It is ostensibly an obvious pillar of executive responsibility, however, and lack of attention in this area has cost some players dearly in 2017. These are three issues that I think will be pivotal in 2018, and their pressing nature may even be giving some decision-makers sleepless nights.

Large medtechs are realizing that they have undertaken some of the very difficult work of transformation, without really being rewarded for it yet.

AND WHAT COULD HELP THOSE LEADERS SLEEP?

There are two areas I would love to see addressed in 2018, and if they were, it could signal improvements across the ecosystem in the coming years. The first is digital health/health tech money flow. There is a tremendous amount of funding going into the sector that we refer to as "digital" and "connected health," and the potential is tremendous. This ranges from monitoring patients in remote areas, to connecting patients with caregivers virtually, to creating feedback loops that bring insight and behavioral change, and everything in between. The promise is to prevent acute events, keep patients out of the hospital, increase independence and facilitate good choices that better manage chronic conditions.

Although there are a variety of stumbling blocks that have slowed down innovation, a big one is money flow. Old payment mechanisms reward the traditional stakeholders and traditional hospital-centric approach to care. While not every "innovation" is worth having, many innovators are simply waiting to figure out how to get paid and overcome the barriers erected by those who would lose. My first wish for 2018 is flexibility and innovation in how we pay for digital health.

The second is the area of longitudinal data interoperability. While we are on the subject of dreaming big, the promise of integrated patient data, captured longitudinally, would be a game changer. Today, patient data are fragmented and focused on interventions and episodes, instead of capturing a complete picture of the patient over time. The true impacts of interventions are not well understood. Sites of care change frequently, as do payers, which makes a comprehensive picture of outcomes over time very hard to come by.

But by truly understanding long-term outcomes from interventions and therapies, we can attach appropriate value and enrich choices. The recent decision of the US FDA to speed the approval process and rely more on real-world evidence would make the impact of longitudinal outcomes data even greater. These are my two standout wishes for 2018.

IV005259

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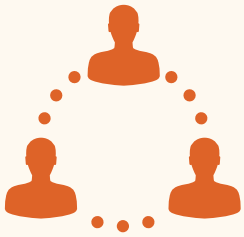
In Vivo's 2017 Deals Of The Year: THE WINNERS ARE...

WE NOMINATED 15 DEALS IN THREE CATEGORIES. YOU PICKED THE WINNERS.

TOP ALLIANCE



Regeneron's Novel Deal With Decibel

Regeneron Pharmaceuticals forged a unique agreement with start-up Decibel Therapeutics in which it will make an equity investment and provide financial support for the hearing-focused biotech's R&D, but claim no share of commercial rights to any therapeutics discovered under the collaboration.

Runner-Up: Medtronic & Aetna's outcomes-based insulin pump deal

TOP FINANCING

Pfizer Spins Off SpringWorks

Pfizer's spun out Springworks in September with four clinical-stage assets targeting diseases with no good cures. The big pharma concurrently contributed to SpringWorks $103 million Series A round, as did Bain Capital Life Sciences, Bain Capital Double Impact, Orbimed and LifeArc.

Runner-Up: Silk Road Medical raises $47 million for stroke prevention devices

TOP M&A

J&J/Actelion – Win-Win-Win

Johnson & Johnson's months-long pursuit of Actelion Pharmaceuticals culminated in a $30 billion cash acquisition last January. J&J got immediate access to the Swiss biotech's lucrative pulmonary arterial hypertension franchise and late-stage pipeline as well as initial 16% ownership in Idorsia Pharmaceuticals, a new spin-out formed around Actelion's drug discovery operations and early-stage clinical assets.

Runner-Up: CVS/Aetna vertical merger aims to change health care delivery

Biopharma 2018: Is There Still A Place For Pharma In The New Health Care Economy?

2018 will be a time of transition in health care, when biopharma's counterparts in adjacent industry segments scale up in a radical redesign of their traditional business models. Biopharma is not moving as quickly, and it confronts a strategic dilemma on how to address the prospect of a much more powerful set of rivals in the ongoing battle to own the patient experience in medicine.

BY WILLIAM LOONEY

For the new year, *In Vivo* offers six areas where the pharma C-suite can counter health policy and system bottlenecks by building to excel.

Cooperation within biopharma to improve safety signals will be crucial in maintaining public confidence in the gene-based therapies now entering widespread clinical use. Success for these transformative therapies will drive long overdue changes in approaches to market access, value and reimbursement.

So what? The push by players outside biopharma to dominate the entire health vertical through size, scale and reach might backfire, imperiling the relationship to patients as well as incurring the wrath of trust-busters and other industry regulators.

The key challenge confronting biopharma in 2018 is the disconnect between an abundance of transformative science and a hidebound commercial and regulatory model that continues to place barriers to making the right medicines accessible to patients who need them. It's a structural problem in the delivery and financing of health care overall, but one that impacts biopharma disproportionately by adding to the cost of drug development, denting the benefits of innovation and diminishing the industry's reputation as a force for social good.

Solving for the imperfections that guide institutional behavior – can human health provision ever be anything but "messy"? – will dominate the commercial and policy agenda for biopharma in 2018. *In Vivo* Editorial Advisory Board (EAB) member and health care portfolio manager at E Squared Capital Management Les Funtleyder describes current attitudes in the C-suite as one of "disembodied anxiety" fueled by a host of factors, including pricing pressures; restive patients; the ascent of adjacent players like Amazon; state government transparency mandates; the soaring cost of deferred IT investments; compliance and anti-trust exposures; and those generic and specialty segment train wrecks. Overlaying all is the market churn caused by the consolidation now taking place in other health industry verticals. Says Funtleyder, "The consensus is the biopharma business model has to keep adjusting in line with these uncertainties – but how, and to what end?"

A mandate to change must first account for the remarkable persistence of traditional rules of engagement. The *diktats* of drug development feed that sedative called complacency. The "gold standard" for drug approval – the randomized clinical trial

– remains largely as it was in the 1940s. The P&R process is complex, arbitrary and almost completely non-transparent, while information – biopharma's greatest single untapped asset – is plagued by the contradictions, duplication and missing links of a disaggregated world of "data islands" with little connection to the actual experience of patients. Biopharma's own promotional practices, at least in the US, seem rooted in a bygone era of unconstrained budgets, following a strident "push" model that is often tone deaf to contemporary notions of clinical value or medical need. Turn down the volume on a TV ad for psoriasis, related auto-immune disorders and other heavily promoted drugs and one might think the subject is sex, not science.

Meanwhile, regulations and markets continue to incentivize R&D resources within an increasingly narrow band of high-promise therapies. But are there really any "niche plays" left among the more than 1,000 trials now underway in immuno-oncology? Is all that investment heading toward a cliff of clinical indistinguishability while the hardest problems of public health – like Alzheimer's disease – remain unsolved?

No Safety In The Middle Lane

Taken together, these institutional realities are slowing biopharma's necessary transition as an integral component of the health care ecosystem. The stakes going forward are high. The alternative is being positioned as a high-cost outlier vulnerable to challenge from adjacent industries with a loss-leader consumer orientation or from emerging geographies such as China that offer a cheaper business model. In the competition among health care providers to "own the patient," biopharma risks being marginalized as medicines access becomes the province of powerful third parties with a different, budget-driven perspective on confronting disease.

As US health care struggles to adapt to an aging population (the 65+ cohort has risen 40% since 2000, to 50 million people), soaring costs (at $3.3 trillion in 2016, US annual health care spend now exceeds the entire GDP of the UK, the world's fifth largest economy) and rising public expectations (15 million new enrollees in the public Medicaid entitlement program since 2013), most service providers outside biopharma are aggressively repositioning their businesses. The imperative is to manage cost exposure risks by controlling the patient journey through the health system, diversifying lines of business and capturing more of the value that leads to better outcomes for patients – and improved returns to shareholders.

Examples of this push toward integrated channel consolidation include moves by **insurers** to purchase home care and rehabilitation vendors as well as to enter the pharmacy benefits business. (*See Exhibit 1.*) The aim is to supplement the processing of claims with adherence and prevention services that provide direct line of sight over costs incurred by their covered populations. The classic **contract research organization** (CRO) is morphing into the **contract commercial organization** (CCO), acquiring analytics and big data providers to fire up its existing strengths in expediting drug development. **Hospitals**, confronting opposition to an absurdly expensive "high-touch" delivery model, are bulking up to secure regional market dominance while acquiring specialty drug pharmacies. The goal here is to increase purchasing power through scale and reach and provide more care on a cheaper outpatient basis. **Physicians** are relying on incentives in the 2010 Affordable Care Act (ACA) to create integrated delivery networks (IDNs) that operate like a closed HMO in providing employer-based populations with both prophylactic and preventive care, at a fixed per-patient cost, usually on a long-term basis – where patient outcomes can be tracked, measured and justified to payers.

Finally, **distributors** are leveraging their logistical strengths to occupy a crucial space in the delicate, time-sensitive transfers of living human cells that form the supply backbone for the newest gene-based drug therapies. "We are now innovating among the best," **Amerisource Bergen Corp.** CEO Steve Collis tells *In Vivo* in explaining his company's recent selection by **Novartis AG** to coordinate logistics for the first FDA-approved gene-modified cell therapy, *Kymriah* (tisagenlecleucel-t). "It's another mission-critical

Les Funtleyder
E Squared Capital Management

Steve Collis
Amerisource Bergen

Michael Ringel, PhD
Boston Consulting Group

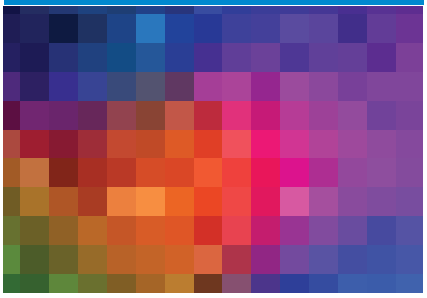


Exhibit 1

Summary Of Recent Health Care Service Industry Deals

DEAL DATE	DEAL CATEGORY	ACQUIRER	TARGET COMPANY OR ASSET	DEAL VALUE	STATUS
Dec. 2017	Asset Purchase	UnitedHealthcare	Primary and urgent care outpatient facilities, Da Vita Inc.	$4.9bn	Pending
Dec. 2017	Asset Purchase	Humana	Home care and hospice services, Kindred Health	$4.1bn	Pending
Dec. 2017	M&A	Advocate Health Care	Aurora Health Care	Debt free, non-cash transaction	Pending approval as Advocate Aurora Health
Dec. 2017	M&A	CVS Caremark	Aetna Insurance	$77bn	Pending
Nov. 2017	M&A	McKesson	Rx Crossroads	$735m	Completed
Oct. 2017	M&A	Express Scripts	eviCore Healthcare Inc	$3.6bn	Completed
Sept. 2017	M&A	Walgreens	Rite Aid Pharmacy	$4.4bn	Completed
July 2017	Private Equity	KKR & Co. Internet Brands	WebMD	$2.8bn	Completed
May 2017	M&A	Thermo-Fisher	Patheon CDMO	$7.2bn	Completed
April 2017	Asset Purchase	Cardinal Health	Patient care, deep vein thrombosis, and nutrition insufficiency LOB, Medtronic PLC	$6.1bn	Completed
Oct. 2016	Private Equity	Blackstone Group	TeamHealth	$6.1bn	Completed
Aug. 2016	Private Equity	Advent Int'l VC	InVentiv Health	$3.8bn	Completed; relaunched as Syneous Health on 8/1/2017

SOURCE: Medtrack | Pharma Intelligence, 2018

activity that biopharma cannot do alone."

Perhaps the biggest example of the urge to control is the move by a network of religious-affiliated hospitals and independent IDNs to address chronic supply shortages and price hikes in generic drugs by entering the business directly, either as a non-profit purchasing cooperative or direct manufacturer. (*Also see "Provider Consortium Will Try 'DIY' Solution To Generic Shortages, Pricing" - Scrip, January 18, 2018.*) "It's no surprise the providers are seeking a solution to these generic market improprieties," comments Les Funtleyder. "Less certain is whether this kind of arrangement will actually work to deliver the purchasing stability hospitals seek. Quite frankly, the federal government could have fixed the problem some time ago – we have a Strategic Petroleum Reserve for oil so why not a Strategic Drug Reserve that can be mobilized quickly to tackle the supply chain problems and the opportunity this provides for price gouging?"

Going Small

Ironically, many drugmakers have bucked this trend to bulk up by "going small," focusing their research on narrow cohorts of patients with rare diseases and no alternative means of treatment. Originally the province of biotech, big pharma has also moved aggressively into the rare disease space. These "orphan" drugs offer inventors a greater measure of control over development and marketing costs due to an accessible and highly engaged community of patients and prescribers. The challenge is to justify the high price points required to achieve a reasonable ROI from a highly selective patient population and to fund the add-on indications that expand market potential and increase sales. *(Also see "Orphan Drug Pricing And Reimbursement: Challenges To Patient Access" - In Vivo, November 2017.)*

Last year, federal government incentives to promote rare disease research were scaled back as this specialized therapeutic field grew more crowded. As a result, investor attention is slowly returning to treatments for diseases for large populations. **Amgen Inc.**, the biggest biotech, has made this point clear in recent meetings with investors. Thinking small does have its limits. But the real issue is the financial stakes in market acceptance in 2018 are much higher than when follow-on medicines aided by a crush-it-all field force were sufficient to drive scrip sales. More population-based options that reach beyond the current standard of care must be pursued to grow revenues.

Then there is the elephant in the room called Amazon. With a soaring market cap of more than $600 billion and a willingness to confront and out-brand any rival on price, Amazon now controls one-half of all online retail sales in the US, notching annual sales of $136 billion in 2016, which places it among the top ranks of health industry leaders like **CVS Health Corp./Caremark Rx Inc.**, **McKesson Corp.** and **UnitedHealth Group Co.** But where Amazon chooses to engage (the retail OTC/HBA or online pharmacy space most likely, facilitated by its 2017 acquisition of the Whole Foods supermarket chain) is less important than the impact of its transparent, loss-leading price model.

Disruptors And Accelerants – It's Fire Just The Same

In a tightly regulated, high-barrier sector like health care, transparency is the biggest disruptive force of all. It's a market-based equivalent to government price controls. That's because, when producers prove reluctant to explain the difference between list price and net price, transparency exposes the role of every player in a transaction – what they *do* and what they *get* in that passage of product to patient. The potential is there for an interloper such as Amazon to use that transparency to render the middleman superfluous, driving down costs, the impact of which is going to be based on where you sit in the health care supply chain. And recent examples from the high-tech start-up world (Uber, Airbnb) show that you can transform an entire industry without making the product that defines it. That puts a damper on the idea that core competence always clears the field.

Like the entry of new rivals, technology also demands biopharma's attention. IT capabilities in health care are growing at a pace equivalent to progress in our understanding of the biological and genetic origins of disease. In fact, the spread of useful information fueled by technology provides the rationale – and the means – for the moves by so many health care players into businesses outside their traditional base.

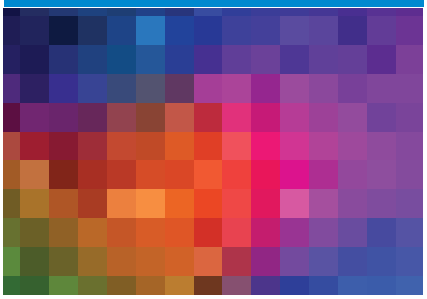
It's another disruptive trend that will gather strength in 2018 as a range of new data management and eclinical platforms come on stream, particularly for clinical trials and postmarketing surveillance. The most important of these are systems that can integrate multiple streams of data and eliminate redundant processes to guide complex decisions on key aspects of the drug development and launch process, from setting the right trial endpoints, finding and analyzing the most relevant information from patients, even expediting the design of human subject studies conducted on a less costly "virtual" basis – all in an accessible but highly secure cloud environment. Oracle Health's recently launched *Clinical One* platform is but one example of this.

"More than ever, analytics rule the world of medicine. Yet many in biopharma still rely on legacy IT devised

Amanda Micklus
Datamonitor Healthcare

Roger Longman
Real Endpoints

Ken Kaitin, PhD,
Tufts



in the chemistry, small-molecule era," Oracle SVP and general manager Steve Rosenberg tells *In Vivo*. Upgrading data infrastructure will be a major expense for the industry through the end of the decade, but we believe the investment will more than pay for itself through higher productivity at every stage of the R&D process and the ability to bring more drugs to market faster for patients waiting in the balance. Most important, creative application of these integrating technologies is critical if drugmakers are to create the necessary regulator and payer confidence in real-world evidence [RWE] that will drive a drug's value proposition in the future," Rosenberg says.

Taken together, the spurt to restructure that dominated other parts of the health ecosystem in 2017 has left biopharma a bit blindsided. All the trends point to health care becoming a more consumer-oriented business, with the patient bearing more of the cost of care. Hence, the different health verticals all want to "own" the patient experience by doing a variety of things, geared to solutions as opposed to products.

Nevertheless, biopharma continues to pursue its singular model of technology "push." Says Bain partner and a leader in the firm's Health Care and Strategy practices Nils Behnke,PhD, "It's still the standard among many big pharma to develop a new technology, obtain approval and create a product marketing campaign with heavy promotion to physicians, often based on a product differentiation strategy where there is already an existing high standard of care. This traditional approach is considered by many stakeholders to be reactive and adversarial. The better approach is to develop superior disease-state solutions around a new drug, which requires biopharma companies to pursue a strategy of market leadership in therapeutic categories and to build new capabilities."

This is not to say that biopharma is completely disengaged. On the one hand, collaborative efforts between drugmakers and other parts of the health sector are becoming more common in diabetes, where payers hold most of the cards on price and market access. Segment leaders **Eli Lilly & Co.**, **Merck & Co. Inc.**, **Novo Nordisk AS** and **Sanofi** have no choice but to position themselves as integral parts of a full-service care delivery platform, beyond the drug itself. It's expensive but necessary in addressing the demands of payers for better outcomes in a prevalent condition characterized by numerous co-morbidities.

On the other hand, industry efforts to create a new class of injectable lipid-lowering drugs (the PCSK9 inhibitors) appear to have misread physician and patient sentiments on what constitutes a real advance against standard of care – and how much that advance should cost. Sales of PCSK9's have posted far below initial launch projections, suggesting that biopharma still has trouble holding its own in a conversation to establish value at the patient point of care. But leading that conversation is going to be far more important as out-of-pocket drug costs for patients increase along with the clout of commercial payers who administer benefits and set plan deductibles.

Breaking The Siege – Six Strategies To Succeed In 2018

So what will biopharma do? Will "strategy accelerators" like tax reform force big pharma off the fence to start investing big in those high-tech partnerships that some observers see as transformative to the industry's basic mission? For big pharma, it's a huge bet to shift direction: from investing in individual drugs to treat a disease to building customized, complex data sets that map the underlying genetic profiles of individual patients, resulting in interventions – not exclusively drug-based – that reverse or prevent the disease itself. To achieve that, everything – from basic discovery to reimbursement – must change.

The good news is that in 2018 the stars are aligned to give drug companies space to pause and take some of these truly strategic steps – to reinvigorate their business models and move innovation forward in ways that matter to patients. *In Vivo* discussions with a cross-section of industry experts suggest a C-suite focus on the following agenda items.

Deal-making: Back On The Table

In 2018, one should see clarity restored to the M&A environment for biopharma after a year of decidedly mixed signals.

WHERE TO FOCUS IN 2018

M&A is back on the table; take advantage

Federal legislative inaction: a mixed bag for pharma

Working with a re-energized FDA

Define and deliver value

Manage a controlled rollout for advanced therapies

Preserve the US innovation climate

Informa's *Strategic Transactions* finds that although the value of acquisitions in 2017 rose to $208 billion from 2016's $104 billion, the number of deals went down significantly (97 in 2017 vs. 123 in 2016). Clearly, the majority of investors chose to sit tight while the new US administration pursued the first comprehensive overhaul of the corporate and individual tax regime since 1986.

Passage of the Tax Cuts and Jobs Act (HR 1) on December 20 removes the uncertainty, although the impact from adoption of the territorial tax structure used in other industrialized countries as well as reduction of the basic corporate rate on profits from 35% to 21% will vary depending on a company's geographic exposure and the tax treatment of intangible assets like IP. A special low rate on the repatriation of industry cash parked abroad from earnings outside the US – estimated at more than $170 billion – gives companies substantial room to maneuver, from pursuing large-scale mergers, a relatively rare event so far this decade, to targeted, bolt-on asset acquisitions, license and partnering ventures as well as to straightforward financial instruments like dividend raises and share buybacks.

"Conditions are ripe in 2018 for big pharma to do some truly transformative deals," says Boston Consulting Group's managing partner for life sciences (and *In Vivo* Editorial Advisory Board member) Michael Ringel, PhD. "There are convincing arguments that mergers are a necessary way to take out waste and deliver

operational efficiencies while doubling the contribution from complementary scientific talent and expertise. It's an opportunity to refresh your strategic focus and avoid that institutional inertia. Yes, the mechanics of a big merger can be as difficult as changing the tires on a car while it's still moving. But there is also opportunity to refresh your strategic focus and avoid that institutional inertia, with the best combination of people, systems, products and science, to cross-sell and introduce more diverse products to the market."

Aiming for more size and reach may work as a defensive play for biopharma as other health sector verticals scale up to become more formidable price negotiators. Industry simply has to do more to gain access to all those covered lives.

Amanda Micklus, Informa Pharma Intelligence principal analyst for *Datamonitor Healthcare*, suggests that big pharma will resist thinning its ranks through large-scale combinations equivalent to the **Pfizer Inc./Wyeth** ($68 billion) and **Merck & Co. Inc./Schering-Plough Corp.** ($41 billion) mergers of a decade ago. "I think we will see many more asset-building acquisitions directed to highly specialized pipeline and therapeutic category objectives. Filling geographic gaps in the business growth plan is another important goal. The consensus remains strong that the big mergers created problems of complexity and cultural fit and ended up doing little to boost R&D productivity and increase the pace of commercialization for new products. This year, there are no objectives more important than these two, and not just for big pharma but for specialty and biotech as well."

Research conducted by professional services firm EY on 278 biopharma transactions between 2010 and 2017, released at this month's *JP Morgan 36th Annual Healthcare Conference*, concludes that targeted bolt-on transactions produced a higher return to shareholders than so-called transformative mergers valued beyond $10 billion. "What we found was that, despite the risks of patent expirations, negative clinical trial outcomes and unfavorable reimbursement decisions, bolt-on transactions showed a slight edge compared to the transformative deals over the survey period," Arda Ural, PhD, partner in EY's Life Sciences Transactional Advisory Service, tells *In Vivo*. "That's because the biggest deals involve operational discipline, dexterity in cultural change management and effective employee communications, the benefits of which only show up over time – two or three years at least." *(Also see "No Seismic Shifts As Torrential Rain Dampens JPM Jamboree" - this issue.)*

> *"Recent examples from the high-tech start-up world (Uber, Airbnb) show that you can transform an entire industry without making the product that defines it. That puts a damper on the idea that core competence always clears the field."*

Biotechs share the same deal-making perspective, as they are increasingly looking for big pharma's help in advancing their most promising compounds toward commercialization. Completing a successful clinical trial requires expertise they don't have. Start-ups are more open to bolt-on buyouts and partnerships if the combination helps fill this gap.

Finally, biopharma deals will be influenced by fresh cues from the FDA seeking to drive innovation in hot areas like gene therapy, neurodegenerative disorders and regenerative medicine. These and other novel treatment pathways – including next-generation drug-devices – will benefit from an agency priority in 2018 to create more clarity in testing and reduce time to market.

All these converging factors ensure the biopharma business development function will be kept busy in 2018 putting tax reform's additional cash reserves to productive use. The range of interests will expand as senior management asks for more small, "kick the tire" partnering in digital, big data analytics and machine learning. One precedent to start the year is **Roche**'s deal with **GE Healthcare** on a new digital diagnostics platform to apply advanced analytics to workflow solutions and apps that support clinical decisions in oncology and in the ICU space, where machine learning will seek to predict patient complications before they strike. *(Also see "GE And Roche Join Forces In First-Of-Its-Kind Tech Pact" - Medtech Insight, January 8, 2018.)*

Significantly, however, many VC players are still skeptical of digital as the "bird in hand" that will revive the biopharma formula for growth. VC money is not flowing into digital at this point, although the convergence of biology and engineering that digital health represents remains attractive. The wait is on this year for evidence that patients will adopt the behaviors that enable digital health to work in line with expectations.

Industry Policy And Politics: Out To Lunch?

Government usually weighs heavily in biopharma's strategic calculations, but 2018 is likely to prove the exception. A feeble effort around industry self-regulation begun last year has been sufficient to prevent legislation to introduce transparency and negotiation on drug prices, and no action by Congress or the Trump administration can be expected this year. In contrast to the massive change taking place on the

commercial front, virtually every aspect of government health care in the US is gridlocked. It reflects a larger ideological conflict about whether access to basic health services is an individual responsibility or a shared commitment of society. The US remains the only industrialized country that has failed to resolve this fundamental value question. Yet the surprising trend is how legislative inaction is actually supporting the growth of publicly sponsored health care programs like Medicare and Medicaid, which are forecast to account for 47% of all US health spend by 2025 – it's entitlements by default.

The point is partisanship has become an enduring feature of the federal landscape. This means that while little of substance gets done – in industry quarters, that's often seen as a good thing – there is also pervasive uncertainty about the long-term direction of public policy toward biopharma. If, as seems likely, control of Congress shifts to the Democratic Party in the November mid-term elections, biopharma will face renewed efforts to introduce price negotiation for Medicare Part D drugs and restore key elements of the 2010 Obamacare health reform law eviscerated last year by the current GOP majority. The pendulum swings both ways, which is never good for a business that must make big bets on capital that pay out only over time.

In addition, gaping deficits from the new tax reform law will reinvigorate congressional budget hawks, making it harder to reauthorize popular benefit programs like the Children's Health Insurance Program (CHIP), which supports reimbursements for a surprisingly high proportion of the industry's most innovative new medicines in the pediatric space. Fiscal pressures may also stimulate regulatory actions to narrow tax subsidies for biopharma's drug compliance and support programs as a promotional tool rather than a legitimate service to patients. Tax law can not only give, it can also take away.

What biopharma must do in such a divisive environment is to cultivate new audiences outside the K Street "swamp" and go deep on CEO demonstrations of public "authenticity" – the new coinage for reputational enhancement in an era where even facts are labeled "fake news." It's also worth noting that business and the military remain the only societal institutions deemed by the polls to be in working order. It's also wise to stay local in affiliations, choosing strong national and regional managers capable of helping HQ interpret the political tea leaves. A global corporation deprived of this intelligence is effectively stateless when trouble arises.

FDA's Friendly Persuasion

The FDA is the go-to destination this year in addressing fundamental supply chain issues neglected by the political branches of government. Under Commissioner Scott Gottlieb, MD, the FDA is tackling topics such as industry competition, where it is reviewing current rules on patents and exclusivity jointly with the Federal Trade Commission (FTC); pricing and access to medicines, where it has launched a vigorous effort to anticipate and prevent single-supplier situations and, through stepped-up abbreviated new drug application (ANDA) approvals, push more competitively priced generics and biosimilars on to the market; and innovation, in the form of increased flexibility in approving novel new medicines on the basis of demonstrated improvement against standard of care. Additional forms of evidence beyond the RCT will, in certain cases, be accepted to demonstrate such improvement. The FDA has also pledged to take better account of what patients and other stakeholders really value in the medicines they take in the clinical setting.

Finally, the FDA is actively encouraging industry-led partnering initiatives to share more trial data and cooperate in the analysis of adverse events, particularly in the sensitive cancer space. Overall, the agenda suggests faster times to drug approvals and a willingness to take account of unmet patient need in the certification of trial endpoints.

One bright spot in the legislative mix is the 21st Century Cures Act (Public L. 114-255), a true bipartisan piece of legislation enacted by Congress in December 2016. A significant portion of the FDA's work in 2018 will be in providing guidance for biopharma on key pro-innovation provisions of the law. This will include measures to advance NDA reliance on RWE and other patient-centered alternatives to the traditional RCT, and providing more support for a positive, risk-based approach to use of digital technologies for both platforms and products. The act underscores how good legislation is not only facilitated when both Democrats and Republicans are engaged, but it also tends to last as well. The FDA is capitalizing on the bipartisan vibe by offering itself as an honest broker between the industry and other stakeholders, especially organized patient groups.

Value: It's Game On

All drugmakers acknowledge the importance of establishing a new medicine's value to payers beyond the standard clinical anecdotes and testimonials from KOLs. But the will to do so continues to face numerous barriers. These include cultural complacency and conservatism within the biopharma enterprise, the short-term orientation of investment decision-making and the absence of a broad institutional mandate to set rules for defining value, along with the tools to measure it.

Private payers are often disinterested in risk-sharing deals due to their emphasis on managing costs through short-term, one-off interventions. Government continues to send out mixed signals. It has endorsed value constructs as an administrative priority linked to quality but has done little to alleviate mandated rules of behavior that make value-based contracting inherently risky. These include:

(1) regulatory requirements, especially the murky rules on engaging with payers on P&R before a product receives full licensing approval;

(2) exposure to violation of the Medicaid "best price" rule, including prosecution for price collusion, resulting in the possibility of hefty fines and denial of access to covered populations; and

(3) anti-kickback rules that may define industry investments in patient support programs for complex therapies as an illegal, anti-competitive promotional inducement.

Exemptions that minimize the legal exposure for participants in any risk-sharing agreement could serve as a useful first step in incentivizing the push for value. Yet, with the exception of an

FDA move to legitimize that broader dialogue with payers prior to authorization, government action to "de-risk" value-based contracting is unlikely this year. "Government is less relevant today as a factor in this transition," observes Roger Longman, CEO of Real Endpoints, a market access consultancy, partner to Informa Pharma Intelligence and member of the *In Vivo* EAB. "The commercial segment is much further along, but it too confronts significant challenges. One is misreading their audience: drugmakers often presume that payers are uninterested in negotiating value, when in fact payers are desperate for new approaches to managing their costs and maintaining credibility with clients responsible for millions of covered lives."

At the same time, however, payers are fighting a largely unseen pitched battle with drugmakers on the basic issue of access to innovative specialty medicines. "Payers and providers are looking for ways to extract every imaginable discount from the manufacturer aimed at preventing enrollees from being moved to low-cost meds once exclusivity ends," says long-time industry managed care expert Mason Tenaglia. The list includes blocking co-pay coupons as well a new twist recently introduced by the leading pharmacy benefit managers (PBMs): comprehensive "accumulator" programs designed to counter any manufacturer incentive to help patients reduce deductibles and other out-of-pocket costs in their drug benefit. PBMs are also fighting a CMS proposal to pass a portion of drug rebates extracted from the manufacturer on to patients to reduce the cost burden. "Such tactics are a negative distraction to reaching that larger consensus around value-based solutions to drug costs," Tenaglia adds.

An additional strategic question likely to surface this year is how the arrival of complex curative and preventive technologies like gene therapy will shape discussion among drugmakers and payers on the very definition of "value" in health care. *(Also see "New Payment And Financing Models For Curative Regenerative Medicines" - In Vivo, July 2017.)* Adds Longman, "These are new science platforms that extend into areas where the traditional biopharma business model has little familiarity. What is the relevant value metric for a long-term cure or a technology that makes the prospect of disease irrelevant to the patient? Much of the patient care experience will be shaped by a cellular engineering process rather than a one-off experience with a drug whose technology is well-known. So there's a new dynamic at work here in how society itself defines value."

> *"What biopharma must do in such a divisive environment is to cultivate new audiences outside the K Street "swamp" and go deep on CEO demonstrations of public "authenticity" – the new coinage for reputational enhancement in an era where even facts are labeled "fake news."*

Nevertheless, numerous experiments to breach the divides are underway this year – the long slog toward a value-driven health care system continues. One project that bears watching is a multi-stakeholder initiative launching this month called LEAPS (Learning Ecosystem for Accelerating Patient-Centered and Sustainable Innovation) organized by the **Massachusetts Institute of Technology**'s Center for Biomedical Innovation. With backing from the state of Massachusetts and three big pharma companies – Merck, GSK and Sanofi – LEAPS will seek to build a treatment protocol, evidence base and value measurement tool that links providers, payers, pharmaceutical and IT firms, regulators and academic researchers around a series of functionally relevant incentives, all geared to achieving patient-centered outcomes in a designated state-wide population with a specific, yet to be chosen chronic disease.

"Over the next year, the plan is to create a shared protocol for defining and delivering value, at three levels of engagement: (1) new product development; (2) regimen/treatment development; and (3) clinical disease management, using RWE," center director Gigi Hirsch, MD, tells *In Vivo*. She notes that the LEADS project is precedent-setting by attracting the participation of all the principal players in the Massachusetts biopharma ecosystem. "We've got the commitment of the right people in the state to make this work as a template for the value-driven system of the future," Hirsch says.

Adapting To The Demands Of New Science

As more advanced, gene-based therapies come on-stream this year, biopharma will need to understand and communicate the complex challenges of moving these technologies from bench to bedside. Instead of the standard hyped-up launch, these new products demand a "controlled rollout" approach due to the potential for severe side-effects (like cytokine release syndrome) in some patients. Administration of these technologies safely to patients carries obligations that include setting up treatment centers at academic teaching hospitals to monitor those receiving therapy, and retention of hundreds of trained professionals with

expertise in everything from handling live cells and tissues to courier logistics, dosing, anesthesia and psychological counseling. There is also the details of coordinating access to hospital ICUs – where reserving a single bed to cover a sudden adverse patient episode can cost upwards of $10,000 per day, even if it's not used.

The opportunity cost of a controlled rollout is high but prudent. Only a few deaths from the new CAR-Ts and related cell transfer therapies could rattle regulators and payers and stop these advances from progressing further into the clinical setting, where active observation can control for these incidences and remove them as a barrier to care. Nevertheless, it's an unprecedented challenge of learning by doing. The lesson here is that extreme care must be taken if these complex actions across multiple potentially hazardous supply and manufacturing touch points are to earn the confidence of regulators, providers and payers. On such confidence depends the approval of additional gene therapy applications and a larger, sustainable market for these technologies, extending forward to a wider patient population.

The year 2018 will begin the testing time for this essential transition. Recognizing the high stakes in the safety of next-generation immuno-oncology medicines, six major biopharma companies active in the space will launch a project next month with the non-profit open access to clinical trials group, Project Data Sphere. In the project, Project Data Sphere will work with all six companies in applying machine learning applications to track and analyze side effects from immuno-oncologic drugs now on the market, including the major checkpoint inhibitors. "Our material will be shared as de-identified open access data sets to help the companies, researchers, regulators and other interested parties compile evidence necessary to control these events and improve the safety and reliability of the newest cancer drugs," says Project Data Sphere CEO Martin Murphy, DMedSc, PhD. The first condition to be reviewed is myocarditis events associated with CAR-T drug use, followed later by pancreatitis and neuropathy. *(Also see "Free And Open: The Next Wave In Clinical Trial Data?" - In Vivo, May 2017.)*

Preserving The US Innovation Ecosystem

For 75 years, the US has led the world in inventing and commercializing new medicines. Generous government funding of basic research; strong academic institutions combining world-class talent with an entrepreneurial bent; an independent, rules-based regulatory infrastructure; and extensive private capital with a high-risk/high-return mind-set continues to keep the US on top. But that is not an indefinite guarantee.

"Some significant vulnerabilities, largely self-inflicted, are raising concerns about the future of US medicines innovation," contends *In Vivo* EAB member Ken Kaitin, PhD, professor of medicine at **Tufts University** and director of the Tufts Center for the Study of Drug Development. "You have a long-term decline in the number of federal grants for disease research, which has reduced opportunity for younger researchers with promising ideas worth commercializing in concert with industry. But the most ominous trend is the backsliding of the Trump Administration on immigration. "The 'America First' polemics is discouraging qualified foreign researchers from coming to this country for study and employment. As a result," Kaitin says, "academic institutions like Tufts are experiencing a decline in their talent convening power, which has negative consequences for keeping our innovation edge against emerging competitor countries like China going forward."

Thus 2018 offers an opportunity for biopharma to re-examine its human capital strategy from a fully globalized perspective. Given the aging US population, a souring national debate on inclusion and the increasing importance of new skills in an era of rapid technological change, it's imperative for biopharma to raise the ante on talent recruitment and retention. The urgency is accentuated by the planned reduction in H1-B visa quotas for high-skill foreign workers and as image issues send applicants to other countries seen as more welcoming to immigrants.

Reviving Health Care's Think Tank

Yes, human ingenuity determines what really matters in health care, which is mounting the best challenge possible against the endless trajectory of disease. It's fitting to end *In Vivo*'s "year beginning" review with a reference to the passing of three prominent economists in 2017 who, through their theories and writings, shaped how the world looks at medicines and health care through much of the 20th century and right through to today.

- Kenneth Arrow, PhD (born 1921) depicted health care as unpredictable and rife with market failures, including a yawning information gap where producers (the physician) know more than the consumer (the patient). His work continues to fuel the premise that everything from insurance to prescription drug testing must be subject to strict government regulation.
- William Baumol, PhD (born 1922) developed the "Baumol cost disease" theorem that holds health care costs are destined to rise without the normal productivity gains that occur in goods-producing sectors because it is a service built largely on labor, an intangible commodity that is harder to measure than widgets.
- Uwe Reinhardt, PhD (born 1937) invented the role of influential activist economist able to spin theory into policy, an example of which was his success in making the individual mandate in health insurance a pillar of the 2010 Affordable Care Act. He worked both as an advocate and an insider, interacting frequently with biopharma companies, where he argued for their support on more transparency in drug pricing. Reinhardt convinced Merck & Co. at one point to endorse the reference-based pricing system of his native Germany.

The passing of these three innovators in ideas speaks to the question: is there a successor generation with the same potential to influence how decision-makers outside the academy, in business and government, look at health care, not just in 2018, but for the decades to come? The agenda is urgent and it does not change. A good health system is one that balances the socializing goals of inclusion, access and cost against the acquisitive animal spirits of invention. It remains an ideal, but disease is the universal experience – there is no opt out.

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Medtech 2018: The Place For Innovation As Value-based Health Care Gains Momentum

2017 was a watershed year in many respects, politically, economically and commercially for many players in the medtech field. Where will the opportunities lie in 2018? Will breakthrough medtech innovation still have a place among providers often riding on fumes when it comes to budgets, and is it all as bad as some would make out?

BY ASHLEY YEO

Medtech M&A in 2017 continued at the impressively high level of recent years, but no matter how many transactions take place, there are always more candidates large and small in the wings.

As stakeholders embrace a focus on outcomes, sustainability and system cost reductions, the industry is moving away from fee-for-service and supply push – but not as quickly as originally thought.

So what? Sharing the total cost of care might not have been in a company's mission statement 30 years ago, but the wording is now indelible across the industry. Forward-looking medtechs will seize the opportunity, as indeed they must, for there are many largely untapped as well as substantially saturated markets available – and they don't tend to shrink.

The value-based health care agenda gains incrementally more currency with each passing month. Medtech companies have long since moved on from "when and if," to "how and whom," as they size up both the opportunity and cost of playing an enhanced role in health care delivery. They must decide whether to commit themselves to a holistic system where efficiency of operational performance, cost reductions, lowering readmissions and patient satisfaction are allied to outcomes improvements.

The technology remains central in this new environment, and innovation paramount. But it is no longer the endgame, rather a stage in the overall process – albeit an essential one. It is an environment where manufacturers, at least, see themselves as partners of the providers in health care delivery. This is indeed a compelling argument in cases such as **Johnson & Johnson**'s *CareAdvantage* and **Medtronic PLC**'s *Integrated Health Solutions* programs that aim to develop tailored services and solutions to improve clinical, operational and financial outcomes. (*Also see "Options For Medtechs In A Value-Based Care World" - In Vivo, November 2017.*)

Those able to take advantage of the shift in health care priorities are building new business models consistent with mandatory bundles like the Centers for Medicare and Medicaid Services' (CMS') Comprehensive Care for Joint Replacement (CJR), and shared services. CMS pulled back somewhat from mandatory bundled concepts in the latter part of 2017, but the move away from fee-for-service remains well underway: up ahead await newer concepts still, such as population health management, which will use data analytics on individuals within population subgroups to improve clinical outcomes

and reduce costs; and risk-sharing deals, such as the Aetna/Medtronic agreement of June 2017 (see right column), on a broader scale.

However, while value-based health care is the present and the future, physicians don't see it as tearing up the tarmac, not yet at least. A June 2017 study by **Quest Diagnostics Inc.** and **Inovalon**, surveying physicians and health plan executives on the penetration of value-based health care in the US, found that the health care industry continues its systemic shift from a fee-for-service delivery model to a value-based system that aims to deliver and pay for health services based on quality rather than quantity, but that progress is only moderate.

In 2016, a quarter of physicians and health plan executives believed the US had a value-based care system; in 2017 the figure had risen to only 29%, according to the Quest/Inovalon survey. Longer-serving professionals were more likely to consider that fee-for-service continues to dominate health care, but the general view remains that a majority of individuals at the point of care believe that US health care is behind the adoption curve. In its ongoing *Global Assessment Initiative* with the Economist Intelligence Unit, Medtronic stresses that many countries have a strong political will and are moving in the right direction. Overall, the value-based health care model is being introduced in step-by-step fashion.

That view is shared by the Boston Consulting Group. Interviewed by *In Vivo* at year-end, health care and medtech specialists at the global management consulting firm said that while up to four-fifths of the US market is talking about risk-based/value-based outcomes, less than 15% of current US payments can be classified as value-based or risk-shared – and even those are still largely fee-for-service plus an incentive, as opposed to a true insurance risk, or population-based payment. The rest remain fee-for-service, for procedure-based reimbursement.

So it's not an overnight transition, to say the least, but it is the direction of travel. US ACOs using value-based concepts are finding that more of them (50%) saved money in the third year of participation than in the first (33%), according to a recent Avalere Health webinar. The notion that users are seeing more benefits of value-based health care is borne out in the Quest/Inovalon survey finding (see above) that 70% of health plan executives had noticed progress in the alignment of health plans and providers of health care. Although fewer than half of physicians were of this view, in all, over eight in 10 of the combined survey group agreed on the pressing need for alignment between payers and providers to achieve value-based care.

The drivers of this won't be the government, CMS or particularly manufacturers, but provider systems – doctors and large health systems that can provide better outcomes quality than other systems – and large commercial payers. **Aetna Inc.**, which has size and influence and an incentive to shift to a value-based world, has shown the way. The story of its mid-2017 deal with Medtronic relating to the supply of insulin pumps was one of *In Vivo*'s most-read features of last year, partly because it pointed to the shape of things to come in terms of supply deals for the medtech sector as a whole. (*Also see "Medtronic's Deal With Aetna Heralds New Value-Based Era" - In Vivo, September 2017 and box, Aetna And Medtronic Show The Way.*)

As long ago as 2012, the American Diabetes Association put the cost of diabetes to the US at $245 billion, with $176 billion in direct costs (including $90 billion in hospital inpatient and nursing home expenses and $7 billion in emergency care) and $69 billion in indirect costs/lost productivity. The figure could now be as high as $322 billion. The question for manufacturers, as they ultimately help to *bring down* provider costs, is how they will be sustainably rewarded, not just in diabetes, but in AF and HF and indeed all other long-term conditions, where the value-based agenda will have most leverage.

The Trump administration, backed by the Republican-led Congress, continues its drive to repeal and replace the Affordable Care Act, which went live just over seven years ago. This uncertainty over the ACA's future may destabilize some facets of health care, but the transition to value-based care is not one of them. Indeed, over 80% of physicians and health plan executives say they believe the transition to value-based care will continue, regardless of legislative reforms spearheaded by the federal government.

The ACA is proving hard to withdraw entirely due to the GOP's wafer-thin Senate majority that includes John McCain and two other Republicans opposed to ACA repeal, and the total opposition of the Democrats. But what could happen to the ACA in 2018? US President Donald Trump has sought to save face after successive repeal failures in 2017 by claiming that the ACA was "essentially repealed" after eliminating the individual mandate in his successful tax reform bill; the mandate required those who opt out of coverage to pay a penalty. It means that Republicans have secured one significant legislative victory against Obamacare, but other aspects of the ACA may still be targeted (Medicaid expansion being the biggest). Repeal will still be on the table in 2018.

The comprehensive tax reform was arguably the president's only major victory in a roller coaster first year in office; it means among other things that corporations will see their headline income tax rate drop from 35% to 21%, bringing the

AETNA AND MEDTRONIC SHOW THE WAY

The non-exclusive, outcomes-based deal between payer Aetna and Medtronic is designed to support the transition of patients with type 1 or type 2 diabetes away from multiple daily insulin injections and toward Medtronic's *MiniMed 530G*, *630G* and *670G* insulin pumps. These devices feature *SmartGuard* technology, which prevents hypoglycemia (which can stop patients from reaching HbA1c goals). The health outcomes in these patients are measured, and part of Medtronic's reimbursement will depend on the achievement of pre-agreed clinical improvement thresholds.

US more in line with the average rate in the developed world.

The Dreaded US Sales Tax

But will the ACA's 2.3% device sales excise tax return? It was due to do so this January 1, the temporary moratorium in force since 2015 having ended at the turn of the year. Industry was getting increasingly agitated at the prospect of a reinstatement of what it has called a job-killing tax as the clock ran down late in the year. Under the legislation, the total cost to the medical device industry would be roughly $20 billion over 10 years. A House bill late in the year, the Bipartisan Market Stabilization and Innovation Act of 2017, included tax repeal wording.

This single issue dominated much of AdvaMed's US market support efforts in the 2013–15 period, when the tax was being levied, but as US equity analyst with Jefferies Healthcare Raj Denhoy says, nobody really expects the tax to return permanently. (*See online sidebar, "Tough At The Top: Raj Denhoy On The Drive For Growth In A Maturing Medtech industry."*)

Nevertheless, the US industry is doing its work anyway, arguing that the tax penalizes US companies unfairly. Medical device trade association AdvaMed president and CEO Scott Whitaker wrote to the president in mid-December, reminding him of the tax's negative impact on medical innovation, a resulting loss of 29,000 jobs (according to the US Department of Commerce), reduced R&D and slowed capital expansion. Whitaker was seeking swift action before the bi-weekly January payments were due to kick in – with any potential refunds not being made by the IRS until the end of the year.

Still A Place For Innovation?

Does this really affect medtech innovation, given that innovation is a moving feast in a fast-changing industry? Johnson & Johnson, for one, says that its continued growth and success depends on its ability to innovate products and services that address the evolving health care needs of patients, providers and consumers. New products introduced within the past five years accounted for around 22% of its 2016 sales, for example.

Innovation, in fact, still means everything. **Boston Scientific Corp.** is not alone warning that any impediment to launching new and enhanced products would negatively impact the group's performance. Boston, **Stryker Corp.** and Medtronic have all made efforts to innovate away from the commodity element of their sales mix, and over the past five years have all managed it to below 50%.

The German industry association, BVMed, ever seeking to underline the totally different marketing models of medtech versus pharma, says that 33% of national medtech sales in Europe's largest medtech market are made with products that are no more than three years old. Its point is that innovation is as crucial a differentiator as ever, even if the real innovation up ahead will be in the delivery paradigm and keeping patients out of the system. And if they're *in* the system, treating them as efficiently as possible, with reproducible methods using robotics and leaning on artificial intelligence and machine learning wherever possible.

Given the higher stakes, targeted and applied innovation is flourishing. **Cleveland Clinic**'s annual list of the medical innovations that could potentially transform the sector shows how medtech innovators will be pushing back the boundaries of patient care in 2018. It's a snapshot of areas where R&D efforts are meeting demand pull – not the supply push that was once the holy grail for manufacturers. The fields where innovation will help global health care break new ground this year, according to Cleveland, include:

• Diabetes Control: A hybrid closed-loop insulin delivery system that helps make type 1 diabetes more manageable by enabling direct communication between the continuous glucose monitoring device and insulin pump to stabilize blood glucose is set for mainstream use. In 2018, with more patients likely to demand the technology, more insurers will reimburse for it. It is also predicted that this will accelerate a type 2 diabetes product.

• Neuromodulation: Another innovation tipped to disrupt the market in 2018 is an implant that delivers stimulation that opens key airway muscles during sleep. Although sleep apnea impacts 21 million Americans, more than 40% of sufferers reportedly dislike the idea of the continuous positive airway pressure (CPAP) device. But the implant, controlled by a remote or wearable patch, helps to synchronize the intake of air with the action of the tongue using a breathing sensor and a stimulation lead powered by a battery.

• Cancer therapy: Targeted therapies will become widely used to treat breast cancer in 2018. PARP inhibitors for patients with specific mutations in BRCA1 or BRCA2, and novel CDK4/6 inhibitors for ER-positive/HER-2-negative breast cancer are having positive outcomes in clinical trials. Novel HER-2-targeted agents continue to show benefit in this subgroup of HER-2-positive patients. These studies point to an increasing survival rate, and perhaps the eventual end of chemotherapy for a significant population of breast cancer patients. That said, the current mechanisms – hormone therapy, chemotherapy and radiation – are still seen as valuable options for prolonging life; however, they are often not enough to keep cancer at bay.

• Chemotherapy hair loss: Loss of hair post-chemo can have a major effect on women. A new FDA-approved technology, "scalp cooling," which reduces the temperature of the scalp a few degrees during and after chemo, has been shown to be highly effective for preserving hair in women receiving chemotherapy for early-stage breast cancer.

• Gene therapy for retinal diseases: In mid-December the FDA approved Spark Therapeutics Inc.'s gene therapy Luxturna (voretigene neparvovec-rzyl), for inherited retinal diseases, which should provide visual function improvements in some Leber congenital amaurosis and retinitis pigmentosa patients. Experts believe the approval could lead to more gene therapies getting orphan drug and breakthrough status.

No Longer Just "Product-Focused" Solutions

Cleveland's selected solutions for 2018 are not just product-focused, however. Mirroring the change in perceptions of what constitutes health care innovation in this second decade of the millennium, its list of innovations includes several broader concepts that assist health care delivery in all settings.

1. One is telehealth, finally making a reality of extending video and sensor monitoring platforms and other distance health concepts to patients' homes. Increasing connectivity through mobile technology has seen hospitals get ready for widespread adoption in 2018: 90% of US health care executives are reportedly building a telehealth programs to cater to 7 million patient users in 2018.

2. Similarly, another long-talked of goal, centralized monitoring of inpatients, is becoming the realistic and efficient alternative to constant attention by bedside caregivers, where the risk is that they may become desensitized to patient needs/alarms among the noise on the ward/unit. Instead, off-site personnel using sensors and high-definition cameras can monitor vital signs, and establish thresholds for when on-site intervention is required.

3. And a third is the implementation of fast-track or ERAS (Enhanced Recovery After Surgery) methods for patients post-surgery. A recent protocol that permits patients to eat before surgery, limits opioids by prescribing alternate medications and encourages regular walking has been shown to both reduce complication rates and speed recovery. The spin-offs include fewer blood clots; less nausea, infection and muscle atrophy; and shorter hospital stays. Such protocols are expected to gain further ground in 2018.

Product pipelines have always driven investment trends in medtech, says BMO Capital Markets, which predicts this same trend in 2018. It believes the evolving diabetes landscape, transcatheter mitral valve repair/replacement market, transcatheter aortic valves, minimally invasive glaucoma surgery (MIGS) and robotic-assisted surgery applications (large joints, spine and surgery) will all merit closer investor attention in 2018. These will help expand the global market (including IVDs, dental and health care IT products to around half a trillion dollars by 2022, according to Jefferies Healthcare). (*See Exhibit 1.*)

Avalere Health adds that a lot of innovation is happening in the digital health space, and also praises the potential for good, in terms of encouraging innovation, of the US' 21st Century Cures Act and FDA commissioner Scott Gottlieb, MD's, risk-based approach to regulation. (*See online sidebar, "Gottlieb's FDA Lights A Fire Under Medtech Policy Activity But Reimbursement Challenges Remain."*) Says Brian Chapman, head of ZS' Global Medtech Consulting practice, "Not every 'innovation' is worth having, but one of my wishes for 2018 is flexibility and innovation in how we pay for digital health." (*Also see "Resilience Is Key For Medtechs Facing Provider And Payer Flux In 2018" - In Vivo, January 2018*)

And there are plenty of areas of substantially unmet need that await greater innovator attention, including depression, deafness, dementia, blindness, peripheral vascular disease, obesity, stroke and aneurysm.

The Drive For M&A Will Continue At A Faster Pace

M&A plays are a quicker if more expensive way of acquiring innovation. The number of $1 billion-plus medtech deals announced in 2017 and reported by *In Vivo* and sister publication *Medtech Insight* hit a round 10. (*See Exhibit 2.*) The standout **Becton Dickinson & Co./CR Bard Inc.** deal continued the trend of the creation of larger, diversified companies that can better leverage hospital relationships seen in recent years. According to BMO Capital Markets, the outstanding potential candidates for such a merger include **Smith & Nephew PLC**, Boston Scientific and **Edwards Lifesciences Corp.**

However, 2018 may well see the renewed prominence of bolt-on acquisitions for technology additions and growth. Products offering a competitive advantage in the non-commodity bracket will be picked off to bulk out sales mixes, and the range of buyers could include **Baxter International Inc.**, Boston Scientific and Johnson & Johnson, and the sellers might include, among others, **Glaukos Corp.**, **NuVasive Inc.**, **Wright Medical Group NV** and chronic pain relief therapy provider **Nevro Corp.**

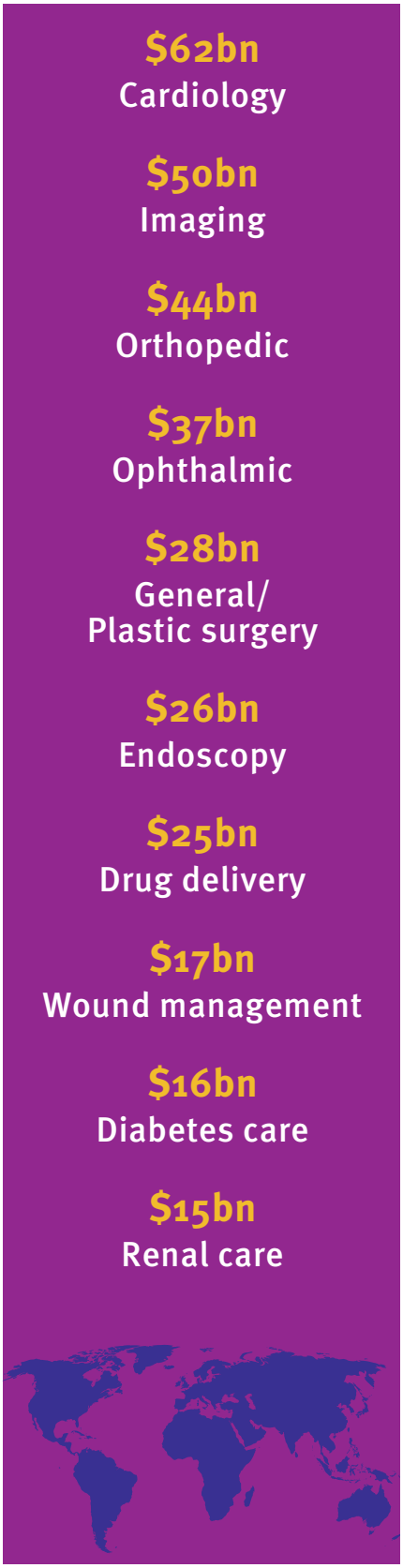
Other Issues To Note In 2018

EU Regulatory Change Is The Market Access Talking Point Bar None

The biggest regulatory change for many years in the leading medtech markets globally finally went live in 2017: the EU Medical Device Regulation and its sister IVD Regulation became effective in May,

Exhibit 1

Major Medtech Markets Worldwide – 2022 Prediction



SOURCE: Jefferies Healthcare

Exhibit 2

The Billion-dollar Medtech Deals Of 2017

ACQUIRER	TARGET	FIELD	CONSIDERATION	ANNOUNCED
Becton Dickinson	CR Bard	Medical devices	$24bn	April 23
Rationale: Creation of a highly differentiated medtech uniquely positioned to improve the process of care and the treatment of disease for patients and providers.				
Cardinal Health	Medtronic's Patient Monitoring and Recovery division	Patient monitoring	$6.1bn	April 18
Expanded product offering, addition of well-established brands that are a "natural fit."				
Allergan	Zeltiq Aesthetics	Medical aesthetics	$2.475bn	Feb. 13
Immediately accretive and enhances Allergan's global medical aesthetics portfolio in a $4 billion market.				
Philips Healthcare (Netherlands)	Spectranetics	Imaging – laser atherectomy catheters for both coronary and peripheral indications	$2bn	June 28
Strengthens Philips' image-guided therapy business in a €6bn market.				
Fresenius Medical Care (Germany)	NxStage Medical	Urology – dialysis market	$2bn	Aug. 7
Supports core business growth with the offering of innovation, better clinical outcomes (through Care Coordination) and improvement of the patient experience.				
Hologic	Cynosure	Medical aesthetics	$1.65bn	Feb. 15
Gives Hologic entry into one of the fastest-growing segments in medtech; expands Cynosure's customer reach.				
Shanghai Pharmaceuticals (China)	Cardinal Health China	Cardinal Health's pharmaceutical and medical products business in China	$1.2bn	Nov. 14
Greater distribution reach in China.				
Teleflex	NeoTract	Urological medical devices – minimally invasive tech for treating lower urinary tract symptoms due to BPH	$1.1bn	May 9
Boosts Teleflex's drive for mid-single digit constant currency sales growth for the next several years with products that have long product life cycles that benefit from patent protection, and demonstrate superior clinical benefit while providing cost benefits to hospitals.				
CooperSurgical	Product asset	Paragard intrauterine copper contraceptive device from Teva (Israel)	$1.1bn	Sept. 12
Non-core Teva product, makes Cooper only company with an IUD on the US market that is hormone-free, long-lasting and reversible.				
Integra LifeSciences	Codman Neuro	Neurology	$1.045bn	Feb. 16
Expands Integra's global leadership with the addition of a broad medical device portfolio in the neurosurgery market.				

Note: US unless stated. SOURCE: *In Vivo* research

subject to three- (MDR) and five- (IVDR) year transition periods. When the MDR enters into full force, it will impose significant additional premarket clinical data requirements, higher-level scrutiny and more stringent postmarket requirements. It will eventually introduce Unique Device Identification (UDI) among many other changes.(*Also see "Medtechs Must Act Fast On New EU Regulations Or Face Gridlock" - In Vivo, April 2017.*)

There are significant capacity and timing concerns surrounding the new MDR. The transition to the EU MDR is the greatest medtech industry challenge for the coming 3–5 years, according to Swiss-based think tank ConCeplus' October 2017 *LimedEx Index* report. It puts the overall ecosystem compliance cost at $18 billion in the coming three years, and notes that it represents an involuntary shift to pharma-style compliance (evidently much to BVMed's displeasure), which will affect R&D budgets and thus the ability to innovate.

The average EBIT impact across manufacturers serving the EU will be –4%. Resources are already thin enough in medtech, but to cope with the changes, it is considered that companies will need to hire an aggregate 31,000 extra FTE staff for their governmental and regulatory affairs departments. Who will pay for all this, and how, are questions that apparently no one has been tempted to tackle with any great alacrity. There is no choice but to comply; the advice remains, as in the previous 18+ months, don't leave it to the last minute and risk your products being EU-market ineligible.

Brexit Is A Storm In A Medtech Teacup

The UK – a soon to be ex-EU member state against most conventional wisdom and advice – has the additional burden of hoping it can use the EU's medtech regulations while being outside the club. The loss of the UK Medicines and Healthcare Products Regulatory Agency's (MHRA's) technical input on EU regulatory matters, as the agency's balanced, free-market, company-friendly thinking, will impede the system, possibly immensely. Brexit is a matter of deep regret for many; however, the "uncertainty" – surely the *Word of the Year* in both the UK the US for the second time running – should be over for the UK by the end of 2020, when the EU-imposed transition period for the UK's exit ends. (*Also see "UK Medtech One Year Post-Brexit Vote: Still In The Land Of Uncertainty" - In Vivo, June 2017.*)

The UK industry association (ABHI) is preparing contingencies for possible loss of market access, and among its many planning and support activities has recently joined the Global Medical Technology Alliance (GMTA). Many companies wonder about the true impact on their business, and should at last know more when EU-UK trade deal negotiations start, which the EU says will not be until March 2018 at the earliest.

For now, medtech is taking a typically balanced view. **LivaNova PLC** CEO Damien McDonald told *In Vivo* that Brexit would not have a material effect on business, and would not encourage it to move its HQ out of the UK. (*Also see "True To Its Word, LivaNova Sheds CRM – To MicroPort" - In Vivo, December 2017.*) **BioMerieux Inc.** says that the UK (representing some 3% of its global sales in 2016) leaving the EU would not present a risk that could have a significant impact on its accounts. In general, medtech industry players outside the UK tend to view the whole Brexit episode with mild confusion.

Dedicated Global Regulatory Systems Are The New Black

The MHRA should soon find an enhanced global role for itself, and will surely bring its skills and experience to bear in matters of the International Medical Device Regulators Forum (IMDRF) and global medtech regulatory harmonization.

Indeed, much is happening elsewhere, in Asia-Pacific especially, with, for example, a new conformity assessment system bedding in Malaysia, a brand-new medtech regulatory system (deferred to January 1, 2019) for Vietnam, smart regulation being prioritized in Singapore, a new IVD regulation in the Philippines and the Asean bloc's regulatory "harmonization" creating a new, potentially industry-friendly system.

Ukraine (a new EU-aligned system based on the EU's three Medical Device Directives), South Africa (the long-awaited device regulatory system finally starts up in 2017) and Russia and the five member-state Eurasian Economic Union are also among those moving into hitherto uncharted territory, strengthening their national regulatory systems and/or harmonizing, in moves that will pay dividends in terms of patient care, quality and support for innovation.

Final Thoughts – Thinking Differently

Global medtechs in 2018 know that health care spending in its current form is unsustainable, and that they must be alive to the shifts in incentives and a realignment of players in health care delivery. Amid the consolidation of and mergers among large hospital systems, buyers will be keener to do business with fewer, broader medtech clients, hence some of the rationale behind the Becton Dickinson and Bard merger, in the example of several of similar or larger magnitude in the past five years.

Medtechs are having to shoulder a new responsibility – sharing the total cost of care. And as the commoditized portion of the typical medtech company's product mix naturally continues to expand, the pressure on that company to offer value with solutions that maximize outcomes means that the premium on true innovation is as high as it's ever been.

It is true that changes in delivery models have forced the industry to think differently, but on the other hand medtech markets remain vast, and many are under-penetrated. Medtech is, in fact, in pretty good shape. Rather than declining in importance, some aspects of "innovation" have simply become different to what the industry has been accustomed to. The culture shift continues in 2018.

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Diagnostics 2018: Steady Progress And The Big Get Bigger

If the beginning of 2017 was marked by doubts around whether and how the FDA would act with respect to complex diagnostics, we enter 2018 feeling that slow-moving vessel may finally be turning.

BY MARK RATNER

We predict that artificial intelligence tools for diagnosis and patient monitoring will continue to gain traction as pharma and medtech gear up in digital health, with diabetes care leading the way.

The diagnostics deal front was largely quiet in 2017, but for a smattering of big-money financings and acquisitions.

So what? Regulatory pathways around innovative cancer tests – especially the long-standing issue of whether and how to regulate LDTs – will continue to be a hot topic. Even as FDA seeks input for greater technical and clinical clarity, the use of complex assays in routine care remains far off.

FDA product reviews were the lead story for the year, as Class II device designations emerged for large-panel tumor-profiling assays and direct-to-consumer (DTC) genetic health risk assessment (GHRA) tests.

In early November, the agency put forth its plan to regulate DTC GHRAs, exempting them from premarket review under certain conditions, when it allowed **23andme Inc.** to launch a set of FDA-validated direct-to-consumer tests predicting individuals' predisposition to genetic diseases and conditions. *(Also see "US FDA Implements 'Firm-Based' Regulatory Approach To DTC Genetic Health Risk Tests" - Medtech Insight, November 6, 2017.)* Under the proposed scheme, manufacturers of these types of tests would have to come to FDA for a one-time review, after which they may enter the market with new tests without further premarket notification. The agency also established special controls for these tests in a separate *de novo* classification order. Several categories of tests remain outside the new rules: those intended for prenatal screening, determining predisposition to cancer that could lead to taking medical action, pharmacogenetics testing, or assessing the presence of deterministic dominant variants.

Critics of DTC testing generally maintain their opposition on the basis that it needs to be done in collaboration with a provider. But they appear willing to wait and see how the agency applies the special controls, which among other things seek to assure that labeling will adequately inform consumers of the limitations of the tests.

Two weeks later, FDA turned its attention to next-generation sequencing-based (NGS-based) large-panel tumor-profiling assays when it granted authorization to **Memorial Sloan Kettering Cancer Center**'s *MSK-IMPACT* laboratory-developed test (LDT).

As with DTC GHRAs, subsequent NGS-based tumor-profiling tests need only show substantial equivalence to a predicate device. MSK's *de novo* submission to FDA included

and extended information previously submitted to the New York State Department of Health (NYSDOH), which had approved use of the test on samples from the state. The FDA used that information in its review, and said that going forward NYSDOH could function as an FDA third-party reviewer of IVDs, including tests similar to MSK-IMPACT. Other accredited, third-party FDA reviewers also may become eligible to conduct such reviews and make clearance recommendations to the agency – a tacit acknowledgment of the need for greater resources to build an inspection program that can handle the increasing numbers of LDTs that may cross the transom. As a result, developers of NGS-based tumor-profiling tests may not need to submit anything directly to FDA in the future.

These moves seemingly opened the door for similar LDTs, but that door may have been slammed shut on December 1, when **Foundation Medicine Inc.**'s *FoundationOne CDx* received a full marketing approval as a companion diagnostic to 15 targeted cancer drugs, benefiting from the agency's expedited access pathway as a breakthrough-designated diagnostic. *(Also see "First Expedited NGS Test Breaks Through FDA Review" - Medtech Insight, December 1, 2017.)*

Along with the nod from FDA, Foundation Medicine obtained a positive proposed National Coverage Determination from the Centers for Medicare and Medicaid Services, which had reviewed the product at the same time as FDA under the FDA/CMS Parallel Review Program. The NCD effectively prevents other laboratories with NGS-based tumor-profiling LDTs from being reimbursed for running their tests, an indirect way of regulating them by kicking the issue to CMS to articulate a payment policy. The molecular diagnostics community, understandably, is taking issue with this action and will no doubt be seeking a compromise position, perhaps arguing for a lesser amount of reimbursement for non-FDA approved LDTs: the public comment period will end in early 2018.

Looking beyond LDTs in oncology, the first traditional IVD (kit) companion diagnostic to identify multiple cancer mutations using next-generation sequencing also gained FDA approval. **Thermo Fisher Scientific Inc.**'s *OncomineDx Target Test* in lung cancer, developed in collaboration with **Novartis AG** and **Pfizer Inc.**, which helps direct the use of Pfizer's *Xalkori* (crizotinib); **AstraZeneca PLC**'s *Iressa* (gefitinib); and the combination of the Novartis drugs *Tafinlar* (dabarafenib) and *Mekinist* (trametinib), got the OK in June. *(Also see "Podcast: Thermo Fisher Talks Regulatory Experience With Oncomine" - Medtech Insight, July 6, 2017.)*

Diagnostics Deal-making

Genetic technology was also the foundation for the biggest oncology diagnostics-oriented acquisition in 2017. In a push to expand its health care offerings with an emphasis on precision medicine, **Konica Minolta Inc.** agreed to pay $800 million in cash plus up to $200 million in earn-outs for privately held genetic testing firm **Ambry Genetics Corp.** The deal was partly funded by the public/private Innovation Network Corporation of Japan. It will create new diagnostic technologies for oncology and drug discovery, and bring a comprehensive genetic-diagnostic portfolio to Japan, among other markets.

The Asian market was also the focus of diagnostics' biggest acquisition of the year. In a bid to further grow its presence outside the US, especially in China and the emerging markets, **PerkinElmer Inc.** paid $1.3 billion in cash for German IVD multinational **EuroImmun AG**.

Although **Abbott Laboratories Inc.**'s $5.8 billion acquisition of **Alere Inc.** in February was technically the year's biggest, we included that deal, which took more than a year and a half to complete, in our 2016 Year in Review. *(Also see "Diagnostics In 2016: From Alere To Zika" - In Vivo, January 2017.)* Last year also ended with **Grail Inc.** on the cusp of completing a billion-dollar Series B round, for which the first tranche, of $914 million, finalized in February 2017. Two months later, the developer of liquid biopsy technology merged with China's **Cirina Ltd.**, which is also focused on early-stage cancer detection using blood-based markers. *(Also see "M&A Analysis: Grail's Chinese Merger Wraps Up Busy May" - Medtech Insight, June 9, 2017.)* Another liquid biopsy firm, infectious disease-focused **Karius Inc.**, took in $50 million in a Series A round in August.

Our other noteworthy private placement of 2017 was to **Verily Life Sciences LLC**, which received an $800 million investment from Singapore investment company Temasek in January in exchange for a minority stake in the company. The two companies will also collaborate on expanding Verily's programs outside of the US.

A major focus of Verily is in diabetes, where it has partnered with **Dexcom Inc.** around smart glucose monitors. We predict that artificial intelligence tools will continue to gain traction as the pharma and medical device industries gear up in digital health, with diabetes care leading the way. **Roche**, for example, bolstered its diagnostics division in June via the acquisition of **MySugr GMBH**. The deal gave Roche a set of apps and services that combine diabetes coaching, therapy management, test-strip supply and automated data tracking to blend with its own glucose monitoring systems and services. **Medtronic PLC** has licensed diabetes prevention and self-management programs and developed a cognitive app that harnesses **IBM Watson Health**'s computing power to process information from Medtronic's pumps and glucose sensors to help patients better manage their disease.

Looking Ahead

In a year dominated by cataclysmic storms, the Northwestern hemisphere was at least spared having to contend with a major viral outbreak. The same may not be true of 2018.

Scott Gottlieb, MD, has pushed hard to streamline FDA regulations following his installation as commissioner in May 2017. The strength of leadership at other federal health agencies, however, is less certain: at Health and Human Services, Alex Azar's nomination is still under review and the Centers for Disease Control and Prevention has felt pressure from the Trump administration to ban terms including "science-based" and "evidence-based." *(Also see "HHS Nominee Azar And The Taint Of Industry" - Pink Sheet, December 6, 2017.)* As we also said last year, it is difficult to gauge how the current administration will respond to a significant public health threat.

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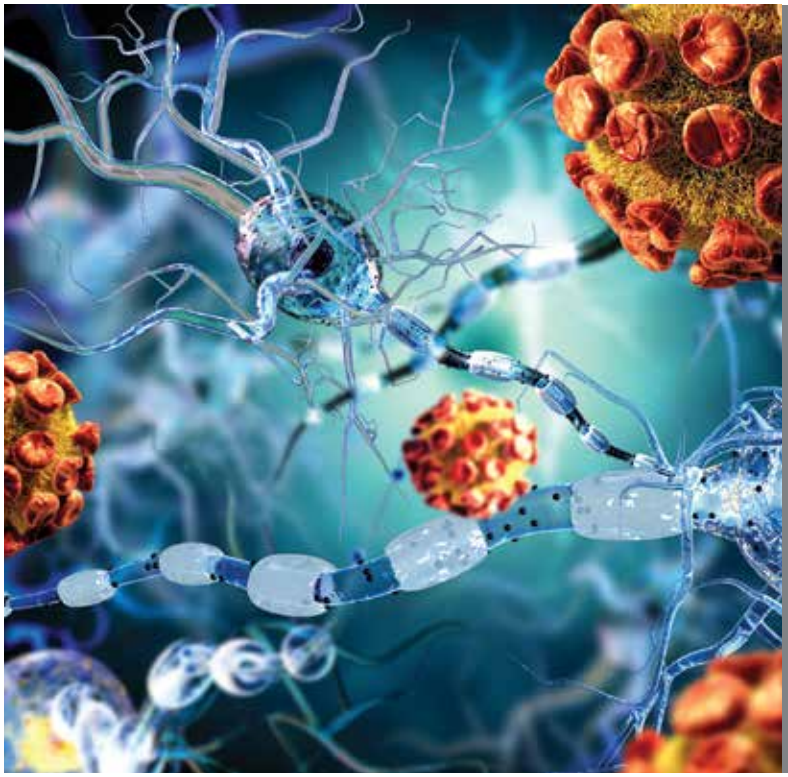
A Virtuous Cycle: What The Immuno-Oncology Revolution Means For Other Disease Areas



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Execs from Merck, Pfizer, Bristol, AbbVie and smaller biopharmas weigh in on how developments in cancer research may benefit other disease areas, especially autoimmune and neurological conditions.

BY EMILY HAYES

Immunotherapy research that has transformed cancer care could benefit other major disease areas, including those where the safety bar has traditionally been much higher.

Panelists at the recent BIO Investor Forum agreed that industry's attention and investor dollars are turning toward wider applications for immuno-oncology discoveries.

So what? Scientific breakthroughs that have driven the IO revolution can accelerate the pace of drug development outside cancer. Biomarkers will be key for driving adoption of immunotherapy into areas where the risk/benefit case is harder to make.

Approval in 2011 of **Bristol-Myers Squibb Co.**'s CTLA-4 checkpoint inhibitor *Yervoy* (ipilimumab) in melanoma signaled the start of the immunotherapy revolution in the field of cancer therapy, followed by the PD-1 inhibitors and with new mechanisms nearing the market. Data presented at the Society for Immunotherapy and Cancer (SITC) annual meeting in November revealed that PD-1/L1 inhibitors such as Bristol's *Opdivo* (nivolumab) and **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) are being tested in about 1,500 clinical trials, of which 74% are evaluating combination approaches with other immunotherapies and traditional targeted agents. *(Also see "Bristol's Strong SITC: IDO, 1L Kidney Cancer And New Mechanism Data Bode Well" - Scrip, November 13, 2017.)*

Development has been fueled by high unmet need and regulatory willingness to speed approvals for drugs aimed at life-threatening diseases. And although immunotherapy has been well established in other fields for years, the burst of immuno-oncology is now feeding back to other disease areas.

"All the data coming out of the huge set of clinical trials in IO will now help drive understanding of other disease areas as well," Luisa Salter-Cid, PhD, Bristol's head of discovery biology for immunology, IO small molecule and genomics, says.

The CTLA-4 mechanism of action behind Yervoy, for example, is also related to drugs traditionally used for immune disorders. Bristol's co-stimulatory *Orencia* (abatacept) blocks the interaction between CD80 and CD86. *(Also see "BMS Q&A: Hunting For Biomarkers To Improve Treatment Of Autoimmune Diseases" - Scrip, November 20, 2017.)*

What Goes Around, Comes Around

During a panel on lessons learned from immuno-oncology at the recent *BIO Investor Forum*, Alex Szidon, PhD, head of the West Coast innovation hub and executive director of business development and licensing at Merck, commented that it's exciting to see the "virtuous cycle of reverse translation."

That includes an increase in investment in immunotherapy across the board. A sign of the times is **AbbVie Inc.**'s deal in October with immune-system focused **Alector LLC** – including a $205 million upfront payment – to access technology that will be used to develop and commercialize drugs for Alzheimer's disease and other neurodegenerative disorders. Alector is exploring the role of immune deficiencies in the central nervous system in neurodegenerative diseases. *(Also see "BMS Q&A: Hunting For Biomarkers To Improve Treatment Of Autoimmune Diseases" - Scrip, November 20, 2017.)*

The "pace with which this innovation is coming is really outstanding and it's not going to stop," Isaac Ciechanover, MD, president and CEO of **Atara Biotherapeutics Inc.**, said during the panel at the *BIO Investor Forum*, held October 17–18 in San Francisco. Atara has an allogeneic cytotoxic T lymphocyte immunotherapy platform that it is applying in cancer and also multiple sclerosis.

"What you are really building on is years of knowledge – this coming revolution is the oldest new science around. People have been tripping over it, now they are just better understanding it," Ciechanover declared. "We are going to stop talking about IO – we are really going to focus on immunotherapy period, across every disease. The revolution is already here."

The lessons are still emerging, but what is most striking is insight about what is visible or actionable from the perspective of the immune system, commented panelist Paul Robbins, PhD, senior director of translational oncology at **Pfizer Inc.** The technology, effort and investment applied to examine what epitopes are recognized and what antigens elicit strong responses "have grown very, very rapidly," he said.

It appears that a relatively small number of antigens are involved in mediating response, though it's unclear which of these are most responsible. There has been a lot of analysis of the immune repertoire and specific antigens have been identified among many diseases with similar state-of-the-art technology. "That will be a huge win for target identification in multiple disease settings once it's a little more robust and economical," Robbins predicted.

Whether you are talking about a neurodegenerative lesion, a fibrotic condition or a tumor microenvironment, there are very similar messengers and the assay capabilities to look at those are going to be common, Merck's Szidon said. Innovators have developed high-resolution tools to look at cell components and interrogate them deeply. Hopefully this will lead to better quality targets – better starting points to go after, he said. "From a pharma perspective we'd like to see things develop a bit more," but given the tools available and the literature as it stands, "these are smaller leaps and it doesn't seem like a moonshot now," Szidon observed.

Tumors are essentially like a chronic infection, and it's not surprising that there would be potential applications in neurology and other pathological environments, Szidon continued. He added that he thinks in the next three to five years there will be an explosion in opportunities. The targets may be the same or they may be new, but "there is going to be suspicion because biology is thrifty and tends to recycle the same mechanisms that work; we are going to probably see similar mechanisms in these different contexts," the exec said in a follow-up interview after the meeting.

One example of how development in oncology can inform other disease areas is that the onset of type 1 diabetes has been reported in trials of cancer patients getting checkpoint blockade treatment; the immune intervention may clear the tumor, but also tips the balance toward autoimmune disease, Szidon explained. The same tools used to understand cancer response may be used to understand autoimmune response.

"I see that as being a very rich area for research," he said. Szidon expects autoimmune diseases will be the first major beneficiary of lessons learned in immuno-oncology.

Brother From Another Mother

In autoimmune diseases, many drugs work by mitigating an overactive immune response. Conversely, in oncology, the goal of treatment may be to increase immune surveillance thereby improving the chances of identifying cancerous cells in order to clear them from the body, Citeline analyst Pamela Spicer notes. Developers can design drugs to treat autoimmune diseases by blocking T-cell co-stimulatory molecules, thus reducing a hyperactive immune system, whereas drugs being developed in oncology might attempt to activate the same co-stimulatory pathways to initiate a T-cell immune response, she explains. (*See Exhibit 1.*)

Scott Brun, MD, president and corporate strategy office head at AbbVie Ventures, noted during the *BIO Investor Forum* panel that AbbVie Inc.'s pipeline includes a bispecific CD40 agonist for cancer and a Phase I CD40 antagonist (BI 655064), which it in-licensed as a Phase I candidate for lupus from **Boehringer Ingelheim GMBH** in March 2016. AbbVie's in-house developed bispecific CD40 agonist ABBV-428 entered the same year and is in Phase I for solid tumors. *(Also see " Boehringer Hopes To Tap AbbVie's ''Humira Magic'' In Immunology Pact " - Scrip, March 7, 2016.)*

AbbVie is somewhat of a newcomer to immuno-oncology and is just beginning to get assets into the clinic, Brun pointed out. But along with oncology, autoimmune/inflammatory disorders and neurodegenerative diseases are the company's key areas of focus, and there is now an opportunity to collaborate on targets across these areas.

The company has been learning how to think about conditional activation of the immune system in the presence of a tumor, and also the conditional suppression of the immune system for a variety of autoimmune diseases. "In the past we would not see that kind of parallel research and development activity," Brun said.

At Bristol, immunology and immuno-oncology are on a parallel track (*see online video*), and the agonist/antagonist approach is part of development, Salter-Cid reports.

Compared with antagonists, agonists

Exhibit 1

IO Targets In Development For Cancer And Non-cancer Indications

TARGET/DESCRIPTION	EXAMPLES OF CANDIDATES IN DEVELOPMENT
OX40: OX40, also known as CD134, is a member of the TNFR superfamily of receptors that is not constitutively expressed on resting naïve T cells. OX40 is a secondary co-stimulatory molecule, expressed 24 to 72 hours after activation. Its ligand, OX40L, is also not expressed on resting antigen presenting cells, but is following their activation. Expression of OX40 is dependent on full activation of the T cell.	Glenmark's GBR 830 (Phase II atopic dermatitis, Phase I celiac disease); Kyowa Hakko Kirin's KHK4083 (Phase II ulcerative colitis, Phase I atopic dermatitis); Roche's RG788 (Phase II bladder cancer); Bristol's BMS986178 (Phase I/II solid tumors); GSK's GSK3117498 (Phase I/II solid tumors)
Programmed death-1 receptor and ligand 1 (PD-1/L1): PD-1, a member of the CD28/CTLA-4/ICOS co-stimulatory receptor family, delivers negative signals that have profound effects on T-cell and B-cell immunity. PD-L1 and PD-L2 are the ligands for PD-1 receptor that are expressed by many tumors to protect against T-cell-mediated immune responses. Class is approved for multiple cancer indications and current development is mostly focused in oncology.	Bristol's BMS936559 (Phase I/II sepsis and septic shock); Celgene/Anaptys Bio's CC-90006 (Phase I psoriasis); Ono – Opdivo (Phase I hepatitis C virus, sepsis/septic shock); Alnylam's ALN-PDL (preclinical liver failure, cirrhosis); Tasly/Genexine's GXP2 (preclinical psoriasis, inflammatory bowel disease); Fate's ToleraCyte (preclinical type 1 diabetes)
Cluster of differentiation 40 (CD40): CD40 is a member of the TNF receptor superfamily. This receptor has been found to be essential in mediating a broad variety of immune and inflammatory responses including T-cell-dependent immunoglobulin class switching, memory B-cell development and germinal center formation. The interaction of this receptor and its ligand (CD40L) is necessary for amyloid-beta-induced microglial activation, and thus is thought to be an early event in Alzheimer's disease pathogenesis. Development is ongoing in a mix of autoimmune and oncology indications.	Apexigen/Boehringer Ingelheim's APX005M (Phase II esophageal cancer and Phase I/II melanoma); Astellas' ASKP1240 (Phase II transplant rejection); Abbvie/BI's 655064 (Phase II lupus); Novartis' CFZ533 (Phase II for Graves' ophthalmopathy/orbitopathy, myasthenia gravis, Sjogren's syndrome); J&J/Alligator's ADC-1013 in solid tumors
Cluster of Differentiation 28 (CD28)/ICOS and B7RP-1 Pathway: The inducible co-stimulator (ICOS) is structurally and functionally homologous to CD28. The B7-Related Protein-1 (B7RP-1) is structurally and functionally homologous to B7.1 and B7.2 (B7.1/2), and is the ligand for ICOS. ICOS/B7RP-1 is emerging as a co-stimulatory pathway for a variety of effector and memory T-cell responses. Manipulation of the pathway results in alterations of immune responses that may be applicable in therapeutic indications as diverse as cancer, infectious and autoimmune diseases, and transplantation.	Atox Bio's reltecimod (Phase III skin and skin structure infections); Bristol's BMS931699 (Phase II Sjogren's syndrome, lupus); AZ/Amgen's MEDI5872 (Phase II Sjogren's, Phase I lupus); GSK's GSK3359609 (Phase I/II solid tumors); Jounce/Celgene's JTX-2011 (Phase I/II solid tumors); Jounce/OSE Immunotherapeutics' FR104 (Phase I autoimmune disorders); AZ's MEDI0700 (Phase I lupus)
Interleukin-2 receptor (IL-2R): The IL-2 receptor is a heterotrimeric protein expressed on the surface of certain immune cells, such as lymphocytes, that binds and responds to a cytokine called interleukin 2. Three protein chains (alpha, beta and gamma) are non-covalently associated to form the IL-2R. IL-2R drugs are approved for cancer and transplant rejection, and development includes a mix of cancer and autoimmune indications.	Avadel's IL2-XL (Phase II renal cell carcinoma); Nektar's NKTR-214 (Phase I/II in range of cancers including bladder cancer and melanoma); Amgen's AMG592 (Phase I/II in inflammatory disorders); Lilly/Nektar's NKTR-358 (Phase I lupus); Roche's RG7461 (Phase I solid tumors); Celgene's DEL-106 (preclinical in autoimmune disorders)
Macrophage colony-stimulating factor 1 (M-CSF1, CSF1R): Granulocyte/macrophage colony-stimulating factors are cytokines that act in hematopoiesis by controlling the production, differentiation and function of two related white cell populations of the blood, the granulocytes and the monocytes/macrophages. CSF-1 induces cells of the monocyte/macrophage lineage. It plays a role in immunological defenses, bone metabolism, lipoproteins clearance, fertility and pregnancy.	Daiichi's pexidartinib (Phase III for pigmented villanodular synovitis (PVNS) and Phase II for solid tumors); Bristol/Five Prime's cabiralizumab (Phase I or I/II in PVNS, solid tumors, rheumatoid arthritis); Daiichi's AC708 (preclinical for inflammatory disorders and cancer)
Stimulator of interferon genes (STING): The STING receptor is involved in the induction of an innate immune response through multiple pathways, inducing the expression of a broad profile of cytokines, including interferons and chemokines.	Aduro Biotech Inc.'s Adu-S100 (Phase I in cancer); Nimbus/Celgene STING autoimmune program (preclinical autoimmune disorders and cancer)

SOURCES: Biomedtracker; Pharmaprojects | Pharma Intelligence, 2018

are more complex. So if a company has an antagonist against a particular target, it may not be straightforward to develop an agonist, even though a sponsor has an understanding of the pathway. The pharmacology can be very different; it's much more complex than just being the opposite of the antagonist, she tells *In Vivo*.

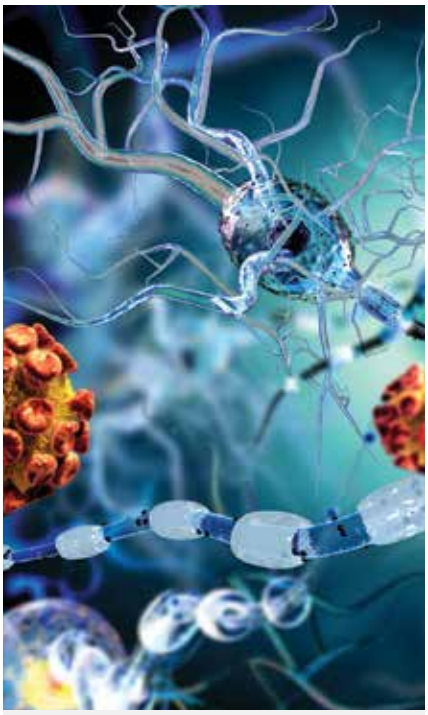
No two agonists are the same; downstream signaling may be completely different from one agonist to another, Salter-Cid explains. Also, it's hard to extrapolate from preclinical to clinical development, she says.

Bristol understands the PD-1 pathway, including T-cell exhaustion, very well and is looking to directly or indirectly leverage that understanding for new targets in immunology and fibrosis, Salter-Cid says. Currently, the only disclosed non-oncology indication for Opdivo is sepsis (Phase I); some researchers are clamoring for development in infectious diseases (*see box*).

In August, Bristol acquired **IFM Therapeutics** for $300 million up front and up to roughly $1 billion for each of two assets in preclinical development against two immune system targets: stimulator of interferon genes (STING) and NLRP3. *(Also see "An Inflammatory Deal: Bristol Commits Up To $2.3bn To Buy IFM Therapeutics" - Scrip, August 4, 2017.)* As part of the deal, Bristol got rights to an NLRP3 agonist for IO indications. IFM is spinning out an NLRP3 antagonist program aimed at inflammatory diseases but has first right-of-refusal for autoimmune disease assets.

Bristol is also partnered with **Five Prime Therapeutics Inc.** on the development of drugs aimed at the colony-stimulating factor 1 receptor (CSF1R) for oncology and non-oncology indications. *(Also see "Bristol Likes What It Sees In Five Prime, Invests More In CSF1R Program" - Scrip, October 16, 2015.)*

Salter-Cid also flags the interleukin-2 mechanism as a pathway that is important for immuno-oncology as well as autoimmune diseases. At the SITC meeting in November, Bristol and **Nektar Therapeutics** presented data showing that the IL-2 targeted NKTR-214 in combination with Opdivo has activity in lung and kidney cancer, and melanoma. *(Also see "Nektar's IL-2 Impresses In Combination With Bristol's Opdivo" - Scrip, November 14, 2017.)* **Novartis AG**'s IL-2 receptor antagonist *Simulect* (basiliximab) is approved for preventing kidney transplant rejection. **Servier SA/ILTOO Pharma**'s ILT101, which stimulates regulatory T cells, is in Phase II for lupus and type 1 diabetes, and other drugs aimed at the target are in preclinical development for autoimmune diseases.



OTHER INDICATIONS FOR OPDIVO?

Aberrant immune checkpoint activity signifies a poor prognosis in both cancer and infectious diseases, Martin Rao of the Karolinska Institute in Sweden and colleagues noted in a March 2017 review article published in the *International Journal of Infectious Diseases*. The authors concluded: "Anti-PD-1/PD-L1 therapy holds promise as adjunctive therapy for chronic infectious diseases such as tuberculosis and HIV, and must therefore be tested in randomized clinical trials."

In a letter published in *Annals of Oncology* on December 1, 2017, Jean-Phillipe Spano, MD, PhD of the Pitie-Salpetriere Hospital in Paris and colleagues reported a dramatic, persistent drop in HIV DNA in a patient being treated with Opdivo for lung cancer. The results suggest that "nivolumab in this patient had induced synergistic 'shock and kill' mechanisms," and "opens new therapeutic perspectives towards an HIV cure," the letter stated.

T-Cell Therapy Branches Out

Breakthroughs with personalized, autologous T-cell therapies in cancer are encouraging for therapies that modify immune cells for other disease areas.

The first two autologous chimeric antigen receptor T-cell (CAR-T) therapies were approved in the US in 2017: **Kite Pharma Inc.**'s (now **Gilead Sciences Inc.**) *Yescarta* (axicabtagene ciloleucel) and Novartis' *Kymriah* (tisagenlecleucel). *(Also see "CAR-T Commercialization Strategies: Views From Novartis And Kite" - In Vivo, October 2017.)*

Atara's lead candidate ATA129 targets patients with Epstein Barr virus and post-transplant lymphoproliferative disease (EBV-PTLD), a hematologic malignancy. But the company also developed a different autologous T-cell therapy called ATA190 that educates T cells to recognize and destroy EBV in multiple sclerosis (MS) patients. MS patients typically have EBV and the hypothesis behind treatment with ATA190 is that the virus cells in the central nervous system cause an autoimmune response, and MS symptoms that could be prevented if these cells were destroyed.

Atara presented updated results from a Phase I study of the candidate in progressive MS at the joint meeting of the Americas Committee for Treatment and Research of Multiple Sclerosis (ACRTIMS) and the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)in October.

In the study, six of 10 patients had a clinical improvement in symptoms two to 14 weeks after infusion with the autologous therapy. Three had an improvement as measured by the Expanded Disability Status Scale (EDSS) score. Atara also reported that the therapy was well-tolerated.

The company has developed an allogeneic (off-the-shelf) T-cell therapy called ATA188 that targets EBV antigens and in

2017 started a global Phase I study in 60 patients with progressing or relapsing-remitting forms of MS. US sites will start enrolling in 2018.

Another example of the application of T-cell therapy outside oncology is **ImmusanT Inc.**'s *Nexvax2* intradermal vaccine, which is being developed for celiac disease patients who have the immune recognition gene HLA-DQ2.5 (most of the patient population); a study is moving into Phase II. *(Also see "First coeliac disease vaccine moves forward in expanded clinical programme" - Scrip, September 6, 2012.)*

According to the company, this candidate is a therapeutic vaccine made up of peptides that reprograms T cells to stop triggering a pro-inflammatory response to gluten antigens. "As a result, by preventing T cells from continuing to cause inflammation in the small intestine, the injured tissue heals and patients would be able to resume an unrestricted diet and enjoy improved health," the company explains on its website.

Safety A High Priority

ImmusanT CEO Leslie Williams and other panelists at the *BIO Investor Forum* session stressed that biomarkers will be essential for driving adoption of immunotherapy outside oncology, where the risk/benefit case is harder to make, and that diagnostics need to be developed early on.

ImmusanT has developed a stand-alone diagnostic that is very selective and specific, enabling the company to "shift the paradigm in celiac disease" with a blood-based tool, Williams said. Safety has to be number one when introducing an immunotherapy, albeit an epitope-specific immunotherapy, in a disease like celiac, which is normally treated with dietary changes, she added. However, she acknowledged that financing biomarker development is a big challenge for a private company such as ImmusanT.

Panelists said there is a need for greater data sharing about toxicities between sponsors of oncology drugs to help minimize the risks. However, Atara's Ciechanover noted that the US FDA sees different datasets and is porting information about safety, manufacturing and assay work from one company to another, across disease areas. The FDA is a "true partner, trying to see the field move forward," he stated.

"If you do any immunotherapy you have to believe in precision medicine and you can't get to precision medicine without diagnostics. That's what it will take," Merck's Szidon said.

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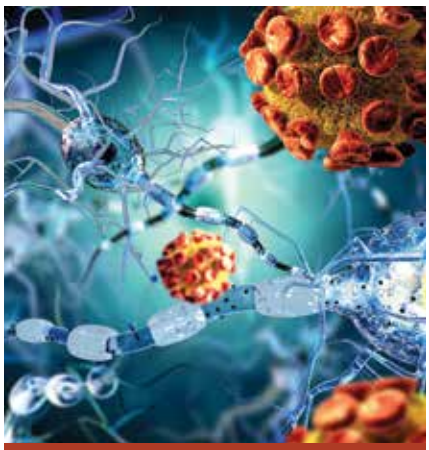

VIDEO ONLINE

Explore Immune System Interconnectivity

At Bristol, immunology and immuno-oncology are on a parallel track, and the agonist/antagonist approach is part of development.

View video at:

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Thirty-five Years Covering Health Care: The More Things Change...

PETER CHARLISH, PhD

The health care industry has come a long way in the past 35 years, although in some areas very little has changed. Recently retired *In Vivo* editor Peter Charlish has seen most of the major developments, and in his final feature he looks back at some of the big stories in a reporting career that began in the early 1980s.

BY PETER CHARLISH

The health care industry has witnessed many changes in the past 35 years or so since I began reporting on it, yet in some ways very little seems to have changed. While there has been enormous progress in the treatment of many diseases, some of the challenges we faced back in the early 1980s remain today.

Perhaps it would be more accurate to say that problems previously thought to have been solved have come back to haunt us. One of the first stories I covered as science editor of *Scrip* in 1981 was the launch of *Augmentin* (amoxicillin + clavulanic acid), the antibacterial product developed by the UK company Beecham (now swallowed up into **GlaxoSmithKline PLC**), which was designed to overcome the problem of bacterial resistance.

The rationale behind Augmentin was elegant in its simplicity. Bacterial resistance to β-lactam antibiotics such as amoxicillin is often caused by the bacteria acquiring the ability to produce an enzyme, β-lactamase, that can break down the antibiotic and thus render it ineffective. By combining an inhibitor of β-lactamase with the antibiotic in a single product, this route to bacterial resistance is blocked. The enzyme inhibitor in Augmentin is clavulanic acid, a compound that is based on the same β-lactam ring structure as amoxicillin and that inhibits a wide range of β-lactamases.

Although Augmentin's approved indications were initially somewhat restricted, they were soon broadened to include a wide range of infections in all age groups as the product's safety and efficacy were confirmed in clinical practice. Indeed, the product was so successful that the combination was awarded its own British Approved Name (BAN), co-amoxiclav. There are now many generic versions available, although clavulanic acid has never been combined with other β-lactam antibiotics in a commercial product for human use (it is also used in veterinary medicine), except for a handful of cephalosporin/clavulanic acid combinations marketed exclusively on the Indian subcontinent.

While the introduction of penicillin and other antibiotics in the 1940s is generally regarded as marking the beginning of the antibiotic era, specific antimicrobial products first entered commerce much earlier in the 20th century. Hoechst (now part of **Sanofi**) launched *Salvarsan* (arsphenamine) for the treatment of syphilis in 1910, for example. From the early days of antimicrobial therapy, resistance was recognized as a problem, with sulfonamide resistance emerging in the 1930s, and resistance to penicillins was recorded relatively soon

after that class of drug entered clinical practice. Interestingly, phylogenetic studies have shown that antibiotic-resistant genes have been present in bacteria since long before the antibiotic era – for many millions of years in some cases.

By the 1980s, bacterial resistance had emerged not only to the first generation of penicillins but also to semisynthetic penicillins and cephalosporins. More recently, resistance has been recorded to the newer carbapenems, which were developed specifically to be less susceptible to the development of resistance. When Augmentin was introduced it raised the hope that the spread of resistance could be overcome, but that unfortunately has not been the case. Resistance to antibiotics now poses a major global threat, and we are at risk of entering a "post-antibiotic era." According to the World Health Organization in 2014:

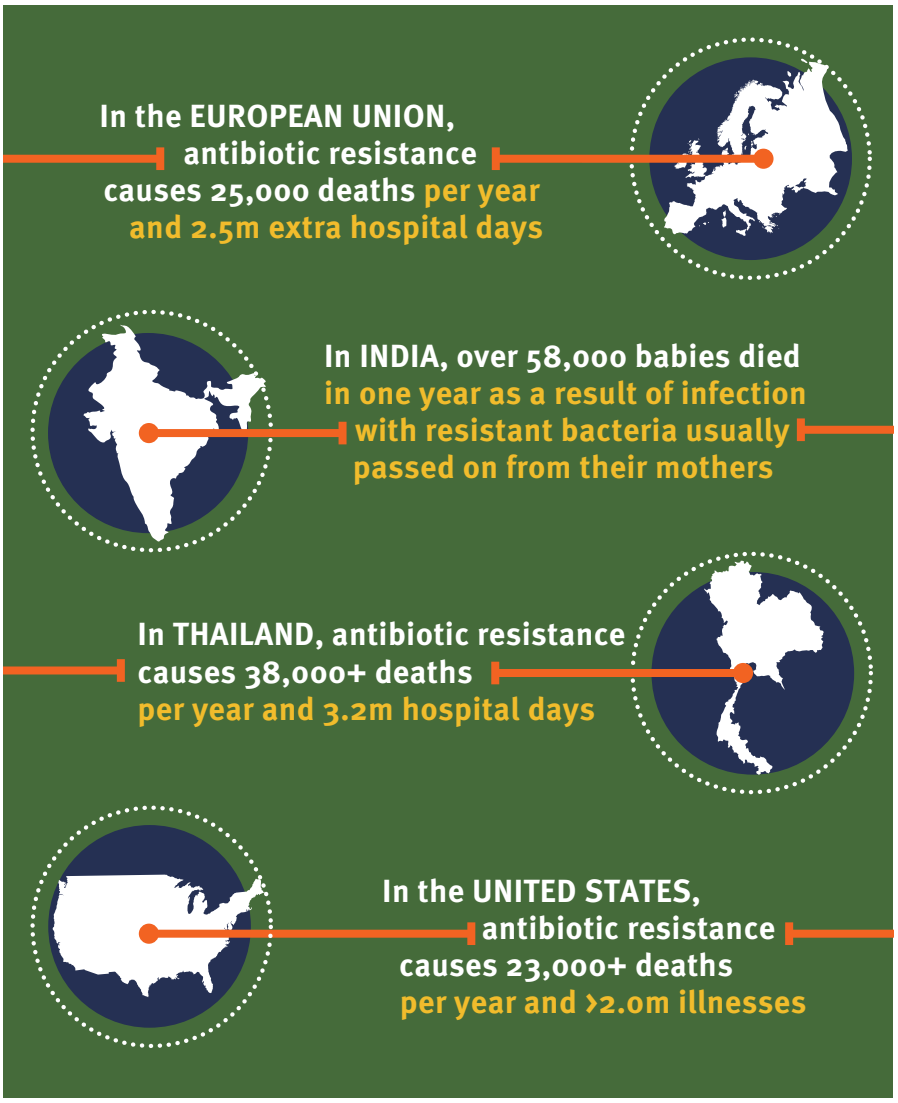
- resistance to carbapenems, which had become the treatment of last resort for life-threatening infections caused by *Klebsiella pneumoniae*, had spread to all regions of the world;
- resistance to fluoroquinolones, widely used to treat urinary tract infections caused by *Escherichia coli*, was also widespread; and
- treatment failure with third-generation cephalosporins, the treatment of last resort for antibiotic-resistant *Neisseria gonorrhoeae*, had been confirmed in Europe, Australia, North America, Japan and South Africa.

In general, the level of antibiotic-resistant infections in individual populations correlates with the level of antibiotic consumption (in other words, the more antibiotics are used, the more common is antibiotic resistance), which suggests they are not being used correctly. (*See Exhibit 1.*) One possible strategy for limiting the spread of antibiotic resistance could be the more appropriate use of antibiotics. In the UK, at least, we are starting to see public awareness of this issue being raised, albeit via a rather excruciating publicity campaign. (*http://bit.ly/2reDcDv*)

Other possible strategies to limit antibiotic resistance include the development of new antimicrobials directed at existing molecular targets, and the identification of new targets for antimicrobial agents.

Exhibit 1

Scale Of The Antibiotic Resistance Problem



SOURCE: Centers for Disease Control & Prevention

Clearly, industry needs to do more in this respect. In 2014, President Barack Obama tried to kick-start research into new antibiotics with an executive order that, among other things, led to the creation of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB). In September 2017, PACCARB voted to adopt a draft report containing recommendations for incentivizing the development of therapeutics, diagnostics and vaccines to combat antibiotic resistance. Hopefully, these recommendations will be accepted and will have the desired effect. Still, it is ironic that 35 years after the first antimicrobial product designed to address the resistance problem was launched, the problem is now more pressing than ever.

Success Against HIV/AIDS

It has not all been bad news in the anti-infective field, however. Another big story in the 1980s was the emergence of AIDS, and the industry's response to it. Although the first cases of human infection with what became known as human immunodeficiency virus probably occurred in the 1920s, AIDS was only recognized as a distinct clinical entity in the early 1980s, when multiple cases of a previously unrecognized syndrome came to the attention of health officials. The syndrome was characterized by the presence of one or more otherwise rare opportunistic infections such as *Pneumocystis carinii* pneumonia, and seemed to be confined, initially at least, to four

groups of individuals: heroin addicts, homosexuals, hemophiliacs and Haitians.

The unusual combination of features initially gave no clue to the origin of the syndrome, until it was realized that all those affected shared one thing in common – a severely compromised immune system, which gave rise to the name Acquired Immune Deficiency Syndrome (AIDS). In 1983, Luc Montagnier's group in Paris announced that they had isolated the virus responsible for AIDS, which they named lymphadenopathy-associated virus (LAV), while shortly afterwards, Robert Gallo's group in the US reported that they had characterized the causative agent as human T-lymphotropic virus type 3 (HTLV-III). In 1984 it was agreed that LAV and HTLV-III were one and the same virus, which was later renamed human immunodeficiency virus (HIV).

This was the signal for both the diagnostics industry and the pharmaceutical industry to set to work to develop diagnostic tests and therapeutic agents for HIV infection. In 1985, the FDA licensed two ELISA tests, from **Abbott Laboratories Inc.**and Electro-Nucleonics (now **Alfa Wassermann SPA**), for screening blood donations for HTLV-III, while a similar test based on the LAV isolate was developed by **Genetic Systems**. In 1987, the first diagnostic test became available when the FDA approved the use of Western blot testing for detecting HIV antibodies in the blood of suspected AIDS patients, and the same year it also approved the use of the reverse transcriptase inhibitor, zidovudine (azidothymine, AZT), for the treatment of HIV infection. The product, developed by GlaxoWellcome (now GSK) and marketed as *Retrovir*, was the first to be approved specifically for the treatment of HIV infection, less than four years after the virus was first identified, an outstanding achievement on the part not only of the researchers who developed it but also the regulators who approved it in record time.

Since then, of course, techniques for diagnosing HIV infection have improved considerably, and the number of antiretroviral drugs available has also mushroomed to include not only reverse transcriptase inhibitors but also protease inhibitors, integrase inhibitors, fusion inhibitors and chemokine receptor antagonists. Research continues: only recently, it was reported that *Opdivo* (nivolumab), a human monoclonal antibody developed by **Ono Pharmaceutical Co. Ltd.**and **Medarex Inc.** (part of **Bristol-Myers Squibb Co.**) as an anticancer, may be able to deplete dormant virus reservoirs in the tissues of patients with HIV, which up till now has been an obstacle to eliminating the virus from the body.

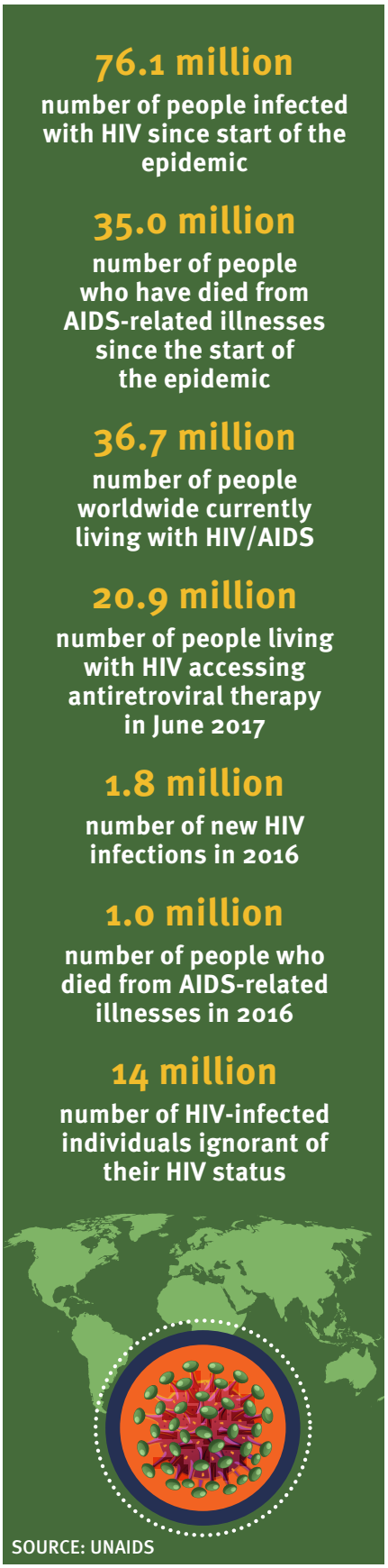
Just to underline the fact that the virus is not yet completely vanquished, some 36.7 million people worldwide are currently living with HIV/AIDS, and last year 1 million people died from AIDS-related illnesses, according to the Joint United Nations Programme on HIV and AIDS (UNAIDS). Nevertheless, the rapidity of the original response to the AIDS crisis demonstrates how effectively the industry can respond in an emergency.

The past 35 years have also seen products successfully introduced for the treatment or prevention of other viral diseases, including hepatitis C (which accounts for most cases of what was then known as non-A, non-B viral hepatitis) and human papillomavirus (HPV, thought to be responsible for most cases of cervical cancer). In the case of hepatitis C, the emergence of safe and effective treatments has brought a new problem, for payers at least: their cost. A 12-week course of **Gilead Sciences Inc.**'s *Harvoni* (ledipasvir + sofosbuvir), for example, can cost $94,500. Responses to these high prices have included use of an indication-specific budget, sliding price-volume agreements with manufacturers, an expenditure cap in combination with a creative taxation scheme and market access restrictions including strict patient-prioritization criteria. Although such measures have tended to restrict the availability of hepatitis C treatments in major markets, the product sector has shown meteoric growth since its inception in 2011. At the same time, however, the threat posed by other virulent viruses, such as Ebola or Marburg virus, remains.

Metabolic Disease Treatments

Turning aside from infectious diseases, major challenges remain in other areas. Diabetes is still a significant problem, especially in view of the prevalence of obesity in many populations. The 1980s

Exhibit 2
HIV/AIDS In Numbers



saw a substantial amount of research into new treatments for diabetes, although these efforts were not to bear fruit until 1990, when **Bayer AG** launched the β-glucosidase inhibitor, *Glucobay* (acarbose), the first new primary therapy for diabetes since the introduction of the sulfonylureas and biguanides in the 1950s. Inhibition of β-glucosidase reduces the rate at which complex carbohydrates are digested, thus lowering blood sugar levels.

The emphasis changed in the 1990s, when new insulin analogs began to appear on the market. The first of these was *Humalog* (insulin lispro), **Eli Lilly & Co.**'s fast-acting human insulin analog that was designed more closely to mimic the body's insulin output in response to eating. Manufactured via recombinant DNA technology, Humalog made its debut in 1996. It was followed in 1999 by *NovoLog* (insulin aspart), a rapid-acting insulin analog developed by **Novo Nordisk AS** for the treatment of types 1 and 2 diabetes. Then in 2000, Aventis (now Sanofi) launched *Lantus* (insulin glargine), a long-acting human insulin analog manufactured using recombinant DNA techniques in bacteria via the pro-insulin route.

In the intervening years one interesting innovation in this area has been inhaled insulin, which was initially promoted as a more patient-friendly alternative to insulin injections. The first such product was *Exubera*, developed by **Inhale Therapeutic Systems** and launched commercially by **Pfizer Inc.** in 2006. But the market did not appear to be ready for such an innovation, and poor sales led to its being withdrawn in 2008. Inhale changed its name to **Nektar Therapeutics** and turned its attention to other applications for its polymer conjugate technology platform. More recently, in 2015, **MannKind Corp.** launched *Afrezza*, a dry powder pulmonary formulation of synthetic human insulin for the treatment of type 1 and type 2 diabetes. That said, Lantus and Humalog continue to dominate the insulin market, although their position over the next few years could be threatened by the introduction of biosimilar versions.

According to *Treatment: Diabetes Type 1*, an April 2017 *Datamonitor Healthcare* report, there is currently a significant unmet need for non-insulin therapies in type 1 diabetes. Alongside insulin-based therapy, drugs with other mechanisms of action could be exploited to improve glycemic control in these patients, as well as reduce insulin dosing and associated side-effects. The existence of this unmet need is demonstrated by the fact that type 2 diabetes therapies are already used off-label in type 1 diabetes patients.

Progress Toward An Artificial Pancreas

Of course, injecting insulin is inconvenient and can only ever approximate normal physiological conditions. A long-term goal since even before the 1980s has been to develop an artificial pancreas that can respond to minute-by-minute variations in blood glucose and deliver the appropriate amount of insulin with minimal intervention by the patient. Such a device would greatly simplify glycemic control and, by leveling out peaks and troughs in blood glucose, would minimize the risk of diabetic complications.

Although a truly autonomous implantable artificial pancreas has yet to be produced, both insulin pump and glucose sensor technology have steadily improved over the years. **Medtronic PLC**'s *MiniMed 670G* system, for example, was approved by the FDA in September 2016 and is the world's first hybrid closed-loop system that constantly self-adjusts to automatically keep the patient's sugar levels in the correct range. It features *SmartGuard* technology, described by Medtronic as "one step closer to The Artificial Pancreas," which provides advanced protection from hypoglycemic episodes. Nevertheless, for many type 1 diabetics, insulin injections look likely to be around for some time yet.

Few Novel Drugs For Obesity

There remains no known cure for either type 1 or type 2 diabetes. The latter is associated with obesity, whose prevalence is steadily increasing in developed countries and for which there also seems to be no cure on the horizon. The WHO calculates that worldwide obesity has nearly tripled since 1975 and that, in 2016, more than 1.9 billion adults were overweight, of whom more than 650 million were obese.

There are currently nearly 40 compounds in clinical trials for the treatment of obesity, according to Informa Pharma Intelligence's *Pharmaprojects*. Receptors for glucagon and glucagon-like peptide-1 (GLP-1) seem to be popular targets for potential anti-obesity products. However, new product introductions over the past few years have been relatively few, and several of those have been new combinations or formulations of older products.

Just three anti-obesity products launched in the past 30 years stand out for having a novel mode of action, but none of them is ideal. The first, launched in 1998, was **Roche**'s *Xenical* (orlistat), which acts by inhibiting pancreatic lipase, thus inhibiting fat absorption. The fact that Xenical does not act via an effect on the central nervous system is a potential advantage in both therapeutic and marketing terms, but it can have unpleasant gastro-intestinal side-effects which can lead to poor patient compliance. Orlistat is now available over-the-counter as *Alli*.

Nearly 15 years after the introduction of Xenical, Novo Nordisk launched the GLP-1 agonist *Saxenda* (liraglutide): it acts on the brain to simulate the effect of endogenous GLP-1 to depress appetite. Its major drawback is that it must be administered subcutaneously, which limits its usefulness (it is also relatively expensive). More recently, **Arena Pharmaceuticals Inc.** introduced *Belviq* (lorcaserin hydrochloride), a first-in-class 5-HT_{2C} agonist as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with at least one weight-related comorbid condition. However, there have been reports that the effectiveness of Belviq is lower than that of some other treatments.

One of the earliest drugs used to produce weight loss was amphetamine, which has anorectic properties, and older anti-obesity products tended to act via a similar central stimulant effect. Such products had obvious abuse potential but, despite the introduction of some innovative new anti-obesity products over the past couple of decades, the ideal therapeutic agent has yet to be found. A handful of potential anti-obesity agents are currently in advanced clinical testing, including: an orally active dopamine, noradrenaline and 5-HT re-uptake inhibitor, under development by **Saniona AB**; an oral angiogenesis and matrix metal-

loproteinase inhibitor targeting adipose tissue, under development by **AngioLab**; and a chewable plant-derived, carbohydrate hydrolyzing inhibitor, under development by **Boston Therapeutics Inc.**

While an effective pharmacological treatment for obesity remains elusive, there has recently been significant progress in the medtech area, particularly in the area of minimally invasive bariatric devices, a market that is growing by more than 15% a year, according to *Minimally Invasive Weight Loss Devices Market*, a July 2017 report from Informa's *Meddevicetracker*. For many years, this sector was dominated by laparoscopic adjustable gastric banding devices, but these are now being overtaken by intragastric balloons, sales of which are expected to grow by over 30% a year between now and 2021. Intragastric balloons, which were first approved in the EU in 1997 and by the US FDA as recently as 2015, are particularly suited for patients with moderately increased BMI (basal metabolic index, a measure of overweight) for whom more invasive procedures such as sleeve gastrectomy are not appropriate. *(Also see "Bariatric Devices: Intragastric Balloons To Eclipse Gastric Banding" - In Vivo, October 2017.)*

Market leader in this sector is **Apollo Endosurgery Inc.**'s *Orbera* system: other players include **ReShape Medical Inc.** (formerly known as EnteroMedics) and **Obalon Therapeutics Inc.** Intragastric balloons are only a short-term solution to appetite control (they are removed after six to 12 months) but are generally well tolerated, although there have been some concerns about the risk of over-inflation.

Lowering Lipids

To return to the subject of lipid metabolism for a moment, one class of drug whose use is widespread now but that was virtually unknown 30 years ago is the statins. I even take one myself, as does President Trump, apparently, so I am in good company. Statins lower LDL cholesterol levels significantly and cause a moderate reduction in HDL-cholesterol as well as having other beneficial effects in dyslipidemias such as reducing inflammation, C-reactive protein levels, plaque size and clot formation. They have repeatedly been shown to lower the occurrence of atherosclerotic cardiovascular disease events (they may also be able to reduce mortality from certain types of cancer), and thus have become, and seem likely to remain, the standard first-line treatment for hypercholesterolemia.

> *"While an effective pharmacological treatment for obesity remains elusive, there has recently been significant progress in the medtech area, particularly in the area of minimally invasive bariatric devices, a market that is growing by more than 15% a year."*

The first statin to be marketed was **Merck & Co. Inc.**'s *Mevacor* (lovastatin) in 1987, but it was *Lipitor* (atorvastatin), launched by Parke-Davis (then part of Warner Lambert but now a part of Pfizer) exactly 20 years ago, in 1997, that really set this market alight. Thanks to clever marketing, Lipitor rapidly outsold every other pharmaceutical product on the market, and even now is still the world's biggest selling prescription drug of all time, when lifetime sales of $148,744 million are considered.

The statin class is now widely generic-ized, which has depressed prices: even so, the global market for these products is currently worth somewhere in the region of $12 billion annually – not bad for a market that didn't exist 30 years ago.

Advances In Oncology

No review of this nature would be complete without a mention of the tremendous progress there has been in the treatment of cancer. Many types of cancer are now considered, like HIV infection, to be chronic but manageable conditions rather than incurable and often fatal. At the beginning of the 1980s, cancer therapy depended largely on surgery and the use of cytotoxic agents – antimetabolites, alkylating agents, plant-derived agents such as the vinca alkaloids, antitumor antibiotics and so on. While these types of drug still have a role to play, cancer treatment is now much more focused on the cytogenetic mechanisms underlying the cellular changes in the disease.

Between 1980 and 1990, only a handful of new anticancer agents reached the market, although the trend toward more specific types of therapy was already apparent, with drugs targeting interferon or interleukin receptors being introduced, for example. Contrast that with the period 2007–17, when over 150 new anticancer products appeared on the market, many with new immunological targets. (*See Exhibit 3.*)

At the same time, the diagnosis of cancer has progressed considerably. In the early 1980s, a new imaging tech-

Exhibit 3
Biological Targets Of Selected New Anticancer drugs, 2007–17

TARGET	NUMBER OF PRODUCTS
erb-b2 receptor tyrosine kinase 2	11
Pinase insert domain receptor	8
Membrane-spanning 4-domains, subfamily A, member 1	8
Epidermal growth factor receptor	7
v-kit Hardy Zuckerman 4 feline sarcoma viral oncogene homolog	6
fms-related tyrosine kinase 1	5
Platelet-derived growth factor receptor, alpha polypeptide	5
ret-proto-oncogene	5

SOURCE: Pharmaprojects | Pharma Intelligence, 2018

nique called nuclear magnetic resonance imaging (NMRI) was introduced that revolutionized the diagnosis of cancer and many other conditions. Although the technique was based on the principle of nuclear magnetic resonance, the word "nuclear" was later dropped for fear it would frighten patients, leaving just the "MRI" acronym we know today. One of the pioneers of magnetic resonance imaging, Peter Mansfield, PhD, who died in 2017, once commented that when the first human NMRI experiments were carried out, he was concerned that the magnetic field would completely erase the subject's memory, rather like a tape recording can be erased with a magnet. Fortunately, that did not happen.

Science Still Matters

Over the years, growth in some product sectors has followed a ballistic trajectory, only to decline as medical practice evolves. In 1976, Smith Kline & French in the UK launched a new treatment for peptic ulcer, the H_2 antagonist *Tagamet* (cimetidine). At that time, a peptic ulcer was a painful, debilitating, even life-threatening condition for which the only drug treatment, antacids, provided at best limited relief. Other treatments used ranged from adoption of a bland diet to truncal vagotomy to restrict acid secretion in the stomach.

That all changed with the introduction of Tagamet, which proved to be a much more effective way of inhibiting gastric acid secretion and which by the 1980s had become the world's first "blockbuster" drug with annual sales of more than $1 billion. Tagamet blocks acid secretion in the stomach by antagonizing H_2 receptors, and was developed by a team led by Nobel Prize winner James Black, later Sir James Black, who used rational drug design to create a molecule that specifically blocked these receptors, an approach he had previously used successfully in the development of the first β-blocker, propranolol (ICI's *Inderal*).

Within a few years, Tagamet sales were eclipsed by those of Glaxo's rival product, *Zantac* (ranitidine). Other H_2 antagonists from other manufacturers followed, but their success was cut short by the arrival of a new class of acid-inhibiting compounds, the proton pump inhibitors (PPIs), of which the first was **AstraZeneca PLC**'s *Losec* (omeprazole).

All the while these new treatments for peptic ulcer were being introduced, evidence was mounting that many cases of peptic ulcer were in fact caused by *Helicobacter pylori*, a Gram-negative bacterium that is typically found in the upper gastrointestinal tract (some cases, though, do have other causes such as frequent use of NSAIDs, alcohol consumption, smoking, etc). Treatment today usually consists of a PPI to lower acid secretion together with an appropriate antibiotic to target the *H. pylori* infection.

The move away from H_2 antagonists for treating peptic ulcer was not the end of the story for that class of medicine. In the mid-1990s, Tagamet was one of several products that were part of a new wave of Rx-to-OTC switching, driven by the need to extend the product's life cycle in the face of changing prescribing habits and by the push by health systems to shift the cost of treating minor ailments onto the patient (OTC cimetidine is used to prevent and treat the symptoms of heartburn associated with acid indigestion). Patent protection of cimetidine has since expired, and GSK has disposed of its Tagamet (and Zantac) assets.

Pharma's Reputation

One theme that has recurred over the past 35 years (and probably longer) is that of the public perception of the industry. Many pharmaceutical companies were founded with altruistic aims and a commitment always to act in the interest of patients. However, as many of these companies have grown to become major multinational corporations, they have become increasingly susceptible to the expectations and demands of the financial markets and are now often perceived to act in the interests of shareholders in preference to those of patients.

This problem was epitomized by the outcry that arose when the first antiretroviral drugs were marketed. Manufacturers kept prices high, even in developing countries where ironically most HIV infections occurred, and resisted attempts to permit the use of generic versions from low-cost countries such as India. Such behavior attracted much criticism, and the companies eventually capitulated and lowered their prices, while President Bill Clinton issued an executive order to prevent the Office of the US Trade Representative from seeking trade sanctions against poor countries that tried to gain access to generic versions of anti-HIV drugs (as they were permitted to do under World Trade Organization rules).

The industry eventually recovered from the damage done to its reputation by the debacle, but since then it seems, whether

through arrogance or naivety, to have blundered into several other crises in public confidence. Among the practices that have attracted public condemnation of the industry are making its products unaffordable to many patients, even in wealthy countries like the US; indulging in mega-mergers that, while they may lead to a lower tax burden, an improved bottom line and amplified executive pay, do little for patients or indeed their own workforce; and indulging in behavior that has attracted financial sanctions, such as inappropriate marketing, promotion of off-label indications and misleading direct-to-consumer advertising. The failure to tackle the problem of antibiotic resistance is another oft heard criticism. The actions of companies like **Turing Pharmaceuticals AG** and its then CEO Martin Shkreli, which acquired the toxoplasmosis drug *Daraprim* (pyrimethamine) and then hiked the price by over 5,000%, did not help.

Lessons Learned

There are a couple of important lessons to be learned from all of this. First, although much changes with the passage of time, much also remains the same. Some of the challenges currently facing the health care industry are the same ones that were faced decades ago – only the means used to tackle them has changed. Second, the future is exceedingly difficult to predict with any accuracy, and even the past is no guide to the future. Markets can appear from nowhere almost overnight: the statins have already been mentioned – phosphodiesterase type 5 inhibitors, used in the management of erectile dysfunction and shortly to become available OTC we are told, is another.

Also apparent is the growing convergence between the pharma and medtech sectors. The story of the discovery of HIV is a good example: once the virus had been identified the way was open to develop antiviral agents with which to treat infected individuals, but these would have had limited use without the availability of diagnostic tests to identify those patients. More recently, companion diagnostics have emerged as a vital component of many new, high-tech pharmaceutical product offerings. Perhaps such convergence will turn out to be the catalyst for successfully addressing some of the outstanding challenges facing the health care sector.

> *One of the pioneers of magnetic resonance imaging, Peter Mansfield, PhD, who died in 2017, once commented that when the first human NMRI experiments were carried out, he was concerned that the magnetic field would completely erase the subject's memory, rather like a tape recording can be erased with a magnet. Fortunately, that did not happen.*

It is sometimes said that the pharmaceutical industry has taken all the low-hanging fruit in terms of treating disease, and that it will be increasingly difficult to address those diseases that remain to be conquered. It therefore seems likely that there will be greater emphasis on the prevention of disease, rather than its treatment. Indeed, this trend is already apparent in the development of HPV vaccines to prevent cervical cancer, and greater emphasis on prevention may well turn out to be a partial answer, at least, to the management of infectious diseases caused by antibiotic-resistant bacteria. Alzheimer's disease, which we have not mentioned previously but for which there are no quick fixes, may also ultimately be beaten by the adoption of appropriate preventive measures (which of course also remain to be discovered).

New and emerging technologies like artificial intelligence, machine learning and data mining will also have an important role to play in the continuing fight against human disease. The next 35 years should be even more exciting than the last.

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On the Move

Recent executive appointments in the life sciences industry

COMPANY CHANGES

BAIN, Gretchen, PhD
To: Jecure Therapeutics, VP, Biology (Dec)
From: PharmAkea Therapeutics Inc., Exec. Dir., Biology
Phone: 619-541-8699

BALAGOT, Joe E.
To: Cesca Therapeutics Inc., SVP, Corp. Dev. (Nov)
From: Dawson James Securities, Managing Dir./Partner, Investment Banking
Phone: 916-858-5100

BECKER, Marc
To: Concert Pharmaceuticals Inc., CFO (Jan)
From: CRISPR Therapeutics AG, SVP, CFO
Phone: 781-860-0045

BOGLIOLI, Elsy
To: Cellectis SA, EVP, Strategy & Corp. Dev. (Dec)
From: Boston Consulting Group, Partner & Managing Dir.
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BOOKER, Harriet
To: BioScrip Inc., SVP, COO (Nov)
From: Option Care, Interim SVP, Revenue Cycle Mgmt.
Phone: 914-460-1600

COOK, Jennifer
To: Grail Inc., CEO (Jan)
From: Roche Pharmaceuticals, Head, Clinical Ops., Product Dev.
Phone: 650-454-6995

COX, Russell J.
To: Vital Therapies Inc., CEO (Dec)
From: Jazz Pharmaceuticals PLC, EVP & COO
Phone: 858-673-6840

DEPIL, Stephane, MD, PhD
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From: Consultant
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GOLDMAN, Neil A.
To: Chembio Diagnostics Inc., EVP, CFO (Dec)
From: J.S. Held LLC, EVP, Corp. Dev. & CFO
Phone: 631-924-1135

GOODWIN, Charles D.
To: Bovie Medical Corp., CEO (Dec)
From: American Optics, Chief Commercial Officer
Phone: 800-537-2790

HAIR, Mark L.
To: Restoration Robotics Inc., CFO (Jan)
From: Zeltiq Aesthetics Inc., VP, Chief Accounting Officer
Phone: 408-883-6888

HANSON, Bryan C.
To: Zimmer Biomet Holdings Inc., Pres. & CEO (Dec)
From: Medtronic PLC, EVP & Pres., Minimally Invasive Therapies Group
Phone: 800-613-6131

ELSY BOGLIOLI
EVP, Strategy & Corp. Development
Cellectis

JENNIFER COOK
CEO, Grail

DEREK HEI
SVP, Mfg., Quality & Regulatory
BlueRock Therapeutics

SCOTT HERSKOVITZ
President & CEO, Qosina

ANDREW KIDD
Chief Commercial Officer
Aptinyx

DAVID MICHELSON
CMO, Proclara Biosciences

ANDREW OH
CFO, Rubius Therapeutics

CADMUS RICH
CMO, Aura Biosciences

CARL ST. BERNARD
President & CEO, Tryton Medical

STUART WOOD
Operations Director
Applied Photophysics

HEI, Derek, PhD
To: BlueRock Therapeutics, SVP, Mfg., Quality & Regulatory (Dec)
From: Cellular Dynamics International Inc., VP, Clinical Mfg., Quality & Regulatory
Phone: 608-310-5100

KIDD, Andrew
To: Aptinyx Inc., Chief Commercial Officer (Dec)
From: Baxter International Inc., SVP, Strategy & Bus. Dev.
Phone: 847-871-0377

LIESENFELD, Oliver, MD
To: Inflammatix Inc., CMO (Dec)
From: Roche Molecular Diagnostics, CMO
Phone: 650-797-1647

MERNON, Mark
To: Biogen Inc., SVP, Chief Information Officer (Dec)
From: Takeda Pharmaceutical Co. Ltd., Global Head, R&D Site Strategy & Ops.
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MICHELSON, David, MD
To: Proclara Biosciences, CMO (Jan)
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NARAYAN, Shakti, PhD
To: Tango Therapeutics, CBO (Dec)
From: Johnson & Johnson Innovation, VP, Head, Transactions
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OH, Andrew
To: Rubius Therapeutics Inc., CFO (Dec)
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PRICE, Michael
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Deal-Making

Covering deals made December 2017

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

Alliances

Oxford Immunotec, **Qiagen** settle patent litigation

Financings

Diagnostics company **Akers Biosciences** nets $6.4mm in FOPO

Cancer Genetics nets $6.5mm through registered direct offering

Quanterix nets $68.6mm via IPO

Public offering nets $24.6mm for **Verastem**

MEDICAL DEVICES

Mergers & Acquisitions

CooperVision pays $80mm for **Paragon Vision**

Edwards shells out $100mm up front for **Harpoon Medical**

LivaNova to pay up to $225mm for **ImThera**

Stryker to acquire **Entellus Medical** for $24 per share

Alliances

ITEM Medical gains Turkish rights to **GTI**'s *LuViva* cervical scan, related disposables

TransEnterix licenses *SurgiBot* to Great Belief International

Financings

Brainsway closes $8.5mm PIPE

PHARMACEUTICALS

Mergers & Acquisitions

Allergan acquires **Repros** for $26.5mm

CVS aims to change health care delivery in $77bn acquisition of **Aetna**

Gilead, **Kite** buy **Cell Design Labs**

Mallinckrodt buys **Sucampo**

Alize, **Millendo** merge to create leading endocrine disease-focused firm

Nestle pays $2.3bn for **Atrium Innovations**

Alliances

Alexion is **Halozyme**'s latest *Enhanze* partner in potential $680mm deal

Almirall licenses US, European rights to **Athenex**'s KX2391 for AK

Ambrx gets Chinese rights to **Tracon**'s endoglin antibody TRC105

Amgen, **Carmot** ally in neurodegenerative deal

BI enters into CNS platform/drug collaboration with **GSK** spin-out **Autifony**

BMS licenses gamma secretase inhibitors to start-up **Ayala**

Flexion gets preclinical OA gene therapy from **GeneQuine**

TC BioPharm and **bluebird bio** team up for gamma delta CART therapies

Collegium licenses US rights to **Depomed**'s *Nucynta*

BioRenal to sell **Rockwell**'s *Triferic* in Chile

Roche signs GPCR discovery deal with **Confo Therapeutics**

Roivant gets rights to **HanAll**'s autoimmune disease candidate

Puma and **Daiichi Sankyo** enter trial collaboration

Genentech signs small-molecule discovery agreement with **DiCE**

Eurofarma gets commercial rights to **Summit**'s ridinilazole

Zai Lab gets exclusive immunotherapy rights from **Five Prime**

Genexine grants *HyLeukin* license to **I-MAB**

HanX gets Chinese rights to **Onconova**'s ON123300

Xynomic, **Janssen** team up in trial collaboration

Juno licenses gamma-secretase inhibitor from **Lilly**

Neon and **Merck** study neoantigen immunotherapy combo

TiGenix gets exclusive rights to mesenchymal stem cell IP from **Mesoblast**

Mundipharma gets rights to sell **NTC**'s ophthalmic products in MENA region

Rockwell licenses *Triferic* to **Quimica Europea** for Peru

Rezolute gets global rights to **Xoma**'s XOMA358 in potential $240mm deal

Financings

Rare disease focused **Acer Therapeutics** nets $10.4mm in FOPO

Public ADS offering nets $249.6mm for **argenx**

Public offering nets $570mm for **bluebird bio**

Catalyst Biosciences nets $9.8mm through public offering

Neurodegenerative start-up **Denali Therapeutics** nets $267.4mm in IPO

Dicerna nets $37.6mm via FOPO

Editas nets $50mm in FOPO

Eyenovia seeks to go public

Fennec Pharmaceuticals closes $20mm public offering

Fibrocell brings in $9.9mm through FOPO

Global Blood nets $96.3mm through follow-on offering

GW Pharmaceuticals nets $299.1mm in FOPO

Public offering nets $142.5mm for **Heron**

Lexicon enters $200mm loan agreement; draws down $150mm right away

Public offering nets $117.5mm for **Madrigal Pharmaceuticals**

Northwest Bio sells $12mm of its convertible preferred shares

Ultragenyx sells *Mepsevii* PRV to **Novartis** for $130mm

Odonate nets $139.5mm through initial public offering

Proteostasis nets $43.2mm via FOPO

Revance nets $157mm in FOPO

VistaGen nets $13.95mm through FOPO

IN VITRO DIAGNOSTICS

ALLIANCES
OXFORD IMMUNOTEC GLOBAL PLC
QIAGEN NV

Oxford Immunotec Global PLC and **Qiagen NV** have settled patent infringement litigation surrounding Qiagen's *QuantiFERON-TB Gold* and *QuantiFERON-TB Gold Plus* tests for tuberculosis. Under the settlement, Oxford received a payment of $27.5mm and granted Qiagen a royalty-free, non-exclusive license extending to current and future customers of the products. Qiagen gained the *QuantiFERON* in vitro diagnostic technology through its $355mm acquisition of Cellectis in 2011. The platform can provide information on the activity of the cell-mediated function of the immune system from whole blood samples. (Dec.)

Financings

AKERS BIOSCIENCES INC.

Akers Biosciences Inc. (rapid in vitro point-of-care screening and testing products) netted $6.4mm through a follow-on public offering of 21.5mm Class A units, including the overallotment, at $0.15 per unit (each Class A unit consists of one share of common stock and one warrant to purchase an additional common share) and 3.675k Class B Units (each Class B unit consists of one share of Series B convertible preferred stock (convertible into 24.5k common shares) and one warrant comparable to the Class A units) at $1k per unit. The warrants are exercisable for a five-year period at a strike price of $0.1875 per share. The company will use the offering proceeds to fund product development and marketing; to expand internal sales; and to further develop sales channels. (Dec.)

Investment Banks/Advisors: Joseph Gunnar & Co.

CANCER GENETICS INC.

Cancer Genetics Inc. (molecular diagnostics for cancer) netted $6.5mm through a registered direct offering of 3.5mm units at $2 apiece (a 17% discount). Units were comprised of one common share and one 18-month common share purchase warrant exercisable at $2.35. HC Wainwright was the placement agent. (Dec.)

Investment Banks/Advisors: HC Wainwright & Co.

QUANTERIX CORP.

Diagnostics firm **Quanterix Corp.** netted $68.6mm through its initial public offering of 4.9mm common shares (including full exercise of the overallotment) priced at $15 each on the Nasdaq. (Dec.)

Investment Banks/Advisors: BTIG LLC; Cowen & Co. LLC; Evercore Partners; JP Morgan Chase & Co.; Leerink Partners LLC

VERASTEM INC.

Oncology drug developer **Verastem Inc.** netted $24.6mm through a public sale of 8.4mm common shares at $2.97. Funds will support launch and commercialization costs of the company's lead blood cancer candidate duvelisib, pending regulatory approval, and will also be put towards continued development of additional pipeline projects. (Dec.)

Investment Banks/Advisors: BTIG LLC

MEDICAL DEVICES

Mergers & Acquisitions

COOPER COS. INC.
CooperVision Inc.
PARAGON VISION SCIENCES

Cooper Cos. Inc.'s CooperVision Inc. is paying $80mm to acquire closely held Paragon Vision Sciences. (Dec.)

Paragon specializes in orthokeratology, which involves the creation of gas permeable contact lenses that temporarily reshape the cornea to reduce refractive errors such as myopia, hyperopia, and astigmatism. The company has developed a corneal refractive therapy (CRT), a non-surgical option that improves vision by gently reshaping the eye while a patient sleeps using specially designed therapeutic contact lenses. The lenses are put in at bedtime and upon waking the vision will be clear and sharp. For the previous twelve months Paragon had about $15mm in revenues and those numbers are expected to increase by low-double-digits in the next few years.

EDWARDS LIFESCIENCES CORP.
HARPOON MEDICAL INC.

Edwards Lifesciences Corp. paid $100mm up front in cash for private cardiovascular device maker **Harpoon Medical Inc.** Edwards could shell out up to $150mm million in pre-specified milestones over the next ten years. (Dec.)

In 2014 Harpoon licensed exclusive rights to technologies for cardiac valve repair from the **University of Maryland** (UMD), from which the firm spun off. Later that year Harpoon received $3.3mm in Series A funding from lead backer Epidarex Capital as well as UMD and other investors. In late 2015 Edwards announced a deal to invest an undisclosed amount in Harpoon (as part of its Series B round) and gained the exclusive option to acquire the company. Harpoon has incorporated the UMD's IP into an image-guided device for surgically repairing mitral valve function and eliminating regurgitation during a beating-heart procedure. The product is designed to stabilize the prolapsed mitral valve leaflet to restore proper coaptation and valve function. Though not yet commercialized, Harpoon's device is expected to receive CE Mark in the near future. Compared to current procedures, the Harpoon method can be performed in just one hour instead of three to six hours and results in faster patient recovery and less morbidity. Edwards says the acquisition complements its own portfolio of treatments for structural heart disease and demonstrates its commitment to the cardiology space.

LIVANOVA PLC
IMTHERA MEDICAL INC.

LivaNova PLC is buying closely held sleep apnea device maker **ImThera Medical Inc.** for $78mm up front and up to $147mm in potential regulatory and sales milestones. (Dec.)

LivaNova (then known as Cyberonics) invested $4mm in ImThera's 2011 Series C round. Thirteen-year-old ImThera has developed the *aura6000* THN (targeted hypoglossal neurostimulation) therapy, a minimally invasive surgically implanted device that uses an electrode and a pulse generator to stimulate certain tongue muscles and open the airway in patients suffering from moderate to severe obstructive sleep apnea. CE marked since 2012, the product was designed for OSA patients who were unable or unwilling to use continuous positive airway pressure

(CPAP) therapy. In the US, ImThera is currently enrolling patients in a pivotal study required to obtain premarket approval by the FDA. ImThera will become a part of LivaNova's neuromodulation segment, which has been a key part of LivaNova's business since its creation in 2015 through the $2.7bn merger of Cyberonics and Sorin.

STRYKER CORP.
ENTELLUS MEDICAL INC.

Stryker Corp. agreed to acquire **Entellus Medical Inc.** (minimally invasive ENT products) for $24 per share in cash (47% premium to prior 10-day stock trading average), or a total equity value of approximately $662mm (enterprise value of $658.1mm accounting for net debt). (Dec.)

Entellus is a medical device company that has developed less invasive treatments for patients with chronic and recurrent sinusitis, nasal airway obstruction, and persistent eustachian tube dysfunction. Product lines include the *XprESS* ENT dilation system, *Latera* absorbable nasal implant, *MiniFESS* surgical instruments, *Aerogel* nasal dressing, and *FocESS* imaging & navigation. The company generated $75.2mm in sales in 2016. While the Entellus board has already approved the transaction, the closing is still dependent on approval from Entellus stockholders. The deal will expand Stryker's small but significant presence in the ENT market and will bring a range of complementary products to the company. Investment Banks/Advisors: Guggenheim Partners LLC (Stryker Corp.); Piper Jaffray & Co. (Entellus Medical Inc.)

Alliances

GUIDED THERAPEUTICS INC.
ITEM MEDICAL TECHNOLOGIES GROUP

Turkish distributor **ITEM Medical Technologies Group** signed a preliminary license agreement to manufacture and sell in Turkey **Guided Therapeutics Inc.**'s cervical guide related to GTI's *LuViva* cervical scan system; each scan with *LuViva* requires a single-patient-use cervical guide. (Dec.)

ITEM has been GTI's distributor since 2012 (under a three-year contract later expanded). If a new definitive agreement is signed, ITEM will pay $3mm in fees, plus a royalty on each cervical guide interface and calibration disposable made and sold in Turkey, where *LuViva* is approved for wide-scale screening of cervical cancer. In addition, over the next five-year period, ITEM would be obligated to purchase 600 *LuViva* cervical scans and produce 3 million cervical guides. *LuViva* uses a biophotonic technology that scans the cervix with light, using fluorescence spectroscopy to measure its interaction with cervical tissue and identify chemical and structural precancerous indicators below the surface of the cervix or misdiagnosed as benign. Used in follow-up screenings and early detection, *LuViva* is designed to provide results immediately and, as opposed to more invasive pap or HPV tests or biopsies, it does not require a tissue sample or separate analysis by a lab, which can be costly and unnecessary. In January 2017 **Shandong Yaohua Medical Instrument** licensed exclusive distribution, sales, and manufacturing rights to *LuViva* in China, Taiwan, Hong Kong, and Macau, replacing GTI's former arrangement with **Shenghuo Medical**, which previously had Chinese rights. In addition to Europe, the system is also approved in Canada, Mexico, Kenya, and Singapore, and is awaiting FDA clearance. A current deal with ITEM would enable GTI to reach more markets globally and would leverage ITEM's expertise in the gynecology field.

TRANSENTERIX INC.

TransEnterix Inc. out-licensed Chinese rights for its *SurgiBot* robotic laparoscopic surgical system to health care asset management firm Great Belief International Ltd. (GBIL) for up to $29mm. (Dec.)

SurgiBot is used during single-incision abdominal laparoscopic procedures, and allows for multiple instruments to be introduced and used in the surgical field through one access site. GBIL pays $7.5mm up front, and will pay another $7.5mm by the end of March 2018 (including a $3mm equity investment through the purchase of 1.29mm TransEnterix common shares at $2.33, an 8% premium). The deal also includes the potential for a minimum of $14mm in royalty payments to be made upon Chinese regulatory approval of the device, or on the fifth anniversary of the second financial closing of the deal. GBIL concurrently entered a manufacturing agreement with China National Scientific and Instruments and Materials Co. for the Chinese market; TransEnterix holds onto an option to distribute or co-distribute *SurgiBot* outside of China, and can also commercialize the product outside of China once manufacturing is underway and ex-Chinese regulatory approval has been obtained. *SurgiBot* is not yet approved for sale in any market.

Financings

BRAINSWAY LTD.

Tel Aviv Stock Exchange-traded **Brainsway Ltd.** (wearable device to treat brain disorders) raised $8.5mm in a private placement led by Phoenix Group (which now holds a 7% stake). Other participants included Noked Capital and returning backer IBI Investment House. The company's transcranial magnetic stimulation (TMS) system noninvasively generates brief magnetic pulses in the brain to activate precise neuronal pathways responsible for different types of CNS disorders. (Dec.)

PHARMACEUTICALS

MERGERS & ACQUISITIONS

ALLERGAN PLC
REPROS THERAPEUTICS INC.

Allergan PLC agreed to acquire all outstanding shares of troubled public US biotech **Repros Therapeutics Inc.** (small-molecule gynecological/urological disorder drugs). Repros' board has approved the transaction, which is expected to close during the first quarter of 2018. (Dec.)

Allergan will pay $0.67 per share in cash (a 52% premium) for all outstanding Repros shares (approximately 39.6mm) for an equity value of $26.5mm. Founded in 1987 as Zonagen, the company went public in 1993 and changed its name to Repros in 2006. In 2015, Repros initially submitted an NDA for its *Androxal* (ZA205; enclomiphene citrate)--an orally active testosterone receptor agonist--to improve male fertility due to low testosterone caused by secondary hypogonadism (associated with obesity). In its complete response letter later that year, the FDA indicated additional Phase III studies would be necessary to gain the compound's approval. That, coupled with a recent report indicating the EMA would likely return a negative opinion regarding *Androxal*'s European clearance (for which an MAA was submitted late last year), slashed the candidate's likelihood of approval (per *Biomedtracker*) to 25% (35% below average). Repros' Phase IIb candidate for uterine fibroids--*Proellex* (ZPU203; telapristone acetate), an oral, selective progesterone receptor modulator (SPRM)--has also been stalled by the FDA, which placed the compound on a partial clinical hold earlier this year due to concerns involving liver toxicity. The agency is requesting substantial safety data before the company can begin Phase III testing (lowering the compound's likelihood of approval to 14% (10% below average)). Repros doesn't have the resources to support completion of the FDA-mandated study necessary for *Proellex*'s approval (as of Sept. 30, 2017, Repros reported just $1.8mm cash on hand). Allergan will decide the future development path and may also re-assess the compound's continued development for endometriosis as well as a vaginal formulation for fibroids. Women's health and urology is a key therapeutic area for Allergan. If eventually successful, *Proellex* will complement Allergan's existing oral SPRM uterine fibroid drug *Esmya* (ulipristal acetate), which is already approved in Europe (2015) and Canada (2013) and has an expected PDUFA action date during H1 2018 for FDA clearance. Investment Banks/Advisors: Stifel Nicolaus & Co. Inc. (Repros Therapeutics Inc.)

CVS HEALTH CORP.
AETNA INC.

In a move to streamline and improve health care delivery, retail pharmacy giant and pharmaceutical benefits manager (PBM) **CVS Health Corp.** signed a definite agreement to buy publicly traded insurance company **Aetna Inc.** CVS is spending $145 in cash and issuing 0.8378 in its shares for each Aetna share, which is valued at $206 (a 16% premium). The entire agreement is worth $77bn, including the assumption of Aetna's debt. Upon deal closing, CVS stockholders will own 78% of the combined entity, and Aetna the rest. (Dec.)

The transaction is considered a vertical arrangement, and its main goal is to help make health care more integrated, and at a lower cost to patients. Aetna will also now have its own PBM through **Caremark** (Aetna was already using CVS for some of these functions), falling in line with other insurers including **UnitedHealth Group**, which has **OptumRx**, and **Anthem**, which is building its own in-house PBM called **IngenioRx** (Anthem also contracts with CVS for certain services). CVS and Aetna believe the combination will broaden capabilities and access to Aetna's provider network at CVS's 1,139 in-store/walk-in MinuteClinics, and allow for more value-based health care decisions to be made through the use of Aetna's extensive claims database. Another key benefit for CVS from a financial perspective is that the addition of Aetna would diversify CVS's revenue, which is heavily dependent on its retail pharmacy segment. Finally, some analysts believe that in buying Aetna, CVS is making a potentially proactive move to combat future competition from **Amazon**, which has secured wholesale distributor licenses in some US states and has been rumored to be making a play in the health care market. The acquisition comes less than a year after Aetna and fellow insurance company **Humana** mutually agreed to terminate their merger, following a ruling from a US federal court that blocked the deal due to the risk of unfair competition and expected price increases (around the same time, **Cigna** and Anthem also abandoned their merger agreement). Aetna's business involves commercial and government health insurance (medical and dental), group life and disability plans, workers' compensation, health IT products and services, and pension and annuity management. Within insurance, Aetna offers Medicaid and Medicare Advantage and Supplement plans. The company covers 22.2mm members for medical benefits and 14.5mm for dental benefits through a network of 1.15mm health care professionals. Aetna realized pro forma revenue of $61.4bn in the last 12 months (most of which comes from insurance premiums and administrative service fees), and an EBITDA of $6.2bn, representing 1.25x and 12.4x multiples, respectively. It had $5.9bn in cash on hand at the end of Q3 2017. Investment Banks/Advisors: Allen & Co.; Evercore Partners; Lazard LLC (Aetna Inc.); Barclays Bank PLC; Centerview Partners LLC; Goldman Sachs & Co. (CVS Health Corp.)

GILEAD SCIENCES INC.
Kite Pharma Inc.
CELL DESIGN LABS INC.

Just four months after thrusting itself into the cell therapy space through the $11.9bn acquisition of **Kite Pharma Inc.**, **Gilead Sciences Inc.** is acquiring privately held **Cell Design Labs Inc.**, another player in the engineered cellular therapeutics market. (Dec.)

Cell Design's key assets are its *synNotch* gene expression technology (requires two antigens instead of one to activate chimeric antigen receptor (CAR) cells), and its *Throttle* "on-off switch" platform (uses a small molecule as a switch to modulate CAR activity). Kite and Cell Design teamed up in 2016 through a deal in which Kite was granted access to the *Throttle* technology for the company's work in developing CAR therapies for leukemia and B-cell malignancies. (Kite holds a 12.2% equity stake in Cell Design as a result of that collaboration and an investment in Cell Design's $28.4mm Series A round.) In the current bolt-on acquisition to enhance Kite's business, Gilead will pay $175mm up front plus up to $322mm in earn-outs related to development and regulatory achievements. (The total deal value, including Kite's existing stake, amounts to about $567mm.) Gilead will direct Cell Design's technologies to existing R&D ongoing at Kite for solid and blood cancer drug development. Cell Design also brings preclinical candidates to the table, including projects for prostate cancer, hepatocellular carcinoma, and multiple myeloma. Investment Banks/Advisors: Citigroup Inc. (Cell Design Labs Inc.)

MALLINCKRODT PLC
SUCAMPO PHARMACEUTICALS INC.

Mallinckrodt PLC agreed to pay $18 per share (an 8% premium) to acquire **Sucampo Pharmaceuticals Inc.**, a public firm developing treatments for GI conditions and rare diseases. Including debt, the enterprise value of the transaction sits at about $1.2bn. (Dec.)

Sucampo's drug development efforts focus on prostones, which are naturally-occurring fatty acid metabolites that restore normal function in cells and tissues. The company's marketed prostone products include *Amitiza* (lubiprostone) for chronic constipation, chronic idiopathic constipation in adults, IBS with constipation in adult women, and opioid-induced constipation in adults with chronic non-cancer pain, and *Rescula* (unoprostone isopropyl ophthalmic solution) for ocular hypertension and open-angle glaucoma. *Amitiza* is partnered with **Takeda** and **Mylan**; the drug brought in net sales of $456mm for 2016, but Sucampo's share of that amounted to about $200mm including sales and royalties. *Rescula* is marketed in Japan, and only accounts for under 5% of the company's revenues. In addition to *Amitiza* and *Rescula*, Mallinckrodt also gains access to Sucampo's investigational projects CPP-1X/sulindac, in Phase III for familial adenomatous polyposis (FAP), and VTS270, in Phase II/III for Niemann-Pick Type C. Combined sales of those compounds, if approved, are estimated to be about $450mm. The acquisition of Sucampo helps Mallinckrodt diversify its assets and revenue stream, most notably to make up for the declining sales of the company's *H.P. Acthar Gel* (repository corticotropin injection), which is used for autoimmune and inflammatory conditions including lupus, multiple sclerosis and infantile spasms. Mallinckrodt bought it from **Questcor** in 2014, but has seen legal trouble from the drug resulting from an over 8,000% price increase since 2001. *H.P. Acthar Gel* accounted for 34% of Mallinckrodt's 2016 sales, but numbers are falling. The Sucampo acquisition announcement seems to have helped boost Mallinckrodt's share price a bit, a welcome sign for company shareholders who have seen a 55% reduction in stock price since the beginning of 2017. The company started out the year with a market cap topping $5bn, but prior to the Sucampo announcement, that had dropped to just over $2bn. Investment Banks/Advisors: Deutsche Bank AG (Mallinckrodt PLC); Jefferies & Co. Inc. (Sucampo Pharmaceuticals Inc.)

MILLENDO THERAPEUTICS INC.
ALIZE PHARMA SAS

In an effort to become a leader in the endocrine space, **Millendo Therapeutics Inc.** is acquiring fellow closely held **Alize Pharma SAS** in a stock swap. (Dec.)

Post-transaction, the combined entity will operate in the US as Millendo Therapeutics Inc. and as Millendo Therapeutics SAS in Europe where it will continue to operate Alize's R&D facilities with Alize's president joining the Millendo board. The company will have two assets. Millendo contributes the ACAT1 inhibitor nevanimibe (ATR101), which is in Phase II for congenital adrenal hyperplasia and endogenous Cushing's syndrome. (According to *BioMedTracker* nevanimibe has a 26% likelihood of approval (2% above average) for CAH and 24% for Cushing's.) Alize adds livoletide (AZP531), a Phase II candidate for Prader-Willi syndrome which has orphan drug status from the FDA and a positive opinion from the European Medicines Agency for orphan drug designation.

NESTLE SA
Nestle Health Science SA
ATRIUM INNOVATIONS INC.

Nestle SA is paying $2.3bn in cash to acquire private nutritional health firm **Atrium Innovations Inc.** (Dec.)

Post-transaction, Atrium will become part of **Nestle Health Science SA** and its president and CEO Peter Luther will continue to lead the team along with existing management. Atrium's products will fit nicely with Nestle's consumer care portfolio. The company offers nutritional supplements, vitamins, probiotics, anti-aging and skin care products, preservatives, and antioxidants. Atrium's *Garden of Life* certified organic, non-GMO brand is the leading natural supplement in the US. It also sells the *Pure Encapsulations* line of hypoallergenic dietary supplements, which is the top recommended brand in the US practitioner market. Other nutritional health brands are *Wobenzym*, *Douglas Laboratories*, *Genestra Brands*, *Orthica*, *AOV*, *Minami*, *Klean Athlete*, and *Trophic*. Atrium is expected to generate $700mm in sales for 2017. The firm is backed by investors including Permira Funds, Fonds de solidarite FTQ, and Caisse. Investment Banks/Advisors: Morgan Stanley & Co.; RBC Capital Markets (Atrium Innovations Inc.)

Alliances

ALEXION PHARMACEUTICALS INC.
HALOZYME THERAPEUTICS INC.

Halozyme Therapeutics Inc. penned its eighth collaboration surrounding the *Enhanze* drug delivery technology, this time with **Alexion Pharmaceuticals Inc.** (Dec.)

The *Enhanze* platform uses a proprietary recombinant human hyaluronidase enzyme to temporarily degrade hyaluronan and help disperse injectable drugs more evenly into the body. The technology improves upon delivery and absorption of subcutaneously delivered therapies, and also allows for favorable modifications to dosing schedules. Through the current deal, Alexion is granted access to *Enhanze* to exclusively develop up to four targets, including a subcutaneous extended dosing formulation of its Phase III C5 complement inhibitor ALXN1210 (ALXO1210SC) for paroxysmal nocturnal haemoglobinuria and haemolytic uraemic syndrome. Alexion pays $40mm up front, plus $160mm in milestones per target and mid-single-digit royalties (*Strategic Transactions* estimates 4-6%). Other firms using *Enhanze* in their drug development work include **Roche**, **Baxter**, **Intrexon**, **Pfizer**, **Janssen**, **AbbVie**, **Lilly**, and most recently, **BMS** through a September 2017 alliance for the enhancement of the Big Pharma's immuno-oncology assets.

ALMIRALL SA
ATHENEX INC.

Almirall SA licensed exclusive US and European development and commercialization rights to **Athenex Inc.**'s Phase III KX2391 for actinic keratosis (AK) and other skin conditions. (Dec.)

Almirall will provide $55mm in up-front and near-term payments; $65mm in milestones related to launch and additional indications; $155mm in sales milestones (potentially more if sales exceed the projected amounts); and tiered annual net sales royalties ranging from a low of 15% and increasing with higher sales. Athenex will conduct all preclinical and clinical studies up to FDA approval. A topical ointment for AK, KX2391 (also known as KX01) is a dual inhibitor of both the Src tyrosine kinase (regulates development and growth of tumors and cells involved in other hyper-proliferative diseases) and tubulin polymerization (essential for cell growth). AK is marked by scaly, crusty lesions caused by damage from the sun's UV rays; if untreated, it can develop into to squamous cell carcinoma. The companies will pursue development of different indications and formulations. Following positive efficacy in Phase II trials, Athenex announced the start of two US Phase III randomized double-blind controlled clinical trials of KX2391 in AK earlier this year. Under a 2012 alliance, **PharmaEssentia** has Taiwanese development and commercialization rights to KX2391 for AK, as well as the indication of psoriasis in Taiwan and China. The current deal enables Almirall to add a late-phase candidate in a new therapy area to its existing five-compound core dermatology pipeline, which includes tildrakizumab for plaque psoriasis (BLA filed); P3058 for onychomycosis (Phase III); P3074 for androgenic alopecia (Phase III); PAT001 for ichthyosis (Phase II); and ADP13612 for rosacea (preclinical). Athenex also benefits by gaining a partner to develop KX2391 in AK, while it focuses on its mostly-cancer pipeline.

AMBRX INC.
TRACON PHARMACEUTICALS INC.

Tracon Pharmaceuticals Inc. granted **Ambrx Inc.** exclusive rights to develop and sell the endoglin antibody TRC105 (carotuximab) in China, Hong Kong, Macau, and Taiwan. The deal covers all indications excluding ophthalmic, for which **Santen** has global rights. (Dec.)

Ambrx paid $3mm up front and could hand over up to $10.5mm in development and regulatory milestones, $130mm in sales milestones, and tiered royalties ranging from the high-single-digits to the low teens. Endoglin is a protein that is overexpressed on endothelial cells, and is vital for the formation of new blood vessels. The endoglin antibody TRC105 is in Phase III for angiosarcoma, and Phase II in combination with other cancer drugs for renal cell carcinoma, hepatocellular carcinoma, gestational trophoblastic neoplasia, and lung and breast cancers. Ambrx will file a clinical trial application in China in 2018 to begin studies there, where its initial focus will be on hepatocellular carcinoma and angiosarcoma.

AMGEN INC.
CARMOT THERAPEUTICS INC.

In a multi-year agreement, **Carmot Therapeutics Inc.** and **Amgen Inc.** are teaming up to identify and develop therapies for Parkinson's and other neurodegenerative diseases. (Dec.)

Carmot will use its *Chemotype Evolution* lead-identification technology to discover leads. The company and Amgen will then jointly select multiple targets and identify candidates. Amgen will handle all clinical development, manufacturing, and commercialization activities of any resulting molecules. Carmot will receive money upfront, R&D funding, and development and commercialization milestones. In all the deal could be worth over $240mm. Amgen will also pay sales royalties on resulting products. *Chemotype Evolution* can identify leads sourced from chemically diverse libraries for validated targets. The companies first partnered back in 2014 under a similar agreement in which Carmot agreed to use its *Chemotype Evolution* platform to discover drug leads for Amgen's targets. That deal was expanded two years later. Carmot also penned a partnership with **Genentech** in 2016.

AUTIFONY THERAPEUTICS LTD.
BOEHRINGER INGELHEIM GMBH

Boehringer Ingelheim GMBH entered into an agreement with **GlaxoSmithKline PLC** spin-out **Autifony Therapeutics Ltd.** for the exclusive option to acquire Autifony's Kv3.1/3.2 positive modulator platform (includes Autifony's lead compound AUT00206). (Dec.)

AUT00206 is a small molecule in Phase I trials for both schizophrenia and Fragile X syndrome (received orphan drug designation for Fragile X earlier this year). A new approach to schizophrenia, modulation of Kv3 channels can treat patients early on and has the potential to address cognitive and negative symptoms of the disease along with positive symptoms. BI itself is currently developing BI409306, a phosphodiesterase 9 inhibitor based on enhanced glutamatergic signaling, for schizophrenia and Alzheimer's dementia (in Phase II trials). After completing the work in schizophrenia under the current partnership, the two companies will work on treating hearing disorders and orphan CNS disorders. The tie-up includes an upfront payment of €25mm ($29.5mm), near-term milestones of €17.5mm ($20.7mm),

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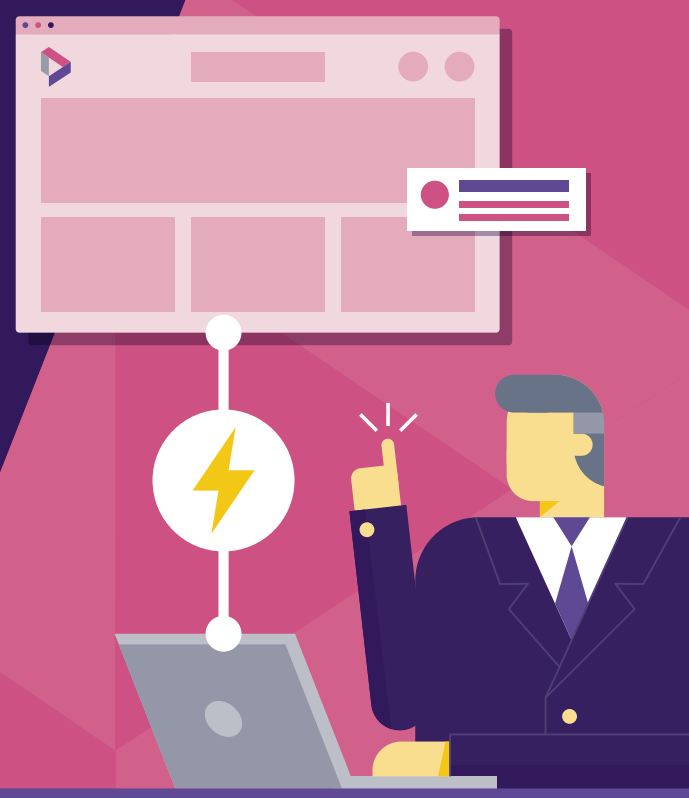

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and future development and pre-commercialization milestones of up to €585mm ($690.3mm) (If all milestones are realized, total deal value would be €627.5mm ($740.5mm).) Autifony was spun out from BI in 2011 by Charles Large, PhD, and Giuseppe Alvaro (prior directors in GSK's Neurosciences Centre of Excellence for Drug Discovery).

AYALA PHARMACEUTICALS
BRISTOL-MYERS SQUIBB CO.

Bristol-Myers Squibb Co. licensed **Ayala Pharmaceuticals** exclusive global rights to develop and sell its gamma secretase inhibitors BMS906024 and BMS986115. (Dec.)

The candidates represent the first in Ayala's pipeline; the company was established this year by Israel Biotech Fund, aMoon, and Harel Insurance. BMS received money up front, an equity stake in Ayala, and is entitled to development, regulatory, and sales milestones, plus tiered annual net royalties. BMS906024 is in Phase I for breast, non-small cell lung, pancreatic, ovarian, and colorectal cancers, as well as melanoma, T-cell lymphoma, and acute lymphocytic leukemia. Preclinical BMS986115 is being evaluated in solid tumors. Both programs target gamma secretase, which activates Notch signaling; Notch pathways are one of the most commonly active in cancer, and are believed to have a pro-oncogenic function and are involved in drug resistance. There are ten other Notch pathway inhibitors in active development, the most advanced of which are in Phase II by **Juno Therapeutics** (LY3039478, to combine with CART (licensed from **Eli Lilly** on the same day as the current deal)) and by **OncoMed** (tarextumab). Ayala claims its strategy for lead candidate BMS906024 will be more targeted than competitors, since the company will be recruiting patients for clinical trials that have certain Notch-activating mutations, and as a result are more likely to respond (however, Lilly, OncoMed, and an earlier-stage company **Cellestia Biotech** have been involved in trials that include a patient preselection or stratification biomarker). Phase II studies of BMS906024 are expected to begin in 2018.

BAYLOR UNIVERSITY
Baylor College of Medicine
FLEXION THERAPEUTICS INC.
GENEQUINE BIOTHERAPEUTICS GMBH

GeneQuine Biotherapeutics GMBH licensed **Flexion Therapeutics Inc.** exclusive worldwide rights to its preclinical gene therapy GQ203 for osteoarthritis (OA). (Dec.)

Flexion will pay $2mm up front, up to $8.7mm in milestones through Phase II proof-of-concept, and up to $54mm in milestones based on later-stage development and global regulatory approvals. Flexion has renamed the candidate FX201. The underlying technology behind the compound was developed by GeneQuine's co-founder Dr. Kilian Guse at **Baylor College of Medicine**. Flexion receives an exclusive license to the IP for human use and will pay Baylor a low-single-digit sales royalty. FX201 is a non-opioid gene therapy being developed for symptomatic pain relief and disease modification in OA patients. It is administered locally and designed to express the anti-inflammatory protein interleukin-1 receptor antagonist when inflammation is present within the joint. Preclinical data suggests that a single injection of FX201 could enable expression of IL-1Ra in an osteoarthritic joint for a least a year. The therapy is expected to enter the clinic in 2019.

BLUEBIRD BIO INC.
TC BIOPHARM LTD.

TC BioPharm Ltd. and **bluebird bio Inc.** penned a deal for the discovery and development of CAR-engineered gamma T-cell therapies for cancer. (Dec.)

The focus of the deal is on TC BioPharm's *ImmuniCAR* platform, which involves modification of gamma delta T-cells to express a chimeric antigen receptor. Such modification helps the cells target and destroy diseased cells while leaving healthy tissue alone. TC BioPharm will use *ImmuniCAR* to discover and develop new solid and blood cancer drug candidates, which it will bring through Phase I/II trials. Bluebird pays $16mm up front and has the exclusive option to take over further development and global commercialization. TC BioPharm could also get R&D and sales milestones, plus tiered royalties. Bluebird's CART pipeline includes lead project bb2121, in Phase II for multiple myeloma with partner **Celgene**.

COLLEGIUM PHARMACEUTICAL INC.
DEPOMED INC.

Collegium Pharmaceutical Inc. is licensing from fellow CNS drug delivery company **Depomed Inc.** exclusive US rights to oral opioid analgesic *Nucynta* (tapentadol), including both the immediate-release (IR) and extended-release (ER) formulations. (Dec.)

Depomed receives a $10mm up-front payment and cash reimbursement for its cost of inventory. For the first four years of the agreement, Collegium provides minimum annual royalties of $135mm (payable at $33.75mm quarterly), plus additional royalties depending on annual net sales thresholds (25% for sales between $233-258mm, plus 17.5% for sales above $258mm). After four years (beginning January 1, 2022), the royalty mechanism remains the same, but without the guaranteed $135mm amount; Depomed will get a 58% royalty on sales up to $233mm, 25% royalties on sales between $233-258mm, plus 17.5% on sales above $258mm. The royalty scheme may be adjusted post patent expiration (which is estimated at 2025, the earliest). Between years one through four, Collegium can terminate the deal for a fee of $25mm, while Depomed may cancel the agreement if during this time the 12-month sales of *Nucynta* fall below $180mm. Depomed gained exclusive US rights to *Nucynta* under a 2015 deal worth $1.05bn with **Janssen Pharmaceuticals**. Janssen's **Ortho-McNeil** division originally licensed the drug in more than 80 countries from its originator **Grunenthal** through a 2003 collaboration. (It's marketed as both *Palexia* and *Palexis* outside the US.) To manage pain severe enough to require daily, around-the-clock, long-term opioid treatment--including indications in low back pain and diabetic neuropathy--IR *Nucynta* was approved in the US in 2008 (for moderate-to-severe acute pain), followed by FDA clearance of *Nucynta ER* (for moderate-to-severe chronic pain) in 2011. For fiscal 2016, *Nucynta* generated $281mm in global net sales (and $183mm so far for the nine months ended September 30, 2017). *Nucynta* complements and broadens Collegium's existing pain management franchise, including oral *Xtampza ER* (oxycodone) for chronic low back pain, approved in the US last year, which uses Collegium's *DETERx* abuse-deterrent delivery technology. Depomed will benefit from Collegium's sole focus on pain management (a business shift adapted in 2012) and the divestiture will enable it to cut marketing costs and its salesforce for *Nucynta* and to build up additional CNS areas in its specialty business.

COMERCIALIZADORA BIORENAL SPA
ROCKWELL MEDICAL INC.

Comercializadora BioRenal SPA licensed exclusive rights to sell the iron replacement therapy *Triferic* (ferric pyrophosphate) in Chile for **Rockwell Medical Inc.** (Dec.)

BioRenal is responsible for all regulatory, marketing, and distribution activities for an initial term of five years (renewable for five years based on annual minimum purchase requirements). *Triferic* is currently the only FDA-approved drug to replace iron and maintain hemoglobin in end-stage renal disease patients who are on hemodialysis and have anemia. **Quimica Europea** got rights in Peru earlier this month, and **Wangbang Pharmaceutical** and **ARAM Medical** have rights in China and the Middle East, respectively.

CONFO THERAPEUTICS NV
ROCHE

Confo Therapeutics NV licensed **Roche** exclusive rights to discover, develop, manufacture, and sell small-molecule G-protein coupled receptor (GPCR) agonists for neurological and developmental disorders. (Dec.)

The deal has an initial term of 30 months, during which Roche will pay €6mm ($7mm) combined in an up-front payment, preclinical milestones, and research funding. The Big Pharma is also responsible for up to €81.5mm in development, regulatory, and commercialization milestones, as well as tiered royalties. Confo, a 2015 spin-off of **VIB** and **Vrije Universiteit Brussel**, has developed a drug discovery tool called *CONFO*, which is used to stabilize signaling conformers of GPCR targets in active states. This allows for targeting of structural features of GPCRs that were previously not druggable. The company is identifying, screening, and optimizing lead GPCR agonists, known as Confobodies. Last year, Confo completed a €6.7mm ($7.3mm) Series A financing to fund its work. Since being founded, Confo has also signed a CNS drug discovery deal with **Lundbeck**, which plans to use the agreement to build new programs in schizophrenia, depression, Alzheimer's, and Parkinson's.

DAEWOONG PHARMACEUTICAL CO. LTD.
HanAll BioPharma Co. Ltd.
ROIVANT SCIENCES GMBH

HanAll BioPharma Co. Ltd. granted **Roivant Sciences GMBH** exclusive rights to develop, manufacture, and sell its Phase I anti-FcRn monoclonal antibody HL161 for pathogenic IgG-mediated autoimmune diseases. (Dec.)

Roivant's rights include the US, Canada, Mexico, EU, UK, Switzerland, Latin America, the Middle East, and North Africa. Industry sources report that HanAll is eligible for a $30mm up-front payment, $20mm in R&D funding, $452.5mm in milestones, and a fixed royalty of $502.5mm. HL161 targets the neonatal Fc receptor and has potential to treat severe autoimmune diseases for which there are currently no cure, including myasthenia gravis, chronic thrombocytopenia, optic neuritis, polyneuropathy, and lupus. Roivant has five drug development companies under its umbrella, each focusing on a separate therapy area. While it was not explicitly disclosed in the current deal which subsidiary will take on HL161, the most likely entity is **Enzyvant**, which houses projects for rare diseases including complete DiGeorge syndrome and acid ceramidase deficiency.

DAIICHI SANKYO CO. LTD.
PUMA BIOTECHNOLOGY INC.

Daiichi Sankyo Co. Ltd. and **Puma Biotechnology Inc.** agreed to study the combination of two of their cancer therapies as a potential new treatment approach for HER2-mutated or HER2-positive solid cancers. (Dec.)

Included in the preclinical-stage collaboration are Daiichi's DS8201 (trastuzumab), an antibody-drug conjugate in Phase II trials for HER2-positive breast, stomach, and esophageal cancers. Puma brings its *Nerlynx* (neratinib), an EGFR inhibitor marketed for HER2-positive breast cancer patients who have already undergone treatment with adjuvant trastuzumab therapy. The partners will co-sponsor the combination research, which is to be undertaken at **Memorial Sloan Cancer Center**.

DICE MOLECULES SV LLC
ROCHE
Genentech Inc.

In a multi-year alliance, **DiCE Molecules SV LLC** will discover and develop small molecules against targets selected by **Roche**'s **Genentech Inc.** (Dec.)

The agreement comes just under two years since DiCE signed its first major Big Pharma deal. In March 2016, the biotech formed a five-year collaboration with **Sanofi** to develop oral small molecules against 12 targets. Including up-front and milestone payments, DiCE could get up to $2.2bn. DiCE and Genentech have not released any financial details about their deal, only to say that DiCE will get an up-front fee plus research, development, regulatory, and commercial milestones. DiCE uses various directed chemical evolution technologies, including DNA-encoded libraries and mix-and-split combinatorial chemistry, to identify molecules interacting with drug targets that were previously inaccessible. DiCE also says this platform, developed at **Stanford University**, can scale up significantly the number of these hits to lead candidates across several different types of structural families. On the same day it announced the DiCE alliance, Roche also formed a partnership with **Confo Therapeutics**, to develop GPCR agonists for neurological and developmental disorders.

EUROFARMA LABORATORIOS SA
SUMMIT THERAPEUTICS PLC

Summit Therapeutics PLC licensed **Eurofarma Laboratorios SA** exclusive rights to commercialize its antibiotic ridinilazole for Clostridium difficile infection (CDI) in Argentina, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Dominican Republic, Uruguay and Venezuela. (Dec.)

Summit will handle all clinical development of ridinilazole, while Eurofarma is responsible for obtaining regulatory approvals in the licensed territories. Summit retains all rights outside of Latin America. Summit receives $2.5mm up front, $3.75mm tied to patient enrollment targets in one of two planned Phase III trials, $1mm upon the achievement of the primary endpoint in the Phase III study, $1.2mm related to the receipt of pricing and reimbursement approval of the drug, and up to $1.2mm upon the first commercial sale of the product in two of certain specified countries. In addition, Eurofarma could shell out $3mm when cumulative net sales equal or exceed $20mm, $7.5mm on sales $50mm or over, and $7.5mm when sales reach $100mm or more. Each subsequent achievement of another $100mm in sales will result in additional milestone payments, which, when combined with the anticipated product supply transfer payments, is expected to provide payments estimated to range from a mid- to high-teens percentage of cumulative net sales. The agreement also includes product supply transfer payments which are expected to provide a return equivalent to a high-single-digit to low-double-digit percentage of net sales. Ridinilazole is an oral small molecule currently in Phase II, with Phase III trials expected to commence in H1 2018. Summit chose Eurofarma as a partner because of its strong network and expertise in Latin America, where CDI is a serious problem.

FIVE PRIME THERAPEUTICS INC.
ZAI LAB LTD.

Five Prime Therapeutics Inc. granted **Zai Lab Ltd.** exclusive rights to develop and sell the anti-FGFR2b antibody FPA144 in China, Hong Kong, Macau, and Taiwan. (Dec.)

Zai pays $5mm up front and up to $39mm in development and regulatory milestones, plus royalties from the high-teens to low-twenties in the licensed territories. (Five Prime has also agreed to pay Zai low-single-digit royalties on sales in the rest of the world.) FPA144, an isoform-selective humanized mAb designed to target tumors that overexpress the fibroblast growth factor splice variant FGFR2b, is in Phase I trials for gastric and gastro-esophageal junction cancers. Zai is responsible for conducting a Phase III trial and eventual commercialization in Greater China. Zai's pipeline includes programs in development for immune-mediated diseases and various cancers, including lead candidate niraparib (ZL2306) for ovarian, breast, and lung cancers. The company has Chinese rights to niraparib under a 2016 collaboration with **Tesaro**.

GENEXINE INC.
I-MAB BIOPHARMA

I-MAB Biopharma licensed exclusive rights in China, Taiwan, Hong Kong, and Macau to **Genexine Inc.**'s engineered IL-7 antibody *HyLeukin*, which completed Phase I for solid tumors. (Dec.)

I-MAB pays $12mm money up front, up to $536mm in milestones, and tiered low-single-digit royalties based on regulatory approvals and sales. This is not the first tie-up for the partners. I-MAB was formed earlier this year following the merger of

Third Venture and Tasgen. Tasgen and Genexine teamed up in 2015 when Tasgen took on rights to five of Genexine's candidates in development (in the metabolic, blood, and GI spaces). I-MAB will now develop and sell Genexine's *HyLeukin*, an immuno-oncology compound that consists of an engineered IL-7 molecule fused with Genexine's hyFc (hybrid Fc) long-acting platform technology and is designed to enhance anti-tumoral T-cell immunity. The deal is the second for I-MAB in just a few months. In November, it took on Chinese rights to MOR202 from **MorphoSys**. That project is in Phase II trials for relapsed/refractory multiple myeloma.

HANX BIOPHARMACEUTICALS INC.
ONCONOVA THERAPEUTICS INC.

Onconova Therapeutics Inc. granted **HanX Biopharmaceuticals Inc.** rights to develop and sell its preclinical cancer project ON123300 in China. (Dec.)

HanX pays money up front, milestones for regulatory and commercialization achievements, and sales royalties. The candidate is a CDK4/6 and ARK5 inhibitor that is being studied for both solid and blood cancers. The partners believe that due to its dual modes of action, ON123300 has the potential to overcome limitations of current CDK4/6 inhibitors including palbociclib (**Pfizer**'s *Ibrance*). HanX is responsible for funding and carrying out all regulatory activities in its territories, while Onconova retains rights in the rest of the world, and can use any regulatory data produced by HanX for IND and further regulatory filings in the US.

JOHNSON & JOHNSON
Janssen Pharmaceutical Cos.
Janssen R&D LLC
MEMORIAL SLOAN KETTERING CANCER CENTER
XYNOMIC PHARMACEUTICALS INC.

Xynomic Pharmaceuticals Inc. and **Janssen R&D LLC** are partnering to evaluate Xynomic's abexinostat with Janssen's ibrutinib for relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) or relapsed/refractory mantle cell lymphoma (r/r MCL). (Dec.)

The Phase I/II trial will be led by **Memorial Sloan Kettering Cancer Center**'s Drs. Anita Kumar and Anas Younes to assess the combination of the two compounds in r/r DLBCL or r/r MCL in addition to studying the biologic predictors of response and resistance to dual BCRi and HDACi inhibition. Abexinostat is in Phase II for various lymphomas (DLBCL, MCL, non-Hodgkin's, Hodgkin's, follicular, and cutaneous and peripheral T-cell), soft tissue sarcoma, chronic lymphocytic leukemia, colorectal cancer, and myeloma, and in preclinical studies for renal cancer. Ibrutinib is sold as *Imbruvica* by Janssen Biotech and **Pharmacyclics** for MCL, chronic lymphocytic leukemia, Waldenstrom's hypergammaglobulinaemia, and graft-versus-host disease. It is also being studied in Phase III for multiple lymphomas and pancreatic cancer; in Phase II for B-cell lymphoma, myeloma, and breast, non-small cell lung, renal, colorectal, stomach, and genitourinary cancers.

JUNO THERAPEUTICS INC.
ELI LILLY & CO.

Eli Lilly & Co. granted **Juno Therapeutics Inc.** rights to its gamma-secretase inhibitor LY3039478, which Juno will investigate as a treatment for multiple myeloma. (Dec.)

Financial terms were not disclosed. Lilly has the candidate in Phase II trials for T-cell lymphoma and acute lymphocytic leukemia (as well as Phase I for solid tumors), but Juno is interested in implications the compound may have for myeloma when combined with B-cell maturation antigen (BCMA)-directed CAR T cells, as research has shown that gamma-secretase inhibitors can increase surface expression of BCMA on tumors, including myeloma, and could increase the strength of BCMA-directed CART therapy. Juno hopes to have a GSI/BCMA CART candidate in clinical trials next year; it is currently recruiting patients for a Phase I trial of its BCMA-directed CAR T cells together with the chemo drug *Revlimid* (lenalidomide). Concurrent with the Lilly deal, the company also licensed GSI/BCMA intellectual property from biomarker firm **OncoTracker** and the **Fred Hutchison Cancer Research Center**.

MERCK & CO. INC.
NEON THERAPEUTICS

Neon Therapeutics and **Merck & Co. Inc.** entered a trial collaboration to study the combination of Neon's neoantigen cancer vaccine with Merck's anti-PD-1 therapy, together with chemotherapy, for lung cancer. (Dec.)

Neon brings to the deal its Phase I NEOPV01, a personal neoantigen vaccine

that uses DNA mutations from a patient's own tumor and is being studied for brain, bladder, and non-small cell lung cancer, and melanoma. Merck brings *Keytruda* (pembrolizumab), an anti-PD-1 antibody marketed for melanoma, non-small cell lung cancer, head and neck cancer, Hodgkin's lymphoma, and bladder, stomach, and esophageal cancers. (It is also in over two dozen clinical trials for other solid and blood cancers.) The companies will study their therapies together as part of a regimen with the established chemotherapeutics carboplatin and pemetrexed in a Phase Ib safety, tolerability, and efficacy trial for untreated advanced or metastatic nonsquamous non-small cell lung cancer. Similar to other trial collaborations involving NEOPV01 (with partners **Apexigen** and **Bristol-Myers Squibb**), Merck and Neon will also examine neoantigen-specific immune response in peripheral blood and tumor tissue, as well as other immune response markers.

MESOBLAST LTD.
TIGENIX NV

Mesoblast Ltd. granted **TiGenix NV** exclusive rights to patents surrounding the use of adipose-derived mesenchymal stem cells to treat perianal fistulas. (Dec.)

The licensed IP will support continued development and the upcoming launch of TiGenix's Cx601 (darvadstrocel), an intra-lesionally injected suspension awaiting approval in Europe and in Phase III US trials for perianal fistulas in patients with Crohn's disease. TiGenix pays €5mm ($5.9mm) up front; €5mm within 12 months; and up to €10mm in regulatory milestones, plus single-digit sales royalties. **Takeda Pharmaceutical** has exclusive ex-US rights to Cx601 under a deal signed last year; the current rights from Mesoblast allow TiGenix sublicense IP to Takeda (and other third parties) as needed.

MUNDIPHARMA INTERNATIONAL CORP. LTD.
NTC SRL

NTC SRL licensed **Mundipharma International Corp. Ltd.** rights to distribute a portfolio of ophthalmic products in the Middle East and Africa Region. (Dec.)

Terms of the deal were not disclosed however included in the agreement are products for blepharitis, dry eye, allergy, and glaucoma. Just last month Mundipharma received exclusive rights from **APR Applied Pharma Research** to sell the *Nexodyn* wound cleanser in Africa and the Levant Region. And three months prior to that the firm got global rights to **CellAct Pharma**'s Phase II etoposide prodrug CAP7.1 for biliary tract cancer.

QUIMICA EUROPEA
ROCKWELL MEDICAL INC.

Rockwell Medical Inc. licensed **Quimica Europea** exclusive rights to sell the anemia therapy *Triferic* (ferric pyrophosphate) in Peru. (Dec.)

The initial term of the deal is five years, and is renewable for an additional five years based on annual minimum purchase requirements. Quimica will pursue regulatory activities in Peru, and Rockwell will be responsible for manufacturing. *Triferic* is the only drug approved by the FDA to replace iron and maintain hemoglobin levels in hemodialysis patients who have anemia. Under deals signed last year, **ARAM Medical** has rights to the drug in the Middle East, and **Wanbang Biopharmaceuticals** can sell it in China.

REZOLUTE INC.
XOMA CORP.

Concurrent with changing its name from AntriaBio, **Rezolute Inc.** received exclusive worldwide rights to develop, manufacture, and commercialize **Xoma Corp.**'s Phase II monoclonal antibody XOMA358 (renamed RZ358) for hypoglycemia caused by congenital hyperinsulinism. (Dec.)

Rezolute will pay Xoma $6mm in cash and will issue $12mm in common stock as Rezolute completes certain financing milestones in 2018. Xoma could also receive up to $222mm in clinical, regulatory, and sales milestones plus royalties in the high-single digits to mid-teens (*Strategic Transactions* assumes 9-16%) on annual net sales of RZ358. Xoma is also entitled to low-single-digit royalties on sales of Rezolute's diabetes compound AB101 and other products developed from its extended-release and oral plasma kallikrein inhibitor platforms. (Just a few months ago, Rezolute received exclusive rights to a portfolio of oral plasma kallikrein inhibitors from **ActiveSite**.) RZ358 is an insulin receptor antagonist that has demonstrated proof-of-concept through Phase IIa trials. It already has orphan drug status in the US and EU and Rezolute plans to advance clinical development in 2018. The company will handle all regulatory approvals and commercialization.

Financings

ACER THERAPEUTICS INC.

Acer Therapeutics Inc. (rare and orphan diseases) netted $10.4mm in a follow-on public offering of 916.7k common shares at $12. The company will use the offering proceeds to fund R&D, and to seek regulatory approval and invest in pre-commercial activities for *EDSIVO* (celiprolol; being developed for the treatment of vascular Ehlers-Danlos syndrome in the US). (Dec.)

Investment Banks/Advisors: HC Wainwright & Co.; William Blair & Co.

ARGENX SE

Therapeutic antibody developer **argenx SE** (cancer and autoimmune diseases) netted $249.6mm through an upsized public offering of 5.1mm American Depositary Shares (including the overallotment; representing 5.1mm ordinary shares) at $52. The company originally filed to sell 3.5mm ADSs. Funds will support a variety of corporate and development activities, including pre-registration work on ARGX113, an antibody fragment entering Phase III trials with potential in severe autoimmune diseases, including multiple sclerosis, immune thrombocytopenia, systemic lupus erythematosus, myasthenia gravis, and skin blistering diseases (Dec.)

Investment Banks/Advisors: Cowen & Co. LLC; JMP Securities LLC; Kempen & Co.; Piper Jaffray & Co.; Wedbush PacGrow Life Sciences

BLUEBIRD BIO INC.

Gene editing firm **bluebird bio Inc.** (oncology and severe genetic diseases) netted $570mm through the public sale of 3.24mm common shares at $185. Funds are earmarked for the potential exercise of co-development and co-promotion rights in the US to bb2121, bluebird's multiple myeloma candidate that is licensed to **Celgene**; for continued development of bb21217 in multiple myeloma; for development, regulatory, and launch activities surrounding *LentiGlobin* for transfusion-dependent B-thalassemia in the US and Europe; and continued R&D of bluebird's pipeline of CAR and TCR projects. (Dec.)

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

CATALYST BIOSCIENCES INC.

Catalyst Biosciences Inc. netted $9.8mm through a public sale of 1.1mm common shares at $9.50. The company is developing protease-based therapies for hemophilia and plans to use the offering proceeds for continued R&D and general corporate expenses. (Dec.)

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

DENALI THERAPEUTICS INC.

Denali Therapeutics Inc. (neurodegenerative disease drug development) netted $267.4mm in an initial public offering of 15.9mm shares (including the overallotment) at $18, the mid-point of its anticipated range. The company had originally planned to sell 8.33mm shares. (Dec.)

Investment Banks/Advisors: Evercore Partners; Goldman Sachs & Co.; JP Morgan & Co.; Morgan Stanley & Co.

DICERNA PHARMACEUTICALS INC.

Dicerna Pharmaceutical Inc. (RNAi therapeutics) netted $37.6mm through the follow-on offering of 5.7mm common shares at $7 to support preclinical and clinical studies of candidates. (Dec.)

Investment Banks/Advisors: Evercore

Partners; HC Wainwright & Co.; Stifel Nicolaus & Co. Inc.; SunTrust Banks Inc.

EDITAS MEDICINE INC.

Editas Medicine Inc. (genome editing) netted $50mm in a follow-on public offering of 1.97mm common shares at $26. The company will use the proceeds from the offering to fund trials of LCA10 (genome editing therapeutic for Leber Congenital Amaurosis 10 using an AAV vector) and other genetic infectious eye disease programs; to help support preclinical studies of non-malignant hematologic diseases; to pay for preclinical studies of engineered T cell therapies for cancer (through existing collaboration with **Juno Therapeutics**); to expand its platform technology; and for potential future licensing or acquisitions. (Dec.)

Investment Banks/Advisors: Morgan Stanley & Co.

EYENOVIA INC.

Ophthalmic-focused **Eyenovia Inc.** filed for its initial public offering. (Dec.)

Investment Banks/Advisors: Ladenburg Thalmann & Co. Inc.; Roth Capital Partners

FENNEC PHARMACEUTICALS INC.

Fennec Pharmaceuticals Inc. netted $20mm through a public sale of 2.49mm common shares (including partial exercise of the overallotment) at $8.50. Funds will support regulatory and launch activities surrounding *Pedmark* (sodium thiosulfate), a Phase III agent designed to prevent cisplatin-induced hearing loss (ototoxicity) in children undergoing platinum-based chemotherapy. (Dec.)

Investment Banks/Advisors: HC Wainwright & Co.; Wedbush PacGrow Life Sciences

FIBROCELL SCIENCE INC.

Regenerative medicine company **Fibrocell Science Inc.** (autologous cell and gene therapies focused on skin and connective tissue disorders) netted $9.9mm through the public offering of 7.7mm units (consisting of 7.7mm common shares and five-year warrants to purchase 13.6mm common shares at $0.77) at $0.77 and 5.9mm pre-funded warrants at $0.76. (In addition, there was a partial exercise of the overallotment of warrants to purchase up to 410.6k shares of common stock.) Fibrocell will use the proceeds to advance its pipeline, which includes FCX007 (Phase I/II for recessive dystrophic epidermolysis bullosa) and FCX013 (preclinical for scleroderma). It will also use the funds for continued development of potential candidates under its 2012 collaboration (expanded in 2015) with **Intrexon**, in which it's using the latter's technology to develop genetically modified fibroblasts for chronic inflammatory and degenerative diseases of the joint. The program, in the research stage, is currently pursuing a gene-therapy for arthritis and related conditions. (Dec.)

Investment Banks/Advisors: HC Wainwright & Co.

GLOBAL BLOOD THERAPEUTICS INC.

Global Blood Therapeutics Inc. (lead candidate is for sickle cell disease) netted $96.3mm through the public offering of 2.6mm common shares at $36.80. Proceeds will support late-stage trials of lead candidate voxelotor (GBT440) for sickle cell disease in adults and children. (Dec.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.

GW PHARMACEUTICALS PLC

GW Pharmaceuticals PLC (cannabinoid products) netted $299.1mm in a follow-on public offering of 2.76mm American Depository Shares (ADS; representing 33.1mm ordinary shares including full exercise of the 360k ADS over-allotment option) at $115 per ADS. The company will use the offering proceeds to fund pre-launch commercialization activities and to expand manufacturing of *Epidiolex* (pharmaceutical formulation of cannabidiol in development for rare childhood-onset epilepsy disorders), and to advance other pipeline candidates. (Dec.)

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

HERON THERAPEUTICS INC.

Heron Therapeutics Inc. (pain and supportive cancer care treatments) netted $142.5mm through a public offering of 9.68mm common shares at $14.75. Funds will support marketing of *Sustol* (granisetron injection) for chemotherapy-induced nausea and vomiting (CINV); commercial launch of *Cinvanti* (aprepitant), also for CINV; late-stage development of HTX011, a bupivacaine/meloxicam combo for prevention of post-operative pain; and additional development and corporate activities. (Dec.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.

LEXICON PHARMACEUTICALS INC.

Lexicon Pharmaceuticals Inc. (gene-targeting therapies for diabetes, carcinoid syndrome, and neuropathic pain) entered into a $200mm non-dilutive term loan agreement with Biopharma Credit PLC and Biopharma Credit Investments (funds managed by Pharmakon Advisors). The loan bears interest at 9%, and matures in December 2022. Lexicon borrowed an initial tranche of $150mm immediately and can access the remaining $50mm until March 2019 if net sales of the company's carcinoid syndrome diarrhea drug *Xermelo* (telotristat) exceed $25mm in the preceding quarter. Funds will support Lexicon's financial commitments under a 2015 Type II diabetes deal with **Sanofi** for sotagliflozin, and will also be used to finalize sotagliflozin applications for Type I diabetes. (Dec.)

MADRIGAL PHARMACEUTICALS INC.

Madrigal Pharmaceuticals Inc. netted $111.7mm through a public offering of 1.5mm common shares at $83. The company is developing thyroid hormone receptor modulators for cardiovascular and fatty liver diseases, and recently announced that its lead candidate MGL3196 achieved the primary endpoint in a Phase II trial for biopsy-proven nonalcoholic steatohepatitis. (Dec.)

Investment Banks/Advisors: Evercore Partners; Goldman Sachs & Co.; HC Wainwright & Co.; JMP Securities LLC; Roth Capital Partners

NORTHWEST BIOTHERAPEUTICS INC.

Northwest Biotherapeutics Inc. (immunotherapies for cancer) netted $11.9mm through the private sale of 7mm Series A preferred shares (each convertible into 10 common) at $1.70 per share. Investors (the majority of whom are new to the company) also received two-year Class D-1 warrants to purchase 70.6mm common at an exercise price of $0.22. (Dec.)

NOVARTIS AG
ULTRAGENYX PHARMACEUTICAL INC.

Ultragenyx Pharmaceutical Inc. sold **Novartis AG** its rare pediatric disease priority review voucher (PRV), which the FDA awarded to Ultragenyx last month upon approval of its enzyme replacement therapy *Mepsevii* (vestronidase alfa) for the rare genetic, metabolic lysosomal storage disorder mucopolysaccharidosis VII (MPS VII; otherwise known as Sly syndrome). *Mepsevii*, originally licensed from **St. Louis University** in 2012, is designed to replace the deficient lysosomal enzyme beta-glucuronidase (required for the breakdown of certain carbohydrates) in both adult and children with MPS VII. (Dec.)

ODONATE THERAPEUTICS LLC

Odonate Therapeutics LLC (cancer drug development) netted $139.5mm through its initial public offering of 6.25mm common shares at $24. The company had originally hoped to sell 5.88mm shares for between $24-27 apiece. (Dec.)

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

PROTEOSTASIS THERAPEUTICS INC.

Proteostasis Therapeutics Inc. (mostly focused on developing cystic fibrosis therapies) netted $43.2mm in a follow-on offering of 9.2mm common shares (including the overallotment) priced at

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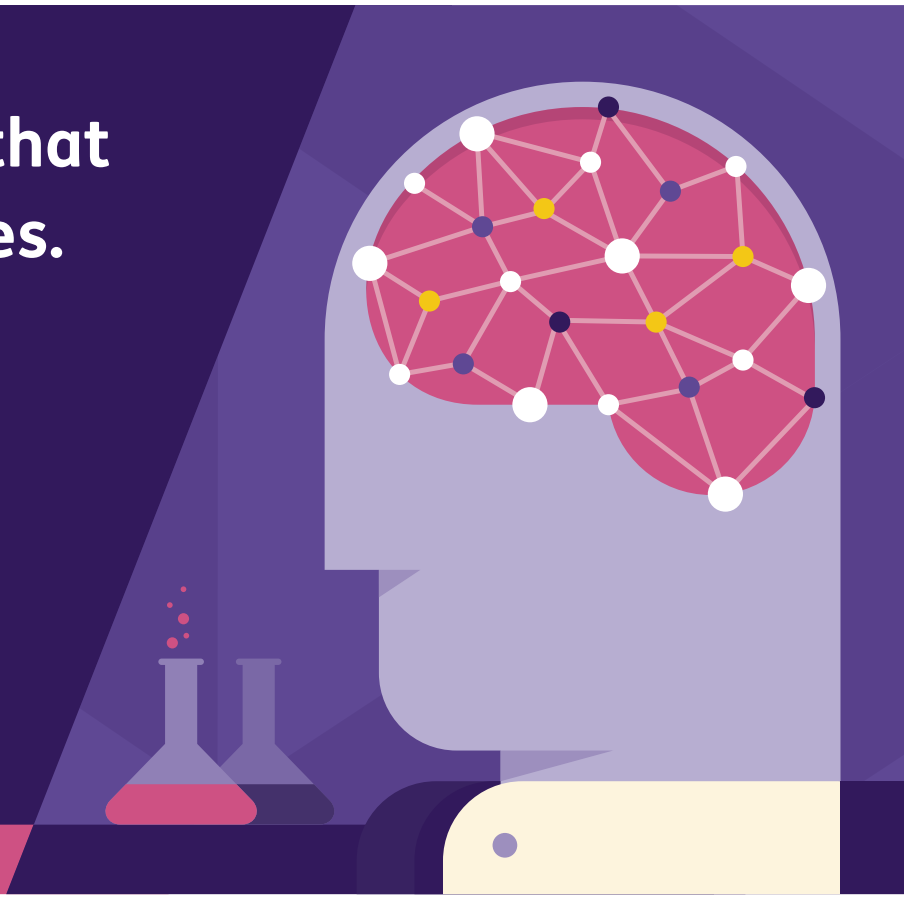

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$5 each. The company will use some of the funds to advance its double and triple combination therapies in dose-range-finding and proof-of-concept studies; move its double combination therapy of PTI801 and PTI808 through the Phase I; and advance triple combination PTI801, PTI808, and PTI428 in a Phase I trial. (Dec.)

Investment Banks/Advisors: HC Wainwright & Co.; Leerink Partners LLC; RBC Capital Markets

REVANCE THERAPEUTICS INC.

Revance Therapeutics Inc. (neuromodulating drug delivery) netted $157mm through the public offering of 5.4mm shares (including the overallotment) at $31. (Selling shareholders sold an additional 750k shares.) The company will use the proceeds for R&D (including potential collaborations) and clinical trial expenses. Its pipeline includes two botulinum toxin Type A candidates formulated using its peptide delivery technology. RT002 is an injectable for glabellar (frown) lines (Phase III, for which it has a 72% likelihood of approval (10% above average), per *Biomedtracker*); cervical dystonia (Phase II); and plantar fasciitis (Phase II). RT001 is a topical gel in preclinical studies for therapeutic and aesthetic applications. Following the failure of RT001 to meet co-primary and other endpoints in a Phase III trial last year, the company discontinued its development in lateral canthal lines (crow's feet) and axillary hyperhidrosis (excessive sweating) indications. (Dec.)

Investment Banks/Advisors: Barclays Bank PLC; Cantor Fitzgerald & Co.; Cowen & Co. LLC; Goldman Sachs & Co.; SunTrust Banks Inc.; William Blair & Co.

VISTAGEN THERAPEUTICS INC.

VistaGen Therapeutics Inc. (neuro-focused stem cell therapies) netted $13.95mm through the public offering of 10mm shares at $1.50 together with five-year warrants to purchase 10mm common shares at $1.50. VistaGen will use the proceeds primarily to advance lead prodrug candidate AV101 (L-4-chlorokyurenine), an oral NMDA receptor antagonist expected to begin a Phase II adjunctive treatment study in major depressive disorder in Q1 2018. Because of its unique mechanism of action, the company believes AV101 may also have potential in multiple other CNS disorders; it has already shown to be safe and well-tolerated in two Phase I safety studies in neuropathic pain. (Dec.)

Investment Banks/Advisors: Chardan Capital Markets; Oppenheimer & Co. Inc.

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