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THE BUSINESS & MEDICINE REPORT
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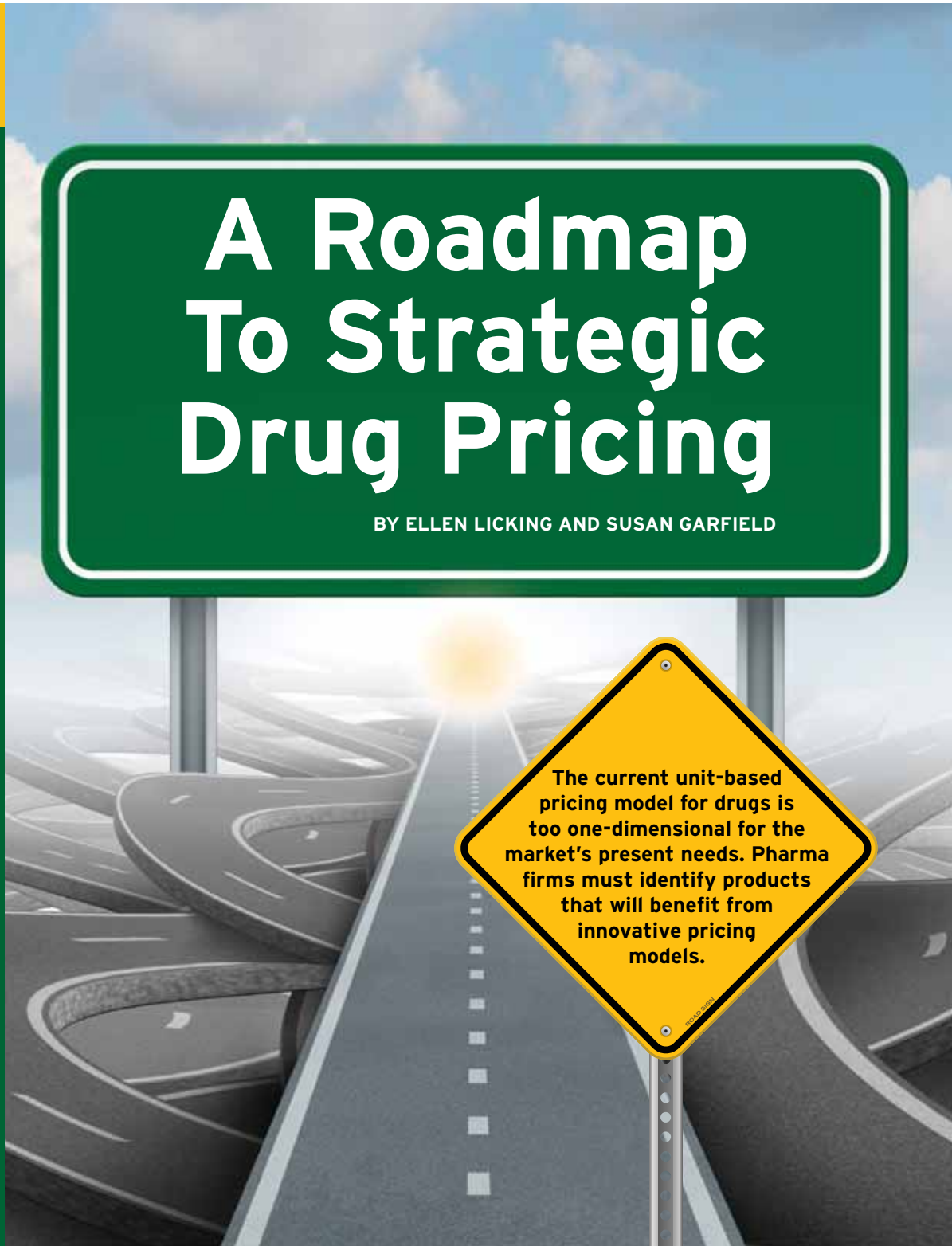
MARCH 2016 VOL. 34 / NO. 3

INSIDE



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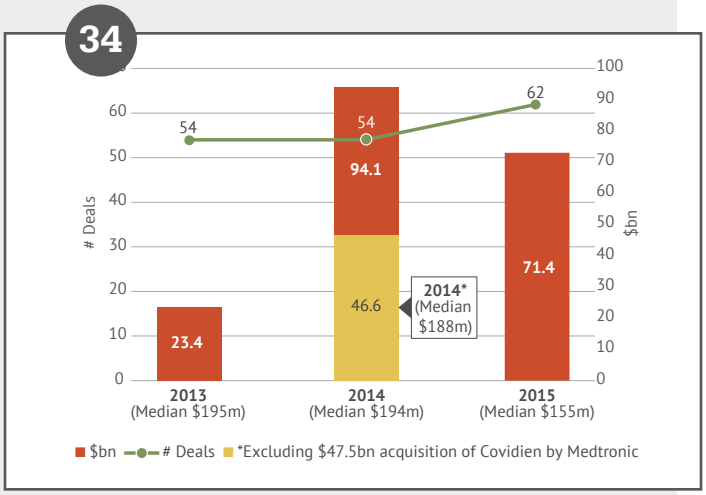

Medtech M&A 2013 - 2015

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Amanda Micklus

Device/Diagnostics Quarterly Dealmaking Statistics, Q4 2015

Amanda Micklus and Maureen Riordan

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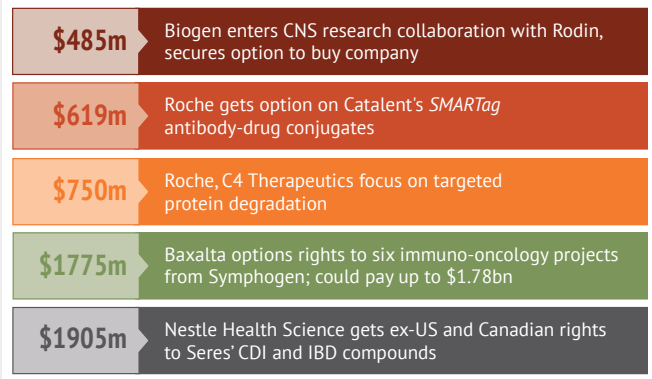
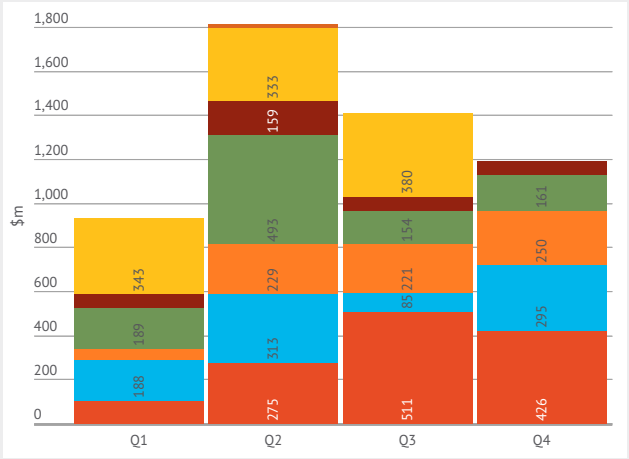


ONLINE ONLY:
Top Alliances In January 2016



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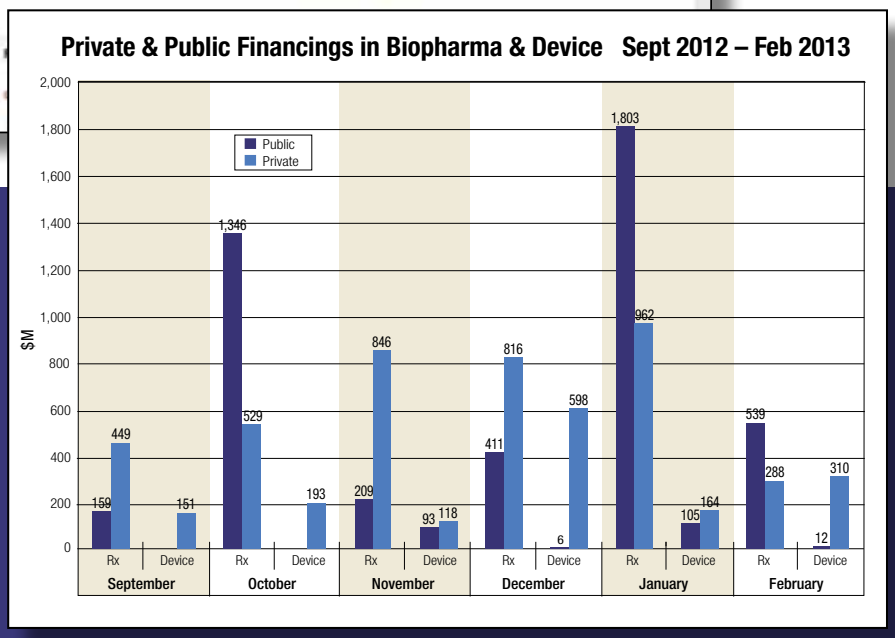

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Biopharma Dealmaking

NESTLÉ GETS SERIOUS WITH SERES DEAL

A year after taking a 17% stake in microbiome specialist **Seres Therapeutics Inc.**, **Nestle SA**'s **Nestle Health Science SA** division (NHSc) has acquired rights outside of the US and Canada to four of Seres' gastrointestinal product candidates. The transaction is noteworthy for both parties. Seres secures one of the biggest up-front payments in several years for an ex-US product license of an unapproved set of drug candidates outside of cancer. NHSc strengthens its brand by demonstrating its continuing commitment to adding therapeutic nutrition products to its GI franchise – an area where previous pharmaceutical development efforts through partners have yet to succeed.

Under the agreement, signed in January, NHSc gains commercial rights to Seres' lead biologic, SER-109, for treating multiply recurrent *Clostridium difficile* infection (CDI); SER-262 for primary CDI; and the inflammatory bowel disease (IBD) candidates SER-287 for ulcerative colitis (UC) and SER-301 for Crohn's disease. NHSc is paying $120 million up front and will contribute to development efforts, potentially paying over $1.9 billion including royalties. Seres expects to receive $30 million in milestone payments in 2016 for the planned start of a Phase Ib study of SER-262 and the Phase III trial of SER-109. It will also receive 33% of development costs for eventual global Phase III trials of the other product candidates included in the deal. Generally, NHSc's deals call for partners to take responsibility for regulatory development.

NHSc has a consumer business and a significant business in medical nutrition feeding patients in hospitals as well as in home care. It also sees a large opportunity in developing nutritional therapies – a space very similar to a biotech in terms of the innovation process and the way products are commercialized, says CEO Greg Behar. In that respect, the company has evolved, he says, from its early days under its founding CEO, Nestlé EVP Luis Cantarell, whose vision for NHSc centered on providing nutritional products tailored to specific needs of consumers and patients. (*See "Nestlé Health Science Plans Continuum Of Care"* — "The Pink Sheet," *June 20, 2011*.)

"The evolution is largely in having a greater understanding of what it takes to develop pharma-like products in therapeutic nutrition," says Behar, who joined NHSc in mid-2014 from Boehringer Ingelheim Pharmaceuticals Inc., where he was president and CEO. NHSc is taking a broad portfolio approach, he says, including investments in both nutritional technologies and drugs. And having compounds derived from natural products allows it to go down different development paths depending on the strength of evidence of therapeutic benefit: consumer products, medical nutrition and therapeutic nutrition.

One of NHSc's first deals was the 2011 acquisition of **Prometheus Laboratories Inc.**, a US-footprint company with a strong reputation in GI diagnostics that also provides some development capabilities for NHSc products globally. It is also a marketer of a few hard-to-use specialty drugs: Prometheus has licensed **GlaxoSmithKline PLC**'s drug *Lotronex* (alosetron) for irritable bowel syndrome after GSK withdrew the product and **Novartis AG**'s *Proleukin* (interleukin 2) for use in cancer treatment, among others.

"Everything leading to better GI health and mucosal healing in IBD is a top-line project for Prometheus," Behar says. That could include better characterization of responders and identifying potential biomarkers for monitoring, detecting and eventually predicting improvement in the healing process in IBD. The acquisition enhanced NHSc's ability to gain access to GI docs. But commercially, Prometheus now appears to be stagnating, especially on the drug side. Other NHSc investments and collaborations have expanded its range in the GI drug development space, but thus far it's hard to point to much success.

In 2012, NHSc launched a 50-50 joint venture, Nutrition Science Partners Ltd., with **Hutchison China MediTech Ltd.** (Chi-Med) focused on traditional Chinese medicine. (*See "With Traditional Chinese Medicine Deal, Nestle's Health Science Business Reaches Into Pharma Development"* — "The Pink Sheet" DAILY, *December 2, 2012*.) An interim analysis of a Phase III trial of HMPL-004, Chi-Med's leading botanical drug candidate, in 2014 failed to demonstrate efficacy in UC and the parties have been working to determine next steps. (HMPL-004 is derived from the botanical plant *Andrographis paniculata*, sometimes known as Kalmegh, an herb native to southern and Southeast Asia cultivated for a variety of medicinal uses. The plant's extract is thought to have anti-inflammatory and anti-infective properties.) "We are in a next phase with that project," Behar says. "We believe there is more to discover and are about to embark on a new wave of development with that compound."

Last September, in keeping with the theme of accessing drugs from natural products, NHSc entered into a partnership with **Lipid Therapeutics GMBH** for the UC drug LT-02 (phoshatidylcholine), which is sourced from soya and being developed in purified form as a drug. NHSc will work with Lipid and **Dr. Falk Pharma GMBH**, which holds European and Australian rights to LT-02 under a 2009 agreement. NHSc is also developing its own novel nutritional therapy for moderate to severe Crohn's disease under the program name Project Crown: according to Behar, it is a product considered a medical food in formulation but is being developed along a drug pathway: FDA recently accepted an IND to start clinical trials. "This is a new approach to developing a first-in-class medical food," Behar says. "We believe we are establishing new ground in how to develop a high level, evidence-based product that could come to market in the next two to three years," he says.

Seres, however, could take NHSc to new heights, especially with the high expectations for microbiome drugs overall. (*See "Mining The Microbiome: Are Gut Microbes The Next Big Source Of Drugs?"* — IN VIVO, *July 2015*.)

The relationship with Seres began in January 2015 when NHSc took a 17% equity stake in the company, a position it maintained when Seres went public.

Although Seres' product candidates are following a drug development pathway, they also have some of the regulatory advantages of foods and check off many of the boxes of NHSc's approach.

Take SER-109, an oral composition of 50 species of bacteria in spore form. The spores become bacteria after ingestion and multi-

Exhibit 1

Largest Recent Ex-US Product Licensing Deals

LICENSER/LICENSEE (DATE)	UP-FRONT PAYMENT*/ POTENTIAL DEAL VALUE ($M)	TRANSACTION DESCRIPTION
AstraZeneca/Tibet Rhodiola Pharmaceutical Holding (Feb. 2016)	310/500	Tibet Rhodiola receives Chinese rights to cardiovascular drug Plendil for $310m up front and ex-US rights to angina drug Imdur.
Exelixis/Ipsen (Feb. 2016)	200/855	Ipsen receives rights to cabozantinib, now under FDA and EU review in advanced renal cell carcinoma and in development for other cancers (also approved in the EU for metastatic medullary thyroid cancer). Deal excludes US, Canada and Japan.
Seres/Nestlé Health Science (Jan. 2016)	120/1905	NHSc receives rights to four product candidates: two for forms of *C. difficile* infection (including the most advanced Seres candidate, now in Phase II) and two for treating inflammatory bowel disease. Deal excludes US and Canada.
Aduro/Novartis (March 2015)	225 (200 cash and 25 equity purchase)/750	Ex-US license to Aduro's preclinical cyclic dinucleotide cancer immunotherapy program.
Intarcia/Servier (Nov. 2014)	171/1051	Servier receives rights to ITCA650, a Phase III injection-free (implantable) form of the diabetes drug exenatide. Deal excludes US and Japan.
Merrimack/Baxter (Sept. 2014)	100/720	Baxter (now Baxalta) receives rights to pancreatic cancer drug MM398 plus right of refusal on three other Merrimack cancer drug candidates. Deal excludes US and Taiwan.

*Cash unless otherwise noted.
SOURCE: *Strategic Transactions*

ply a thousand-fold in a few days. Because the drug reproduces in the colon and is not systemic, there was no need to measure pharmacokinetics/pharmacodynamics in a Phase I study. Because there is no dose response to measure, no Phase II dose-finding trial is needed, nor are measurements of drug-drug interactions. In the US, the Food and Drug Administration has agreed that Seres did not have to do carcinogenicity or other preclinical toxicology testing. (FDA's Center for Biologics Evaluation and Research granted SER-109 a Breakthrough Therapy Designation – the first such designation by CBER.)

Taken together, these features strip out time, money and risk, says Seres' president and CEO Roger Pomerantz, MD. They also apply to the company's other candidates: its UC drug candidate, SER-287, for example, which is part of the NHSc deal, was first conceived of in February 2015. "We tested it, got in front of FDA with an IND which they approved without comment, and were in patients the same year, in December," he says.

In effect, while Seres is a young company, it has a late-stage development feel. "We are more late-stage in what we try to implement," Behar says. And microbiome therapeutics are "the most significant innovation in the GI space," he says.

According to Pomerantz, Seres had a dozen companies at the table seeking a deal. "We had clear parameters for what we wanted," he says, including being able to launch SER-109 on its own in the US and Canada. "We only wanted a company that would take this narrow deal," he says, only for commercializing *C. difficile* and IBD indications ex-North America and only in infectious disease – not the rest of GI, and not for metabolic diseases, another core focus for the company.

The transaction terms make it one of the largest rest-of-world deals done in the last several years by a US biotech. (*See Exhibit 1.*) "Part of the reason is that most biotechs do not have a commercial organization," says Pomerantz, formerly SVP, head of global licensing and acquisitions at Merck & Co. Inc. "So they tend to prefer US co-marketing arrangements."

NHSc had the global reach and the understanding of how to get to GI docs but also intensivists where Seres needed them, Pomerantz says. That was important to commercializing SER-109 in particular, because multiple recurrent *C. difficile* patients are not the same as all the others.

"We have shown the reason these people can't be cured is because the dysbiosis of their microbiome is so intense that antibiotics alone can't help it," Pomerantz says. "On a microbiological molecular level, it is a different disease." But unlike in ultra-orphan diseases, these patients are in every medical center and are seen by GI docs and certain infectious disease docs, largely as outpatients. "In a lot of ways we have to look at this as a chimera between a true rare disease and something with a larger patient group," Pomerantz states. What makes it tractable for both Seres and for NHSc is the call points are clear, he says. Plus, Prometheus could help develop a variety

of biomarkers for Seres' drugs – something Pomerantz would prefer not to focus on in-house. "I never liked developing a diagnostic within a therapeutic company," he says, reflecting on his experience at Merck, which has never been a great believer in drug-diagnostics co-development. "But being able to work with a GI diagnostic company that is in place and functioning is a bonus for us."

As they are naturally existing gut bacteria, Seres' products are eligible for categorization under the Generally Recognized As Safe (GRAS) standard. The same is true for the amino acid proteins in development at **Pronutria Biosciences Inc.**, which secured a $42.5 million investment from NHSc six weeks after the Seres deal.

Pronutria has a library of hundreds of millions of potential food protein sequences from which it takes sequences it thinks are relevant to wellness and disease treatment. The company has development programs in the broad areas of muscle diseases, neurological diseases and liver diseases.

That the sequence is present in the human diet makes these proteins GRAS eligible, says CEO Robert Connelly, and allows Pronutria to test them initially in food safety trials that are a relatively quick way to then assess their physiological effects. (Food safety trials do not require an IND.) The company expects to be able to market different proteins both as nutrients and as drugs, basing the decision on the human data it gathers. "The path allows you to evaluate food and with that data you can make a decision based on the strength of that data whether you want to go ahead and get therapeutic claims," he says. "So when we file an IND we will have a considerable amount of human data."

NHSc uses the term "nutritional therapy" to describe one of the pillars of its strategy. "We could have stolen that," Connelly says. "There is a tremendous overlap between how NHSc is positioning itself more and more as a company that can also go into the therapeutic space, and what we are trying to do here." A#2016800042

Mark Ratner

Marketing

MARKETING EFFORTS PAY OFF AS ADMEDUS UPS CARDIOCEL CENTERS BY 50%

The tailwind behind **Admedus Ltd.** continues to blow: its half-year sales to December 2015 were up strongly. At A$2.3 million ($1.7 million), revenues from the flagship cardiovascular bioscaffold *CardioCel* almost matched the previous full-year's sales (A$2.6 million). Infusion product sales were the highest to date at A$4.3 million for the half year, producing an operating business sales total of A$6.6 million, up by 37%. Including grants and other income, the company closed out at A$8.8 million in revenues for the first half year.

The Australian-listed company (ASX: AHZ) also made big strides in its immunotherapies programs, completing recruitment for its HSV-2 Phase II study and progressing its HPV therapeutic vaccine toward initial clinical studies, having completed work on the manufacturing process for the vaccine. R&D spending on the next HPV vaccine from Ian Frazer, MD, the brains behind Admedus' immunotherapies program, helped send the loss up by 19% to A$13.6 million. CEO Lee Rodne says that Admedus now targets moving into profit in 2017 at the earliest.

But the financial performance was not top of the agenda when *IN VIVO* spoke to Rodne and Admedus Chief Operating Officer Julian Chick on a visit to London in early March. Neither was the share price (March 9, A$0.46), which has trended down since mid-December (A$0.88) – Rodne attributing this as a reflection of the general trend in the biotech index, and declining market prices for small cap stocks. It could also be related to macro statements about the Australian economy, and brokers taking a conservative approach. "As for us, we haven't reported any negative statements during this time," said Rodne.

Quite the opposite, in fact. A month ago, Admedus appointed a new non-executive chairman in Wayne Paterson, who comes with a pedigree of experience at Merck & Co. Inc. and Roche, having held senior positions at both. "A very commercial guy and well-connected globally," Rodne sees him boosting global product launch efforts. Paterson has already helped review commercial strategies. He is also seen as potentially good for partnerships, and feedback from the market has been good. Another non-executive director may be added in the coming months.

Elsewhere, the number of centers using Admedus' flagship bioscaffold, CardioCel, has risen by 50% in the past six months, and is now at over 135 globally. The market strategy has been to build credible relationships with top-tier surgeons and KOLs. Most of the centers are in Europe, where CardioCel is now approved for valve and annular repair, and in the US. The number of centers will go up by 20 to 30 in the coming six to nine months, says the company. Additionally, CardioCel is now approved in Canada, Hong Kong, Singapore and Malaysia, and available in Australia through early access programs.

First sales have just begun the Middle East via a partnership with Genpharm Services under a special access program. "This is a key region and we expect more centers regionally. We also expect full regulatory approval there in the next six months," said Rodne.

PARTNERSHIP WAGON ROLLS ON WITH CORONEO DEAL

Partnerships are a key part of the strategy at Admedus, which in late January announced an exclusive distribution agreement with Canadian company **Coroneo Inc.** Admedus will sell Coroneo's aortic annuloplasty ring and heart valve surgery instruments in Germany and the UK, through its existing sales and marketing infrastructure, as of April 2016.

"Coroneo is part of our aim to build our brand and position in valve repair and recon of valves," said Rodne. The aortic ring is designed to surgically repair the aortic valve with a proven, standardized technique. It has an element of elasticity, which permits the tissues to expand by about 10% between diastole and systole, thus mimicking the native valve root physiology. This is an early example of what Chick last year called adding more strings to Admedus' bow.

All of which is getting the Australian company on the radar screen globally. "Some companies in this sector have been on the market for over 20 years, so as a new entrant to the market place (*see "Admedus Charts An Eclectic Path To A Global Future"* — IN VIVO, *October 2015*), getting our name and brand recognized in a credible way does take some resources," said Rodne. "We've been able to do that in the year and a half that we've been on the market."

Credibility is a major issue. The market features both early adopters of technology and skeptics, and there are cases where surgeons have been "burned" by marketing claims that were simply untrue or products that have not lived up to expectations. "There are obstacles for us in our drive to be credible with those surgeons, so we opt for a wait-and-see, conservative, approach," said Rodne. Some companies have spun things in certain ways. "We're not one of them; we want to focus on results, data and outcomes."

When it comes to market size for CardioCel, China surpasses the US and Europe combined. "There's a huge unmet CHD market in China, with a 50% need for repeat surgeries within 12 months," said Chick. Admedus is keen to get into that. Consequently, the company has been building relationships with cardiovascular centers. "We are looking to work with local partners to enter the market, and will be initiating the registration studies fairly soon," said Rodne. Shanghai and Beijing are the first targets.

As to reimbursement, the Chinese centers say Admedus' pricing model fits in well in that country. "That gives us confidence in the opportunity that presents itself and makes us feel comfortable about our pricing strategy," said the CEO. But given the IP risk, the company will manufacture the base CardioCel technology product in Australia, and "may look at a finished product in China."

China Food and Drug Administration (CFDA) registration is now typically a three-year process, but Admedus hopes to beat that in getting CardioCel into China. The firm has direct sales models for the major markets, and in Asia it has its own direct employees for Southeast Asia, headquartered in Singapore. It works with select partners in Taiwan, including for the registration process, where it expects registration within

15 months, that is, before the end of 2017.

Rodne admits to being "very excited" about a new postmarket study in aortic valve reconstruction over the next 12 months. The company has reported a world-first study in sheep models, where surgeons have reconstructed the whole aortic valve. There are 165,000 procedures per annum in the US alone for people with late-stage aortic valve disease, but the potential market is actually much higher for Admedus, which wants to treat the disease much earlier. "Big valve companies are not focused on that, but on TAVR transcatheter valves," says Rodne.

Most aortic valves are replaced rather than repaired. But if treated earlier, there are better outcomes, hemodynamics, long-term survival rates and blood flow, and no ongoing calcification with repair, rather than replacement with a bioprosthetic valve, according to Admedus.

The regenerative tissue bioscaffold pipeline extends to hernia repair and dura mater, and the company wants to do a large preclinical study to get a product for dura mater onto the market. The tissues on the market tend to have a high incidence of causing infection leading to brain fluid leakage. Admedus, which is working with a well-known neurosurgeon, says its product overcomes those issues.

Elsewhere, its vascular product is nearing the US market for repairing carotid endarterectomies to reduce incidence of stroke. Pilot studies are underway ahead of roll-out and launch in mid-2016.

Immunotherapies are the second platform in Admedus' unique product mix. Rodne said, "As we gather the clinical data from our immunotherapies program, we'll be looking for early revenue opportunities to do partnerships and licensing."

The company closed recruitment for the HSV-2 trial at the end of 2015, and in the third quarter of calendar 2016 will be looking at unblinded data from the 20 patients of the Phase II study. For the HPV vaccine, Admedus will be looking at two studies that should start by mid-2016 – the first in intraneoplasic patients to look at irregular cells around neocervical cancer/pre-cervical cancer; and the second at the role of therapeutic HPV vaccine in head and neck cancer (around 65% of head and neck cancers are HPV-related).

The program also extends to "Frazer's next vaccine," looking at RNA vaccines to target HPV infection. The US Centers for Disease Control & Prevention estimates that there are 14 million new HPV patients globally every year, and over 70 million carry HPV.

The overall R&D activity also embraces a cellular therapies study, involving seating stem cells on a tissue scaffold for various applications, such as treating myocardial infarction.

"We will continue to look for further complementary products as the company grows," said Rodne, "but we already have a lot of potential with our two platform technologies." There are numerous other oncology targets and large pharma technologies such as checkpoint inhibitors and PD-1 inhibitors in the market. These are examples of where Admedus could collaborate, said Rodne.

Rodne says Admedus' immediate priorities are:

- achieving quarter-on-quarter sales growth, with A$13 to 14 million expected in the current financial year. CardioCel sales are expected to increase along at least the same trajectory as in the first half of 2015–16;
- bringing new products and new applications of CardioCel online, post regulatory approval;
- getting successful clinical data out of the aortic valve study;
- looking at future partnerships and collaborations, including in Asia, with partners that are credible and have long-standing relationships with surgeons;
- developing the Coroneo partnership; and generally "investing in the areas that will lead to profitability."

Admedus has been sounded out by strategic investors. Rodne said: "That's natural and to be expected. And some competitors have approached us to work together in certain segments. But a strategic sale is not on the agenda – not yet anyway."

A#2016800052

Ashley Yeo

DEALS OF THE MONTH

IN VIVO's editors pick February's top alliance, financing and M&A deals.

TOP ALLIANCE:
SYNTHETIC BIO TIE-UP FOR SYNLOGIC AND ABBVIE

Synlogic Inc. signed its first-ever partnership in early February, agreeing to a multi-year collaboration with **AbbVie Inc.** to develop what it calls "synthetic biotic" therapies for Crohn's disease and ulcerative colitis. The partners did not disclose financial terms of the deal, in which Synlogic will discover, characterize and optimize microbiome-altering inflammatory bowel disease candidates, and then hand them off to AbbVie for clinical development, regulatory filings and commercialization. Synlogic closed a $40 million Series B round a week after announcing the AbbVie deal.

TOP M&A:
ALCON BUYS INTO MIGS VIA TRANSCEND

Barely a month after vowing to up investment in its surgical eye-care business, **Novartis AG's Alcon Inc.** has signed a deal that will bring a new microinvasive glaucoma surgery technology into its portfolio. Alcon will acquire **Transcend Medical Inc.**, developer of the CE-marked *CyPass* micro-stent, for an undisclosed sum. CyPass is implanted just below the surface of the eye and acts as a drainage channel to reduce the build-up of intraocular pressure in glaucoma patients. Investors' interest in MIGS is evidenced by the successful up-sizing of an IPO last year by Transcend's biggest rival **Glaukos Corp.**, which is commercializing its FDA-approved *iStent* technology in more than 20 countries.

TOP FINANCINGS:
BIG A ROUNDS FOR IMMUNO-ONCOLOGY AND VIRTUAL REALITY

MindMaze Raises $100 Million Series A

Switzerland's **MindMaze SA** raised $100 million in a Series A round led by Hinduja Group India Ltd. to develop virtual reality rehab devices for patients with stroke or brain injuries. The start-up's CE-marked *MindMotionPRO* is designed to trick a patient's brain into thinking an immobilized limb is still working by using immersive neurorehabilitation exercises. MindMaze is selling the technology to hospitals for in-house use and in the future plans to offer other versions for home rehab and video game play. It is also exploring applications in other medical conditions such as memory loss, tremor from Parkinson's disease, depression, post-traumatic stress disorder and phantom pain in amputees.

Forty Seven Inc. Spins Out With $75 Million Commitment

Forty Seven Inc., the company formed to commercialize **Stanford University** professor Irving Weissman, MD's CD47 research, has raised the first tranche of a $75 million Series A round. Lightspeed Venture Partners and Sutter Hill Ventures led the financing with participation from Clarus Ventures and GV. The start-up has licensed the rights to multiple immuno-oncology programs from Stanford, including Phase I molecule Hu5F9-G4, an anti-CD47 monoclonal antibody that potentially has broad applications spanning multiple tumor types and treatment modalities.

A Road Map To Strategic Drug Pricing

The current unit-based pricing model for drugs is too one-dimensional for the market's present needs. Pharma firms must identify products that will benefit from innovative pricing models, and then forge the types of collaborations that will support those models.

BY ELLEN LICKING AND SUSAN GARFIELD

- Current pricing practices create conflict between drug companies and other health care stakeholders, fostering a negative reputation for the biopharmaceutical industry and a slowdown in growth.
- Because products come to market with clinical trial data and not real-world evidence, stakeholders may see them as having "potential," not "proven," value at the time of launch. As a result of this evidentiary divide, many products already enter the market with a "value gap."
- To accelerate the shift to proven value and bridge the value gap, biopharma companies should consider multi-stakeholder collaborations aimed at co-creating data to support innovative pricing models.
- EY's qualitative pricing methodology helps companies understand which products will derive the greatest benefit from innovative pricing models, enabling a proactive and systematic approach to pricing decisions.

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The debate about drug pricing has reached a fever pitch. In early February 2016, the US Congress held a half-day hearing on pharmaceutical pricing. Long on spectacle and short on solutions, the meeting was a reminder that even in the US, the most "free" market for drug prices and access, there is widespread concern about the impact of rising drug costs on the sustainability of health care spending. Instead of viewing drugs as one of the most efficient and cost-effective solutions to illness, it's clear the public views biopharmaceuticals – and the companies that make them – as one of the central problems contributing to an affordability crisis.

It is time to acknowledge that our historical pricing model, which is built on unit-based pricing, is too one-dimensional for the marketplace's current needs. It has resulted in incentives that encourage biopharma companies to make pricing decisions that are driven by what is possible rather than what other stakeholders consider reasonable. It should be no surprise, then, that when important therapies for life-threatening diseases reach the market, these products frequently come with budget-straining price tags. In the US, the current pricing dynamics have also enabled annual (or in some cases, biannual) price increases for products already on the market.

Admitting "we've done things we shouldn't do," Leonard Schleifer, CEO of **Regeneron Pharmaceuticals Inc.**, told the audience at the *2015 Forbes Healthcare Summit* in December the industry has "to think about a different pricing approach that is a little bit more responsible."

In truth, there won't be just one pricing approach, but many. The strategies that will be implemented will depend on the competitive intensity of the therapeutic area, the economics of the individual market and specific product attributes. Moreover, given the complexity and time required to implement new pricing models, not every drug in a portfolio will be worth such investment. When, and how, should biopharma companies place their bets?

We outline a qualitative methodology designed to help biopharma leadership teams proactively identify when to adopt novel pricing strategies. The truth is many companies take an overly transactional view of market access, viewing stakeholder engagement as a negotiation game. In this context, innovative, value-based pricing collaborations are more commonly seen as a defensive hedge, deployed only when reimbursement is delayed. However, as pricing pressures grow and the evidentiary demands increase, more products, not fewer, will require innovative pricing strategies.

> "For biopharma companies to meet their future growth objectives, they must embrace holistic pricing solutions now before payers use blunt methods to curb costs and limit patient access.

Instead of defaulting to unit-based pricing methods, companies need a more systematic approach that helps identify, across a portfolio, which products should be candidates for innovative solutions in the different markets where they will be sold. To work, this approach must be grounded in an honest assessment of how other stakeholders, especially the payers, value the medicine's different features.

Getting there won't be easy. There will be new business risks and real implementation challenges. For starters, biopharma companies must identify which stakeholders are most ready to embrace these more collaborative pricing models. In addition, manufacturers must work with stakeholders to define what is meant by an "outcome" and develop the infrastructure to capture and analyze the data.

But biopharma companies must also acknowledge that maintaining the status quo comes with significant business risks. Because of cost constraints, infinite resources to support access to innovation no longer exist. For biopharma companies to meet their future growth objectives, they must embrace holistic pricing solutions now before payers use blunt methods to curb costs and limit patient access.

A MODEL UNDER INCREASING PRESSURE

The economic drivers that guide the pricing of televisions, mobile phones or clothing don't apply to the pricing of drugs. There are multiple reasons for this, including market exclusivity and a disconnect between the economic buyer (the payer) and the end user (the patient). But the primary reason for high drug prices stems from the structure of the current system, which relies on unit-based pricing, a methodology that needs to evolve as the larger health care ecosystem itself evolves.

Biopharma companies have responded to the existing market incentives in rational and predictable ways. They have established public, unit-based list prices for products and then negotiated, on a market-by-market basis, specific, undisclosed discounts or rebates based on in-country regulations and health technology assessment criteria. This approach has had two benefits: 1) it is relatively simple to implement; and 2) it preserves pricing flexibility, especially in markets where reference pricing is the norm.

In the past, this lack of net pricing transparency worked to manufacturers' advantage. However, in today's environment, where the list prices of drugs are high and publicly available, the public doesn't discriminate between the perceived cost of a medicine and the amount actually spent. Moreover, the heterogeneity of drug costs globally – for instance, certain cancer drugs can cost half as much in Europe as in the US – reinforces perceptions that pricing practices are "unfair," fueling industry's negative reputation.

Biopharma's historical pricing model is now under threat. One reason: the temporal misalignment between when drug costs occur and when the benefits are realized. Companies must be rewarded for the difficult and risky work of developing

new drugs. But this means many specialty products come with high up-front price tags. Resource-constrained payers, however, need drug utilization policies that are consistent with tight annual budget cycles. With very few exceptions, the benefits associated with a therapy won't be measurable until many years in the future. As Kenneth Frazier, the CEO of **Merck & Co. Inc.**, noted at a November 2015 forum sponsored by the US Department of Health and Human Services, "the value of a drug is like an annuity. The issue for the health system is the return on investment needs to be made up front."

Hit hard by their own budget constraints, payers are therefore adopting new restrictions that limit the use of newly launched products. As multiple drugs with similar indications and clinical impact compete for share in therapeutic battlefields such as oncology or diabetes, it can be difficult to differentiate newer entrants from existing players. A flood of biosimilars creates additional downward price pressure in categories that have historically enjoyed pricing flexibility.

In this environment, steep discounts and aggressive rebating strategies to establish market access have become the norm. The more comparable the drugs, or the greater the number of competitors in a particular market, the greater the likelihood companies find themselves sacrificing pricing power – and future revenues. (*See "Game's Up, Pharma: The New Drug Pricing Dynamics"* — IN VIVO, *March 2015.*)

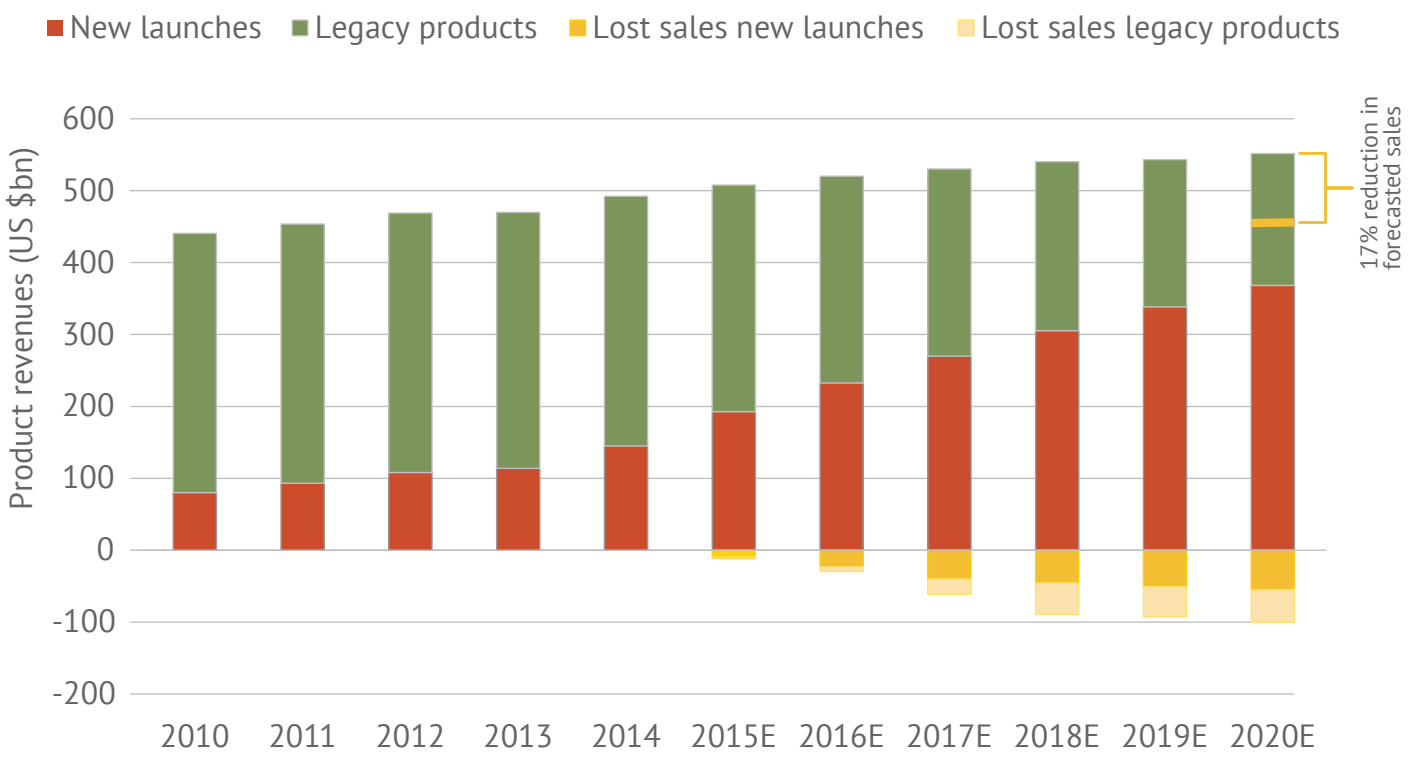
We've seen it already. Recall what happened in 2014 after **AbbVie Inc.** launched *Viekira Pak* (ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets), an alternative to **Gilead Sciences Inc.**'s all-oral hepatitis C regimens *Sovaldi* (sofosbuvir) and *Harvoni* (sofosbuvir/ledipasvir). As Gilead noted on its February 2015 earnings call, the presence of a competing product put pressure on the Foster City, CA-based biotech to offer larger discounts to keep its products on payers' formularies.

The near-simultaneous launches of two new PCSK-9 inhibitors in mid-2015 provided another signpost of payer behavior: payers delayed coverage decisions until both products were approved in order to leverage competition in the marketplace when negotiating access to this class of drugs. The upshot: slower-than-anticipated sales for both products.

Recent analysis by the industry association PhRMA suggests payer pushback has already negatively affected revenue growth across the industry. In its 2015 report "Prescription Medicines: Costs in Context," PhRMA estimated that net brand price growth for biopharma products fell from a high in 2012 of $16.8 billion to a low in 2014 of $10.3 billion as a result of increased rebates and price concessions.

Exhibit 1

Impact Of Payer Skepticism

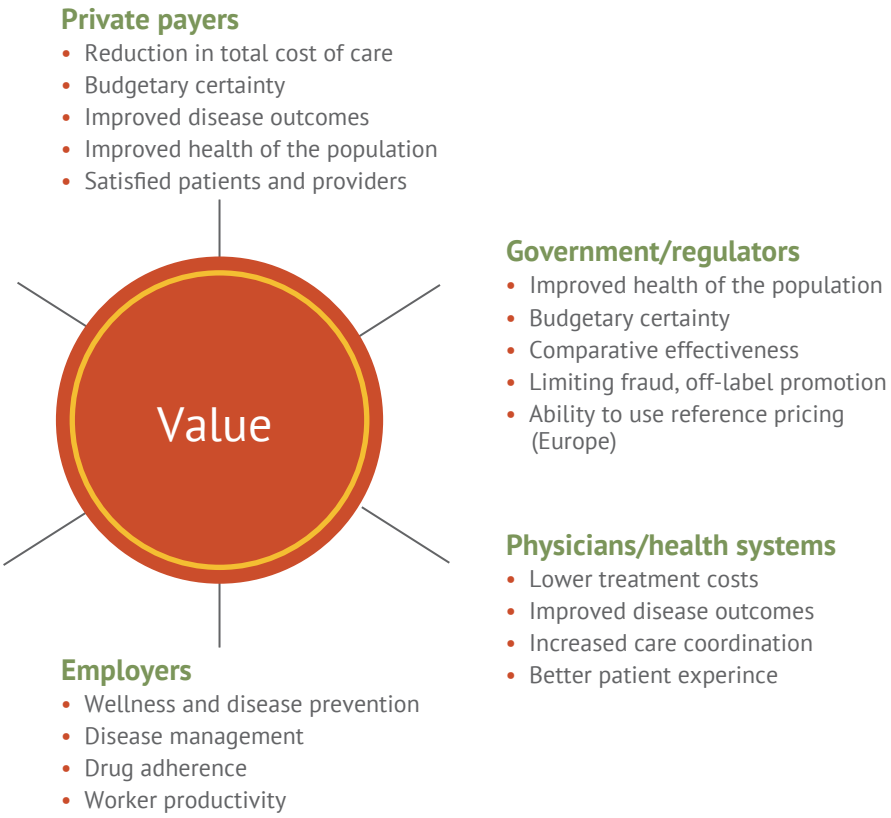


Note: From 2015 to 2020, sales of newly launched products are forecast to have an imputed 17% compound annual growth rate (CAGR), while sales of legacy products are projected to decline by an imputed 9% annually. To model the potential payer pushback, EY assumed the CAGR for sales of new launches slowed modestly to 14%; EY also assumed the annual decline in legacy product sales increased modestly to 13%. Together this mix of potentially slower than projected growth from new launches and accelerating erosion from legacy drugs represents about $100 billion in lost product sales, roughly half of which would be felt by big pharma companies.

SOURCES: EY; Decision Resources

Exhibit 2

Value Is In The Eye Of The Beholder



SOURCE: EY

What if the situation worsens in the coming years, as drug costs become a bigger line item in national budgets? Modeling by EY suggests that even as biopharma companies deliver on their R&D pipelines, payer restrictions could eliminate $100 billion in newly launched and existing product revenues by 2020. That's about 17% of forecasted sales. (*See Exhibit 1.*)

VALUE IS IN THE EYE OF THE BEHOLDER

A critical challenge when developing balanced pricing strategies is the fact that there is no single arbiter of product value. The health care marketplace is populated by several different types of stakeholders, each of which defines value and influences prescribing decisions slightly differently. (*See Exhibit 2.*)

It's still true that stakeholders value product efficacy and safety, but as with improvements in quality of life, these attributes should be considered necessary but not sufficient. In today's increasingly fee-for-value world, value drivers embraced by European health systems have emerged as drivers of acceptability in the US:

- Significant differentiation compared with the standard of care
- The ability to subsegment the population most likely to benefit
- Real-world outcomes
- Up-front affordability of the medicine
- Total cost to the health care system
- Time required to achieve cost savings

Even in Europe, where health technology assessment organizations delineate value via clinical effectiveness and cost-effectiveness, there is no standardized value definition. Not only do the value formulas vary from country to country, but how those formulas are implemented within a given market may be inconsistent. In the US, where there is even greater payer fragmentation and it has been politically intolerable to use cost-effectiveness measures to determine drug prices, it is even more difficult to reach a universal viewpoint on the subject.

That doesn't mean payers stateside are disinterested in objective frameworks to define the concept, however. Thus, in 2015, one of the key new developments in the value discussion was the proliferation of third-party tools that compare the efficacy, side effects and costs of different products. (*See "Scoring Value: New Tools Challenge Pharma's US Pricing Bonanza"* — IN VIVO, *October 2015.*)

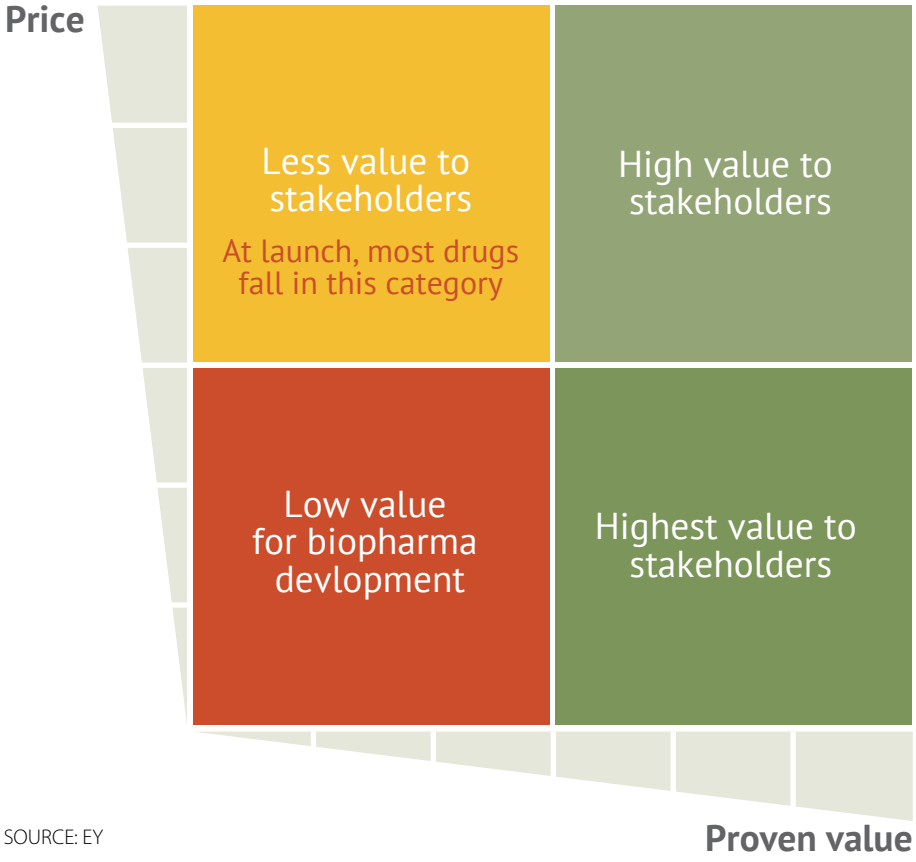
Whether these value frameworks originate from health technology assessment organizations or private groups, their existence directly affects the pricing of biopharmaceutical products. That's because these different assessments provide credible pricing alternatives that manufacturers must address head on when trying to justify a product's value.

Absent credible alternative data about product value, payers will use the information gleaned from such tools to demand deeper and deeper discounts in the mar-

Exhibit 3

Categorizing Newly Launched Drugs

At launch, drugs map to one of four categories based on stakeholders' perceptions.



SOURCE: EY

ketplace. Such payer behavior ultimately limits biopharma value creation, turning drugs into commodities and manufacturers into vendors.

MOVING FROM POTENTIAL TO PROVEN VALUE

Although biopharma companies amass considerable efficacy data during clinical trials to support regulatory decisions, these data don't necessarily demonstrate real-world value – that requires evidence outside a clinical trial showcasing improved outcomes against the current standard of care.

With multiple therapeutic options available in almost every drug class, a majority of products now coming to market will be classified as having "potential value" until there is proven evidence. As a result, at launch, many products must bridge an evidentiary "value gap." Because of their high price tags, this gap is especially pronounced for specialty medicines.

Indeed, as *Exhibit 3* illustrates, stakeholders typically categorize newly launched drugs into one of four categories based on existing data:

- High price/high value product
- High price/low value product
- Low price/high value product
- Low price/low value product

High price/high value products include curative therapies such as the all-oral hepatitis C regimens and medicines that provide a step change in the standard of care. These medicines are of high value to stakeholders but, because of the up-front costs, raise concerns about affordability.

High price/low value medicines include specialty products that are undifferentiated relative to standard of care or me-too products that offer incremental improvements in efficacy or real-world outcomes. This category may also include chronic disease products that treat broad populations but are not well targeted. Thus, although the therapeutic may be very effective in a subsegment of the population, the observed efficacy in the broad population may be underwhelming because a majority of patients are non-responders. Products in this category are most at risk for pushback from payers and skepticism from providers and patients since benefits achieved relative to their costs are harder to determine.

Low price/high value products include vaccines and generics and are viewed by stakeholders as having the greatest utility because the benefit/cost ratio is highest. Even products in this category, however, may be susceptible to up-front affordability concerns, depending on the macroeconomic conditions of the market and the number of patients affected.

Low price/low value therapeutics, which include over-the-counter medicines and topical ointments, traditionally hold the least value because their therapeutic benefits can't be broadly attributed across the population. For pharmaceutical manufacturers, these products have been viewed as the lowest development priority because the likely returns are lower relative to their development and commercial risks.

INCHING TOWARD INNOVATIVE PRICING

Pricing approaches of the future will require companies to work with other stakeholders, especially payers, to co-create data that bridge the value gap. To be most effective and accelerate the shift from potential to proven, these data will ideally be collected not just after launch but during development. Thus, companies serious about innovative pricing strategies must also rethink their organizational structures to establish closer relationships between the product development and commercial strategy teams.

Change is already under way, albeit on an ad hoc basis: payers and manufacturers in different markets are experimenting with a number of innovative pricing models that represent a shift from unit-based pricing. (*See Exhibit 4.*) In Italy, for example, access

Exhibit 4

Moving To Fee For Value: Selected Solutions

SOLUTION	DEFINITION	USE IN MARKETPLACE	EXAMPLE
Indication-specific pricing	Differential product pricing depending on its performance in specific indications (e.g., lung versus head and neck cancer)	Emerging	Express Scripts pilots program to test indication-specific pricing in US
Bundled payment	A global payment for all treatment costs, including prescription drugs	Procedures and physician services: high Therapeutics: emerging	United Healthcare Group partners with multiple physician groups to test model in oncology
Financial-based risk sharing (FBA)	Agreement links price to utilization (either via script volume or drug dosage) Agreement provides budgetary certainty to payers	Europe: high US: emerging	Gilead Sciences and government of France agree to a volume-based cap on Sovaldi
Performance-based risk sharing (PBA)	Agreement helps manage utilization and/or provide evidence of drug efficacy Agreement provides payers with clinical outcomes data	Europe: medium US: emerging	Bristol-Myers Squibb and Italian government establish PBA for Yervoy that includes payment-by-result and a cost-ceiling
Annuity model	Financing instrument covers the acquisition cost of breakthrough biopharmaceutical products Instrument can be structured as bond, mortgage or credit line Pay-for-outcomes agreement likely to be a component	Emerging	Health impact bonds used to improve care delivery for chronic diseases such as asthma To date, life sciences companies have not participated in creation of such instruments Could be important future solution for high cost, curative therapies

SOURCES: EY; Company reports; French Ministry of Social Affairs and Health; Italian Medicines Agency

to most high-priced oncology products requires some kind of pay-for-performance arrangement that necessitates monitoring via patient registries. In the UK, financially based risk-sharing agreements have become the preferred approach, in part because of the complexities and costs associated with creating effective outcomes-based contracts.

In the US, there has been more limited experimentation with innovative pricing, due to concerns that novel pricing arrangements would jeopardize government contracts and regulations related to Medicaid price. Still, budgetary pressures stateside mean payers and drug companies have increased motivation to make value-based contracts work.

Indeed, by the end of 2015, biopharmas had struck at least seven novel pricing arrangements with payers, according to publicly sourced documents. **Novartis AG** is one of the most vocal proponents of new pricing models; the Swiss pharma hopes to use outcomes-based pricing to enable greater access to its first-in-class congestive heart therapy *Entresto* (sacubitril/valsartan). Thus far, only **Aetna Inc.** and **Cigna Inc.** have disclosed novel contracts for Entresto, which Novartis acknowledges has had slower-than-anticipated sales due to reimbursement delays. (*See "Novartis On Payer Contracts, Other Updates From BIO CEO & Investor Conference"* — "The Pink Sheet" DAILY, *February15, 2016.*)

EY'S STRATEGIC PRICING METHODOLOGY

In a general way, the categories described above help segment products based on the views of payers and other stakeholders. To discriminate between products that are better suited for innovative pricing models and those that can be supported by traditional pricing strategies, a more systematic analysis is required. Thus, EY has developed a qualitative, three-step strategic pricing methodology.

Based on a combination of market- and product-related attributes that take into account the actual payer in question, our approach identifies which factors are most likely to have the greatest impact on a company's ability to achieve maximum pricing flexibility ahead of a new product launch. As a result, a biopharma can preemptively develop specific tactics, including targeted data collection and novel contracting mechanisms, to maximize the value creation – and minimize the uncertainty – associated with any specific attribute. In this way, the model accelerates the shift from potential to proven and closes the value gap.

When applied across the entire portfolio, companies can use the methodology not only to tailor the right pricing approach to the right product, but also to improve strategic business decision-making. Moreover, the methodology is flexible enough to adapt to evolving market conditions,

including rapidly changing definitions of the standard of care. (*See sidebar, "Applying The Methodology."*)

The three steps in the process are:

- Assess the market and product attributes.
- Confirm the pricing analysis.
- Tie the pricing strategy to the commercial strategy.

1. ASSESS MARKET AND PRODUCT ATTRIBUTES

To accurately determine a product's pricing flexibility at launch, a company must first assess a number of attributes that are both market- and product-specific. Eight different factors play a role in determining how much pricing flexibility a company will have when launching a particular product. (*See Exhibit 5.*)

Given the current complexity of drug pricing and the diversity of payer types, it is difficult to rank order the eight factors in a decision tree that holds true across all therapeutic areas. Instead, depending on the severity of the disease, the total projected costs of treating the indication and the competitive intensity of the market, certain attributes will be more central than others in determining a product's pricing flexibility.

As a result, this assessment provides directional guidance about not just how to price a product, but also where the biggest evidence gaps reside. Notice that a high degree of uncertainty around any one attribute increases a stakeholder's skepticism, and thus, the likelihood that there will be a value gap at launch. By understanding which factor results in the greatest uncertainty, a company can proactively develop data to address the stakeholder's concerns. In effect, this attribute becomes the fulcrum for stakeholder engagement around new pricing models.

There is little that companies can do to influence the competitive intensity of the therapeutic area or the severity of a given disease. At a strategic level, companies must decide if these attributes make a particular disease attractive for drug development more generally.

If a new product is a late entrant into a

Exhibit 5

Market- And Product-Specific Attributes Determine Pricing Flexibility

	ATTRIBUTE	DEFINITION	IMPACT ON PRICING FLEXIBILITY
Market-specific	Competitive intensity	Assesses number of therapies on the market to treat the disease	Pricing flexibility increases the fewer the number of competing products
	Economic burden of disease	Examines the potential budgetary impact of the therapy to the stakeholder	Pricing flexibility increases the lower the up-front costs associated with treating a disease.
	Disease severity	Evaluates the seriousness of the disease	Pricing flexibility increases with disease severity given the high level of unmet medical need
	Payer archetype	Considers how different behaviors motivate payers to make drug coverage decisions as well as willingness to engage in novel types of contracting	Pricing flexibility increases if the payer is focused on wellness and prevention rather than cost and has a stable membership population. Such payers are also more likely to engage in innovative pricing models
Product-specific	Differentiation	Measures a product's effectiveness relative to available treatments, especially standard of care	Pricing flexibility increases if the product provides a step change in care relative to the competition
	Time to outcome	Analyzes the time required to demonstrate effectiveness to the stakeholder	Pricing flexibility increases the shorter the time to a credible real-world outcome, including a demonstrable cost-offset
	Degree of targeting	Measures the therapy's use in population subsegments	Pricing flexibility increases when precision medicine tools narrow the population from all comers to responders. Such targeting not only improves outcomes but addresses the budgetary concerns of payer stakeholders
	Patient experience (e.g., a dosing schedule that facilitates adherence to therapy)	Assesses a therapy's impact on quality-of-life metrics and potential costs of switching to alternate therapies	Attributes may be of greater importance to patients than traditional payers. Thus, patient-centric attributes are unlikely on their own to result in pricing flexibility; real-world data demonstrating differentiation relative to the standard of care will be important

SOURCE: EY

class with multiple established products (e.g., high competitive intensity), it will be imperative to differentiate the product in head-to-head trials against the comparator stakeholders determine to be most relevant. This may be a product with a similar mechanism of action; alternatively, it may be a much cheaper generic, or even a device or digital app. In today's value-oriented world, the most relevant comparator is the one that currently provides not only the best health outcome but is also affordable.

Novel pricing strategies can play a critical role in facilitating uptake in a number of instances, including when the economic burden of the disease is high and the time to outcome is long. Drugs aimed at larger swaths of the population will incur greater up-front costs. The higher these costs to other health care stakeholders, regardless of the demonstrated outcomes, the higher the likelihood that pricing decisions will generate scrutiny. This has been the case for the all-oral hepatitis C regimens that are curative. Similarly, therapies that require a longer time to demonstrate a real-world outcome, including demonstrable cost offsets, will be subjected to more stakeholder skepticism than products that demonstrate outcomes quickly.

Finally, the nature of the buyer, the payer archetype, is another critical issue when considering a novel pricing strategy. Different types of payers are motivated to make different coverage decisions based on their individual preferences and constraints, including the market dynamics in which they operate. In the US, for instance, Medicaid payers are very focused on up-front medication costs because of fixed budgets. Integrated delivery networks, however, might be less sensitive to up-front costs if the medicine results in credible cost offsets in an acceptable period of time. Note, since integrated delivery networks traditionally keep their members for long periods of time, this particular type of payer may have more flexibility on the time-to-outcome parameter than a traditional commercial payer who will have the patient as a member for only one or two years.

Because of these behavioral differences, the payer archetype will likely influence a range of factors, including whether or not a given payer is open to an innovative pricing strategy in the first place. Given the complexity of these collaborations and the required investments in time and capabilities, it makes sense for companies to engage first with payers that are most receptive to novel contracting arrangements.

Once companies have identified payer partners, they will also have to determine which market and product attributes are of greatest importance to that particular organization. Here again, the payer archetype is likely to play a role. Indeed, an analysis of five recent outcomes-based contracts in the cardiovascular space illustrates the diversity of endpoints that can be considered: adherence to therapy, cholesterol lowering and a reduction in cardiac events or hospitalizations have all been adopted, or suggested, as possible measures for value-based pricing collaborations.

2. CONFIRM THE PRICING ANALYSIS

The second step in any pricing decision is to refine the analysis relative to the list prices of currently available products. These list prices act as price anchors, defining the value of new entrants in the market. In therapeutic areas that are already heavily genericized, companies must determine if the outcomes data they have are sufficient to enable reimbursement, and thus market share gains, given the existence of much cheaper therapeutic options.

Increasingly, stakeholders are willing to embrace "good enough" innovation if products satisfy basic safety and efficacy requirements but come with lower price tags. This is the value proposition associated with biosimilars and the second and third entrants in the all-oral hepatitis C category. Thus, companies need to understand that pricing flexibility occurs at only one specific time: when a drug is "only-in-class." (*See "The Shrinking Value Of Best-In-Class And First-In-Class Drugs"* — IN VIVO, *July 2015*.)

That scenario obviously puts increased pressure on companies to deliver on their innovative pipelines. It also puts increased pressure on companies to embrace innovative pricing models. For instance, consider a new high-cost, but potentially high-impact product that is launching into a heavily genericized space, where there are "good enough" alternatives. To preserve as much flexibility as possible, companies in this situation could benefit from adopting innovative pricing strategies that allow them to collaborate with payers on the collection of outcomes data that accelerate the shift from potential to proven.

Novartis' decision to pursue an innovative pricing strategy for Entresto provides important real-world context in this regard. Although the drug is first in class, its direct competitors include much cheaper angiotensin-converting enzyme inhibitors that provide "good enough" treatment for some percentage of CHF patients. But if Novartis is able to replicate in the real world the clinical trial data showing Entresto reduces expensive cardiac events, the downstream cost savings associated with reduced hospitalizations would offset its up-front price tag. This scenario makes the drug a good candidate for a novel pricing strategy. (An added bonus: the endpoint defining an improved outcome – reduced hospitalizations – could be easily measured using payers' existing IT systems.)

3. TIE PRICING TO COMMERCIAL STRATEGY

The final step when articulating a product's price is to link this decision to the overall business strategy, including the potential effect on the uptake of other medicines in the portfolio. For instance, the greater a product's importance to a company's overall portfolio, the greater the pressure to accelerate that product's market share and close the value gap quickly. If there is significant stakeholder skepticism around a particular product attribute (for instance, time to outcome), a biopharma company might choose to adopt an innovative pricing strategy to bridge this particular value gap. In this instance, a novel pricing solution might be a means of co-creating additional data that are useful for demonstrating real-world value.

In addition, it is important that companies harmonize individual pricing decisions across the portfolio to create a coordinated commercial strategy. This step will become more important as more products are used in combination. Moreover, such a portfolio analysis enables companies to align portfolio decisions with overarching strategic choices, including decisions to invest in one business unit rather than another or the potential value creation that can come from divestitures.

APPLYING THE METHODOLOGY

In *Exhibit 6*, we assess the pricing flexibility of three different kinds of products: a genetically targeted oncologic, a curative gene therapy and a long-acting multiple sclerosis (MS) therapy that provides symptom relief. For each of the three products, we first assess eight factors independently, using the values of a traditional US commercial payer as our guide. Then, based on the pricing flexibility associated with each factor, we make a qualitative assessment of the overall pricing flexibility for each product type.

In the second step, we further refine the pricing analysis to reflect the actual competition in the marketplace. As noted, this is especially important if the novel product is launching into a heavily genericized space where "good enough," cheaper medicines limit pricing flexibility. Finally, we link the individual product pricing strategy to the company's larger commercial goals. By methodically evaluating the pricing decision at each of these levels, we identify which of the three products will benefit the most from innovative pricing strategies.

The MS medicine appears to have less pricing flexibility because of two critical market factors: competitive intensity (high) and the economic burden of disease (high). With numerous products available to treat the condition, payers and at-risk providers are more likely to be unconvinced of a new entrant's worth relative to existing therapies. Similarly, the prevalence of multiple sclerosis means the economic burden of treating the disease will be greater than for a rare or niche disease. Hence, because of the potential budgetary impact associated with care, companies should anticipate needing to overcome payers' skepticism with some kind of innovative pricing arrangement.

Of the product-specific attributes, the MS medicine might result in payer skepticism due to its lack of targeting and a perceived lack of differentiation relative to the current standard of care. The medicine's patient-friendly attributes will give it high value to certain stakeholders; others, however, will want to know if the drug's dosing advantage translates into improved patient adherence and, therefore, better long-term outcomes.

An analysis of the prices of competing MS products suggests the novel entrant retains some, albeit limited, pricing flexibility. Although a large-molecule generic exists, the price differential between it and other marketed products isn't so great that premium pricing could only be preserved via an innovative pricing scheme. Moreover, one of the unique attributes of the MS market is that stakeholders dislike switching stable patients to different agents, even when those medicines are much cheaper. That's because there are costs, both economic and non-economic, associated with such a switch. (Patients will require additional physician oversight during this drug calibration period, for instance, to make sure their disease remains stable.)

Note the high switching cost associated with MS drugs also comes into play when the company aligns its pricing strategy to its overall commercial goals. With switching costs high, a new product is only likely to gain market share in newly diagnosed patients. To penetrate this "market" as quickly as possible, the company might want to consider an innovative pricing strategy that provides additional differentiation from existing therapies and allows the company to collect real-world data on the potential dosing advantage.

Despite the high cost associated with the novel oncologic, given the disease severity and the ability to narrow the population based on genetic information, this type of product should face little payer pushback in the US marketplace – at least until a competing product is introduced. Again, a pricing analysis of competing products provides little evidence that an innovative pricing arrangement is required. However, since oncology drugs are frequently used in combination, companies should be mindful of how the price of the individual drug may affect the cost of the treatment regimen overall. This is especially true if the regimen contains drugs from multiple pharmaceutical players, which might complicate the use of innovative pricing models. In this instance, the manufacturer will want to bolster its unit-based

THE ROAD AHEAD

The ongoing debate about drug pricing requires that, for their key products, biopharma companies embrace different pricing methods now, when the risks are lower and there is an opportunity to be an active partner in discussions with other stakeholders.

When drug pricing wasn't as big a concern to other stakeholders, biopharma companies had the luxury of viewing alternative pricing mechanisms as a defensive option, reserved for use after negative value assessments resulted in market access delays that limited patient access. Going forward, however, companies need to understand that new pricing models enable access to valuable real-world data, the current currency of the reimbursement realm, and improve their reputations with other health care stakeholders.

EY believes that maintaining today's pricing status quo comes with significant business risks. Current pricing practices already put biopharma companies in direct conflict with key stakeholders. Left unchanged, there is a real risk that payers will use blunt methods to curb costs, constraining revenue growth for the biopharmaceutical industry. More importantly, such tactics could limit patient access to vital therapies that improve the productivity and health of our global society.

Biopharma companies genuinely want to reorient stakeholder conversations to discuss the value drugs provide to patients and society. Those conversations will only be productive if biopharma companies first accept responsibility for developing drug pricing solutions that take into account stakeholders' definitions of product value. Now is the time to think differently about drug pricing.

A#2016800044 IV

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

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Exhibit 6

Assessing The Pricing Flexibility Of Three Different Products

SOURCE: EY

pricing decision with additional analytics that support the product's value.

Of the three products we qualitatively assess, the curative gene therapy seems least likely to face payer scrutiny at launch. In this instance, the disease severity is high and the competitive intensity is low. Absent competing products in the marketplace, the product also enjoys only-in-class pricing flexibility. However, the durability of the therapy's effectiveness is likely to be a concern for payers, especially if the price tag makes it difficult for payers to meet annual budgetary thresholds. Depending on the gene therapy's cost, payers might desire some kind of pay-for-performance arrangement linked to the duration of the response.

Although the curative gene therapy is unlikely to require an innovative pricing arrangement at launch, a manufacturer could build considerable goodwill with stakeholders by considering other novel payment options. For instance, an innovative financing approach built on an annuity model would be one way to amortize the very significant up-front costs associated with the therapy. This strategy would provide cost-conscious payers with the budgetary certainty they need, while enabling patients access to a life-changing medicine.

A#2016800045

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This article in an excerpt from a forthcoming book co-written by EY and Dr. Francoise Simon, Special Lecturer of Health Policy and Management, Columbia University.

Acknowledgments

The authors would like to acknowledge the following individuals for providing assistance with the creation of this article: John Celentano, Russell Colton, David DeMarco, Patrick Flochel, Glen Giovannetti, Kim Ramko, Jeff Stoll and Gabriele Vanoli. Andrew Forman and Jasraj Sokhi developed the financial model presented in Exhibit 1.

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ANGLE Targets A Rich CTC Niche In Liquid Biopsy

Liquid biopsy, which allows the measurement of markers present in biological fluids, could replace some invasive biopsies and allow clinicians access to tissues that have been inaccessible with current methods. Within this dynamic, multibillion-dollar field, ANGLE PLC is coming closer to market readiness with its circulating tumor cell harvesting technology, as CEO Andrew Newland explains.

BY ASHLEY YEO

- UK company ANGLE is aiming to shift clinician and industry sentiment away from the view that the easy collection of viable cancer cells from blood on a regular basis for analysis cannot be done.
- Its liquid biopsy system, Parsortix, is a disruptive technology that can be used to collect all types of cancer cells in all forms of cancer, and could be used as a companion diagnostic in the future.
- ANGLE has high hopes that its cell harvesting technology will win acceptance from clinicians who have hitherto been using tools that are both more expensive and have greater limitations.
- Its goal is to partner with as many companies as possible, both medtech instrument companies and pharma firms that are developing new drugs.

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In our annual review of the diagnostics industry, we identified liquid biopsy as one of the big stories of 2015. Investors have flocked to the space and **Roche**, the market leader in molecular diagnostics, was just one of many companies that expanded its presence in the field through acquisitions or strategic alliances last year. (*See "Diagnostics In 2015: Past Trends Coalesce, New Roads Open" — IN VIVO, January 2016.*) The timing couldn't be better for **ANGLE PLC**, which has been developing its liquid biopsy technology for a decade and is preparing it for clinical commercial launch.

Originally an IP commercialization specialist, ANGLE saw the potential in a cell isolation technology invented by Philadelphia scientist George Hvichia, PhD. The UK-based firm acquired the technology and set up a company around it in 2006. The *Parsortix* technology was originally invented for use with fetal cells, but ANGLE changed the initial focus to cancer. The UK AIM (ticker AGL) and US OTCQX (ANPCY)-listed company has since disposed of all its other investments in order to focus 100% on the Parsortix system, which it has patented to capture rare cells in patients' blood. CEO Andrew Newland says that harvesting circulating tumor cells (CTCs) as a liquid biopsy will change the paradigm of cancer diagnosis.

IN VIVO: How did ANGLE identify and develop the Parsortix cell separation tool?

Andrew Newland: Our company has built a business around the patented microfluidic cell separation technology invented by microfluidics expert George Hvichia, who now works for ANGLE's Parsortix division [**Parsortix Inc.**] in Philadelphia.

The technology went through milestone developments and eventually we proved that it worked with fetal cells in maternal blood, and [we] decided in 2011 that there was a big opportunity to use this technology to capture cancer cells from patients' blood. The ability to do regular, non-invasive biopsies is what this technology is all about, particularly as cancer is different among patients, and also changes throughout the disease lifespan and with treatment within an individual patient.

In 2011, we decided to exit our other developments – including the successful computer graphics company Geomerics [sold for £6.2million/$8.74million in 2013] – and have since been working exclusively on Parsortix.

Is this a truly disruptive technology that represents a major difference/advance over what we've seen so far?

We think it's completely disruptive. We've changed the paradigm because, with only one cancer cell in one billion blood cells, getting hold of cancer cells has been very difficult. The literature until now has said that it's easier to do ctDNA – analyzing the fragments of dead cancer cells that sit in the plasma. This yields some information; however, richer medical information comes from the CTCs – the living cells in the blood that are seeking to cause metastasis. Harvesting them is what we can do easily and reproducibly.

We are working with some of the world's leading cancer centers to change perceptions. They have evaluated the system, shown that

ANDREW NEWLAND
ANGLE PLC

it can indeed capture the cells, and they are now working with us on translational research to determine how best they can get clinical outcomes to benefit patients. There's a multibillion-dollar liquid biopsy market coming.

Our CTC system is compatible with ctDNA analysis. With ctDNA it is relatively easy to get the plasma out of the blood by spinning and separating out the cell components. The rest is then thrown away. But under our system, we add liquid to it, run it through the Parsortix system and capture the CTCs. We think that the labs that already do ctDNA should keep the cellular component and run it through our system in what is a relatively inexpensive process. They then get the added medical benefit and information from analyzing those cells as well. It all comes from the same standard 10-mL blood draw.

What is the idea behind the system, how does it work and what is the consumable element?

George Hvichia was the first to realize that structures as small as ± 1 micron could now actually be made. The Parsortix consumable is a thin, single-use polycarbon cassette with a plastic film on top of it. The blood flows through it via an inlet port and runs along channels with looped ends. The channels are stepped, over which the blood runs, but the cancer cells, which are larger and less compressible than blood cells, get held on the steps. Even the largest white blood cells can get through, while the cancer cells are captured. The system then reverses the flow and harvests the cancer cells back out. It's unbelievably simple and it does not affect the living cells.

The world-class cancer centers that have used our Parsortix system have published excellent results showing how well the system works. Research use is increasing and we are moving ahead with plans for our first clinical application.

How does the competitive landscape look?

The competition is mainly utilizing antibody-based capture. This process is both expensive and has problems because it requires the CTCs to have particular cell surface markers, which often is not the case.

Johnson & Johnson's antibody-based *CellSearch* is currently the only US FDA-approved system, but it counts cells rather than harvests them. The antibody segment features several other systems [including **Cynvenio Biosystems Inc.**'s *ClearID*, **Biocept Inc.**'s *OncoCEE*, **Fluxion Biosciences Inc.**'s *IsoFlux*, Gilupi GMBH's *CellCollector* and **AdnaGen AG**'s *AdnaTest*], but they suffer from drawbacks of the antibody capture mechanism that misses clinically relevant cells and damages or kills the cells.

In contrast, the third and most recent peer-reviewed publication [see below] on Parsortix [by the University Medical Centre Hamburg-Eppendorf (UKE)], showed that 99% of the cells harvested using the Parsortix system are alive.

There are also membrane-based systems for CTC isolation. These, like Parsortix, are simple, low cost and can capture all kinds of cancer cells. However, unlike Parsortix, they have difficulties in harvesting the cells out of their system for molecular analysis as the cells get stuck in the membrane, which is a major weakness.

Because of these flaws, there is a general viewpoint, which we are seeking to change, that it's not practical to get CTCs, as other techniques have not been that successful.

ctDNA works up to a point. Medically, it is limited to DNA and provides no information on the crucial areas of the cancer's RNA or protein expression, and it does not provide live cancer cells which can potentially be cultured and grown outside the patient for investigation.

What activities are you undertaking to expand awareness in the clinical and research communities?

We are working with some of the leading cancer centers globally, which have published strong evidence in support of Parsortix. Three peer-reviewed papers have now been published in the last six months, the first by Barts Cancer Institute [BCI], on prostate cancer, in the *PLOS ONE* journal; and the second by Cancer Research UK [CRUK], Manchester, on lung cancer in the *Royal Society of Chemistry Analyst*. The UKE study [see above] was published in January 2016 in the *International Journal of Cancer*.

Cancer Research UK Manchester Institute has five of our systems in their labs, and is moving toward adopting it as standard in their GCLP laboratories. They went on record as saying that "this system is ideally suited to routine clinical analysis of patient samples."

We are just one part of an overall equation: we present the tissue in a form that can be analyzed repeatedly and easily. Those aspects you would have looked at with a solid biopsy can be done with our system too, such as immunohistochemical staining, and looking at cells morphologically under the microscope; with our system these can be seen more clearly than with a solid biopsy. And in terms of molecular analysis it is ideally suited for real-time PCR, digital droplet PCR and next-gen sequencing.

What are the actual benefits of using Parsortix from the lab's point of view?

There are seven advantages of the ANGLE system:

- It is simple to use, yet highly effective.
- It is low cost, at £100 per single-use cassette compared with the several hundred pounds for the CellSearch disposable [the CellSearch system's capital costs are some $250,000, against ANGLE's £40,000].
- Parsortix captures all kinds of cancers, where other systems typically work only for certain type of cancer; and in ovarian, the antibody-based systems do not work at all – that's one of the reasons we chose that as our first clinical application.
- It captures all kinds of cancer cell, including mesenchymal cancer cells – those involved in the process of metastasis – and the antibody systems generally fail to capture those.
- The system valve allows reversal of the flow out, so it's easy to harvest the cancer cells into a collection tube for analysis.
- It's a high-purity system that is some 30 to 50 times purer than other systems in terms of not having residual white blood cells.It has high cell viability – the cells are alive – so you can grow the cells and potentially test drugs on the cells outside the patient. It also lends itself to xenografts.

What is your business model?

Our proposition is to provide an instrument to sell to the hospital lab; and a consumable which is used one per patient. The hospital likes that model as it remains in control of the testing, which can be done close to the patient and repeated as many times as necessary.

US hospitals in particular like the fact that they can make money out of the process. With the US ovarian cancer reimbursement code [$516], we would anticipate that the hospital would retain, say, $300, for running the analysis, and we would get $200. The hospitals would use the income to strengthen their R&D capability. In contrast, the model used by the existing tests involves the hospital mailing the patient's blood sample to the commercial lab, which runs the test, sends the results back and takes all of the $516. But this degrades the hospital lab's revenue base. And it's not an easily scalable model, whereas ours is. The ctDNA companies are all service labs too. We believe that it is a major advantage to have a product-based solution rather than a service lab.

We could also build quite a lot of flexibility into the business model. We will have a flexible pricing structure depending on the nature of the customers' needs and adopt whatever approach is required. We would initially suggest an outright sale, but it would depend if the customer has a capital or revenue budget. Customers could rent the system and pay more for the consumable. It's customer-driven at present, and we are at the early stages – we've only just announced our first sales on a research use only [RUO] basis in December 2015.

What will your pricing strategy be?

The system represents tremendously good value, but we also need to get a good return for shareholders too, as they've invested in us and funded development costs over many years. We can undercut the antibody system providers easily, and still make good profits. The membrane companies are also low cost, but can't do the things we can do; and the ctDNA people can get their tissue easily, but the cost of analysis is high because it's only fragments and requires expensive next-gen sequencing.

The general economic picture is one of saving health care costs, not increasing them. There are ever-increasingly complicated drugs to address cancer, and some work really well – but only in a proportion of patients. Immunotherapies are really exciting and show a lot of promise, but those drugs work well in only one in three patients and cost around $150,000 per patient per year. If a blood test could be used to determine which patients the drug will work in, the system has saved the $300,000 that would have been spent on cancer drugs that do not actually work in the other two patients.

Have you factored in a reimbursement strategy for the clinician-use applications?

While we haven't engaged with the payers as yet, we do consider them when planning our strategy. As such we've deliberately chosen our first clinical application – in ovarian cancer – to be one that already has a reimbursement code [in the US]. We want to bootstrap onto that code [see above]. Once we have got our patient data, we hope to demonstrate to the payers that we have got a much higher specificity than current alternatives. The current CA125 blood-borne marker that is used for ovarian cancer has a typical specificity of only 50%, but because we test for ovarian cancer CTCs, our specificity is 100%. Our sensitivity is typically 80% to 100%, depending on how many RNA markers are used. We will take a similar approach for our other target indications.

You've been quite cautious in the selling the RUO use so far. Why is that?

It is all a matter of time. We've put systems in place with KOLs to secure data and clinical evidence, and we aim to convert them into paying customers following successful results.

On the RUO side, we've made several sales in Europe and the US. When it comes to selling RUO systems, we need to be sure that the researchers know how to work with the cells that come out. What we want to avoid is unnecessary criticism of the system, particularly at this early stage, when a problem has arisen due to a user handling the harvested cells incorrectly. So we are putting a lot of effort into setting up protocols for how users should process the cells efficiently and effectively.

As of mid-January 2016, we have had 12,000 blood samples through our systems already, and 80 systems are out and in use within our own labs, the KOLs and the RUO customers. The system has been through a rigorous phase of optimization.

And our customers are pleased. We are working with some of the largest cancer centers in the world. When they start talking, people start listening. One big cancer center has just bought two more systems from us. This approach is creating confidence among our customers.

We are also sponsoring conferences and are getting strong exposure on social media, with tens of thousands of followers. We have a series of major cancer conferences coming up in the next six months in the EU and the US [including World CDX, Tri-Con, Molecular DX and AACR].

Who has ANGLE teamed up with as it has moved up the maturity scale – and which types of partner are still in its sights?

The technology is all owned by ANGLE, and we have led the whole project, but we have outsourced in key areas to improve efficiency and enable rapid growth. The manufacturing is all outsourced, with German company thinXXS making the consumable cassette and UK manufacturer Cogent Technology making the instrument. The R&D is all driven by the cancer centers. This approach gives us easy scalability as we build sales.

Longer term, we're committed to partnering with other companies. As we see it, we do one part of the equation well – capturing and harvesting cells for analysis. We're not planning to move into the Roche and Applied BioSystems [**Applied Biosystems Inc.**] space with a new PCR system or go up against Illumina [**Illumina Inc.**] in NGS. What we do want is to have our harvested cells go through their systems. Our declared approach is to partner with as many companies as possible, and with both medtech instrument companies and pharma partners who are developing new drugs. This is a system that can help them with trials processes and potentially provide them with a companion diagnostic to identify patient responders.

The liquid biopsy market is huge. Goldman Sachs puts the US market alone at $14 billion in 2025, while the market potential figure we quote for the Parsortix system is £8 billion per annum – in all cancer types globally.

For us partnering and sharing with other companies is not a problem, and we would be seeking to leverage their distribution, which is particularly relevant for the clinical applications. That's where the real money is to be made. As to the stage we're at right now, we are opening up dialogue with commercial partners, but we're not trying to go too fast with them; we want to get our data lined up and increase our value before we do too many commercial deals.

If you are taking the cautious approach to longer-term strategic partnerships, what are the near-term goals and priorities?

There are three for 2016.

The first is to progress the ovarian cancer application through robust patient studies of women being subjected to surgery for an abnormal pelvic mass to identify in advance whether the pelvic mass is malignant or benign. Studies in Europe should be complete by the end of 2016 allowing an LDT clinical application in ovarian cancer. These studies will be followed by similar studies in the US.

The second is to progress clinical studies in the US toward FDA authorization of the system first in metastatic breast cancer. There is the potential to be the first system ever authorized by the FDA for harvesting cancer cells from blood for analysis.

The third priority for 2016 is to grow the sales via more RUO business – a market valued at £250 million per annum. As well as their economic value, the RUO customers are valuable in publishing results of their research and helping to define new clinical applications.

There should also be newsflow over the next few months surrounding the KOL patient studies in relation to other potential additional clinical applications. During 2016 we expect updates on the ovarian cancer clinical study and from the US breast cancer clinical study.

What are the aims on the financial front?

Analysts' forecasts for sales are £0.3 million to £0.5 million in the year to April 30, 2016. These first sales numbers – initially modest – may drive quite a bit of interest. The year after may be a mix of additional RUO sales and initial sales of ovarian cancer clinical application sales in Europe.

We've put all our resources into this opportunity, which has the risk profile and capital profile of a software business, but the financial and revenue and capital returns of a big pharma. Usually you don't get a patent-protected position in a multibillion-dollar market with this relatively low level of investment.

And when you're not putting in the hours on Parsortix, what keeps you awake at night?

Simply how long it all takes. It is challenging bringing a diagnostic device into the market given the hurdles of proof. I'm confident we have a good pathway, but it's frustrating. In other sectors, it's "launch and you're off." In health care, you need opinion leaders, data, and you've got to run studies, and it all has to be has to be done in a very specific way.

But we've got a clear view that there is an exceptional market opportunity out there, and we know what steps we need to take to position ourselves for that. The history of the development path of companies with this sort of ground-breaking technology suggests that they end up with several partnerships with big companies.

We could imagine that all the big medtech analytical platforms would have a Parsortix built onto them – in the fashion of the famous PC chip branding – there might be a "Parsortix Inside."

A#2016800050

COMMENTS: Email the author: *Ashley.Yeo@Informa.com*

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Institutionalizing M&A Excellence In Health Care

M&A deals, particularly smaller ones, are the lifeblood of the health care industry. Despite evident success in dealmaking, McKinsey says that pharma and medtech firms can benefit by bringing better consistency, transparency and accountability to their M&A programs.

BY SPRING LIU, MATTHEW VAN WINGERDEN, ANKUR AGRAWAL AND RUTH DE BACKER

- The need for innovative technologies continues to be the main driver for pharma and medtech M&A.
- Mega-mergers may grab the headlines, but the health care industry's smaller deals are equally important. We can expect to see a steady stream of them going forward.
- To maximize dealmaking success, McKinsey advises health care companies to follow the examples of peers in other industries and systematize their M&A processes.
- M&A teams need to act quickly, develop customizable playbooks and build in more post-integration analysis.

Executive Summary >> 52

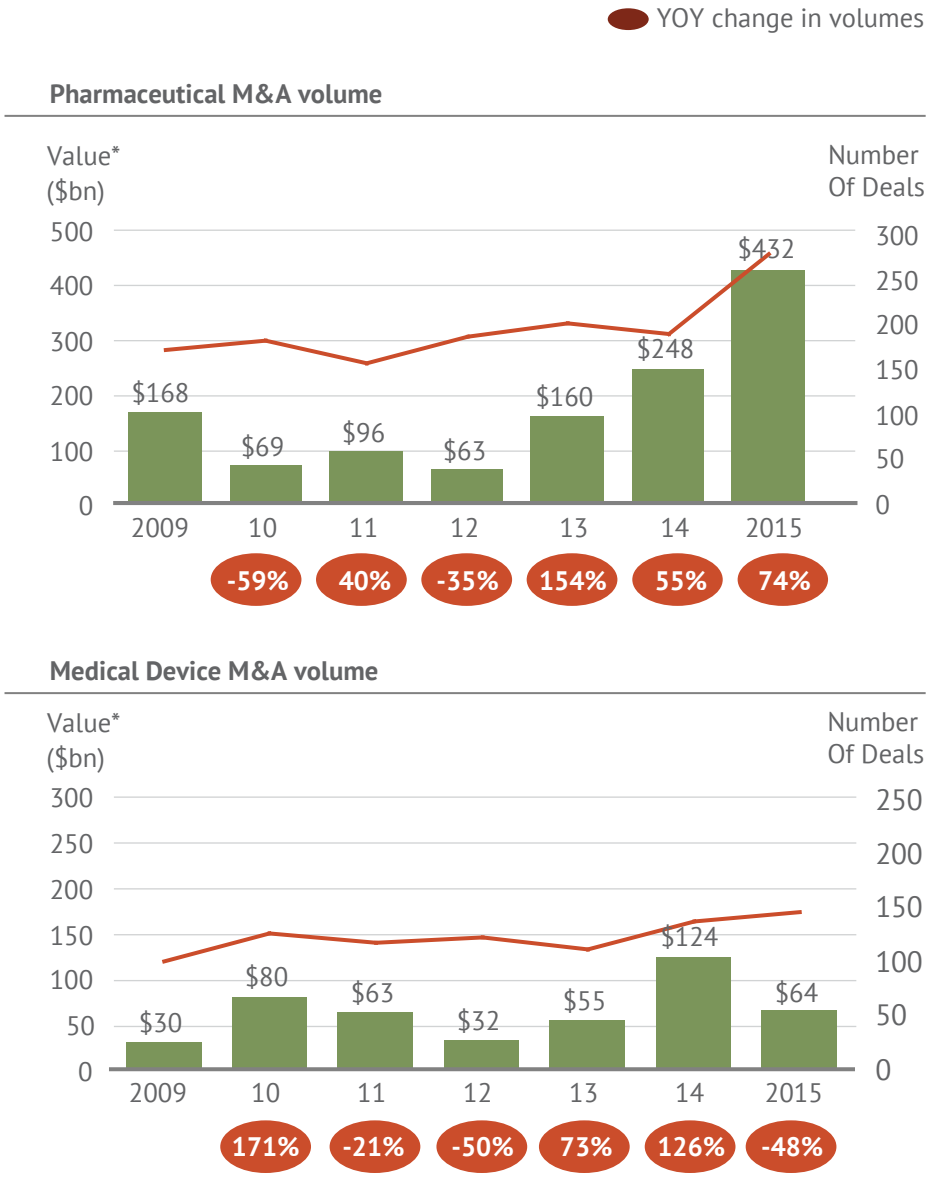
The past few years have seen a boom in health care mega-mergers, with headline-worthy examples in both biopharma and medtech. In terms of total M&A deal value, 2014 was the most productive year in recent memory for medical devices, and 2015 was even more productive than 2014 for pharma. (*See Exhibit 1.*) (*Also see "Mega Medtech M&A Momentum In 2015" — this issue.*) This boom was fueled partly by the overcapacity that persists throughout the industry, particularly in support and commercial functions. That much is evident from the scale of the cost synergies announced in recent acquisitions. The largest acquisitions in the last year have declared significant cost synergies, even if that was not the main objective. In medtech, **Medtronic Inc.** announced $850 million of cost savings when acquiring **Covidien PLC** in June 2014; and in Pharma, **Pfizer Inc.** announced a $2 billion cost synergy in the merger with **Allergan PLC**.

However, these mega-mergers, while important in reducing overcapacity, have done little to change the rationale for most health care deals, which continue to follow the traditional model: using M&A to acquire external innovation to fill gaps in a company's product portfolio or capabilities. In a recent McKinsey survey, health care manufacturers were 78% more likely than a wide cross-industry sample to cite the "expansion of product or service offerings" as the main reason for their company's recent M&A deals, and 133% more likely than the broader group to cite the "acquisition of new assets."

In addition, the survey found that 86% of health care manufacturers expect the number of deals to increase in the next 12 months, and a similar percentage expect the average size of deals to stay the same or become smaller. For the foreseeable future, then, we can expect a continuation of past trends, in the form of a high volume of smaller deals that bring innovation and growth. A strategy of multiple small deals is also value creating for the manufacturer's shareholders. An analysis of 1,000 companies over the past decade shows that health care manufacturers with high-volume M&A programs deliver better returns to shareholders than their peers – a finding consistent with

Exhibit 1

Pharma And Medtech M&A Volume, 2009–2015



SOURCE: McKinsey

the results from other industries.

A brief summary of recent health care M&A deals will help to provide a context for this discussion. Large, attention-grabbing deals worth more than $5 billion rose from four in 2009 to 15 in 2015, according to McKinsey research, with mega-deals worth more than $10 billion accounting for seven transactions in 2014 and nine in 2015. The bulk of M&A deals were much smaller, however, and have increased considerably in number. Deals between $25 million and $5 billion were stable at around 320 to 380 per year between 2009 and 2014, but rose to 536 in 2015. The median deal size remained stable and small over the last five years from $88 million in 2011 to $89 million in 2015. (*For another look at recent medtech M&A, see "Mega Medtech M&A Momentum In 2015," this issue.*)

AUTONOMOUS TEAMS DRIVE THE DEALS

Given the high volume of deals in the health care sector and the relatively low value of most of them, it is hardly surprising that CEOs of pharma companies and medical device manufacturers do not get closely involved in the early phases of a deal. (*See Exhibit 2.*) When it comes to identifying targets, reaching out to them, and conducting due diligence, health care manufacturers are roughly one-third less likely than companies from other sectors to report that their CEO was "very involved" in the process. Such delegation is consistent with the targeted nature of these acquisitions. A deal that involves only one molecule or device, for instance, will require depth of expertise rather than senior-level oversight or breadth of consensus.

Senior leaders in pharma and medical device companies focus more on setting the high-level strategic direction of their business development teams and check in on the last stages of a deal. Among survey respondents from the health care sector, 95% agreed that executives have an understanding of the assets they need to buy and sell to realize their company's aspirations, compared with 82% of respondents from other industries.

In our cross-industry sample, we found that both high and low M&A performers have room to improve external-facing activities such as building relationships with attractive targets. Although this is also true of health care manufacturers, their reported performance varies considerably across M&A-related activities, and they have a clear lead over other sectors in some of them. For instance, they consistently outperform the cross-industry average in identifying the right targets and engaging them properly. (*See Exhibit 3*).

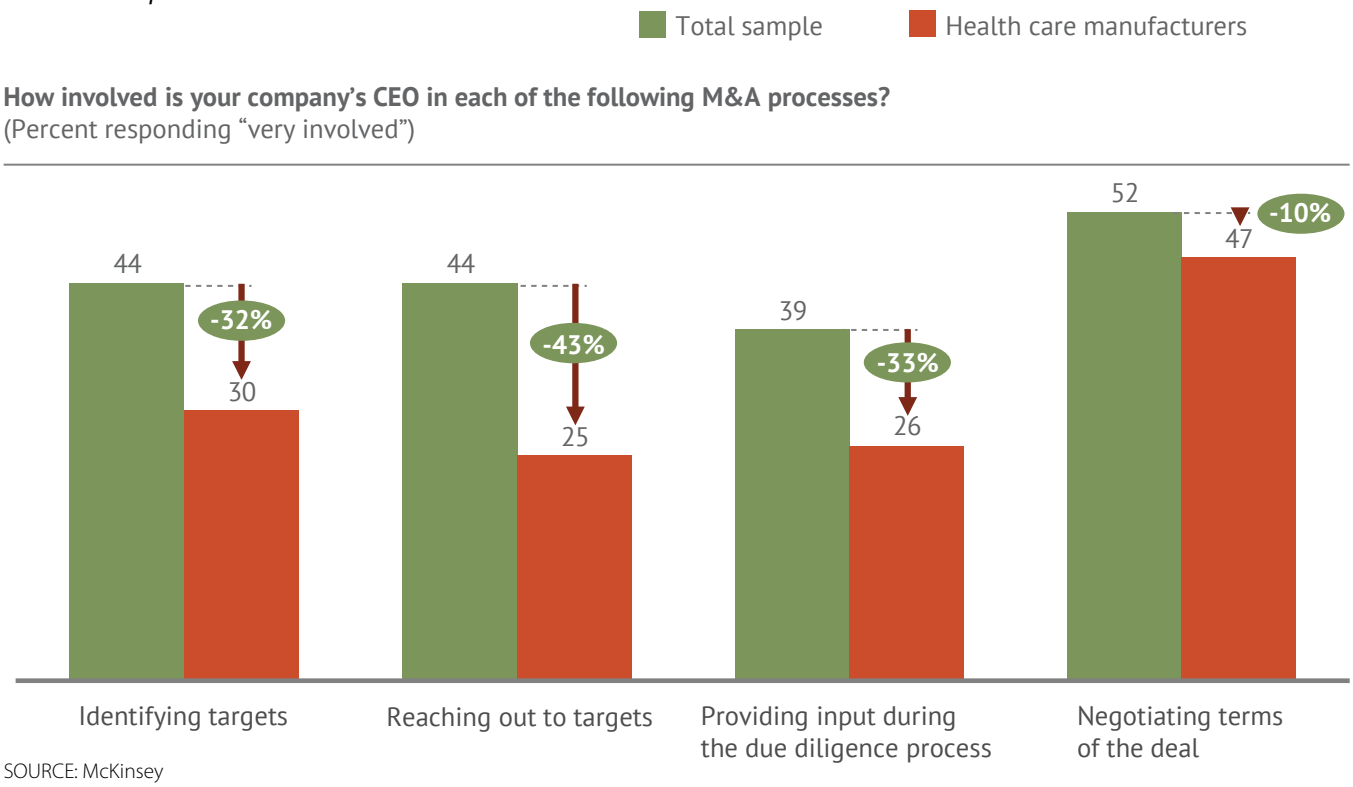
For activities connected to defining M&A processes, such as assigning the right people to develop targets, health care manufacturers perform on a par with other industries. This could be because they focus more on execution than on processes, or simply because they are less successful at the latter.

Greater autonomy for M&A teams and superior performance on target-sourcing activities are not the only differences in the way health care manufacturers approach deals. They also tend to have less well-defined dealmaking processes, criteria and roles than other industry sectors. (*See Exhibit*

Exhibit 2

Senior Health Care Executives Less Involved In M&A

Percent of Respondents



SOURCE: McKinsey

4.) Their focus on agile execution rather than adherence to set processes may stem from the more variable nature of the asset-based expertise required for deal diligence in the health care industry and the importance of staying ahead of the game by conducting diligence quickly. A rigid process in which the same functions are brought into the deal analysis in the same way on every occasion might not meet the needs of the pharma and medical device sector.

BUILDING A CONSISTENT PROCESS

Over the years, McKinsey has analyzed many M&A deals across industries to understand what good practice looks like. One of the hallmarks of success is having a well-run and consistent M&A process and tailoring it to the strategic requirements of each deal. Although agility is important, it is not an excuse to take an ad hoc approach. Companies would do better by developing a systematic process that can accommodate a range of scenarios.

Any strong M&A operation rests on three underlying elements: consistency, transparency and accountability. Consistency in particular can be hard for health care manufacturers to maintain, given that deal types range from mega-mergers to pure IP (intellectual property) acquisitions, and can demand highly specific technical expertise that varies from deal to deal. Given this variability, companies may rule out any type of standardization, but to do so can, in McKinsey's experience, limit the effectiveness of an M&A program.

Although agility is important, it is not an excuse to take an ad hoc approach. Companies would do better by developing a systematic process that can accommodate a range of scenarios.

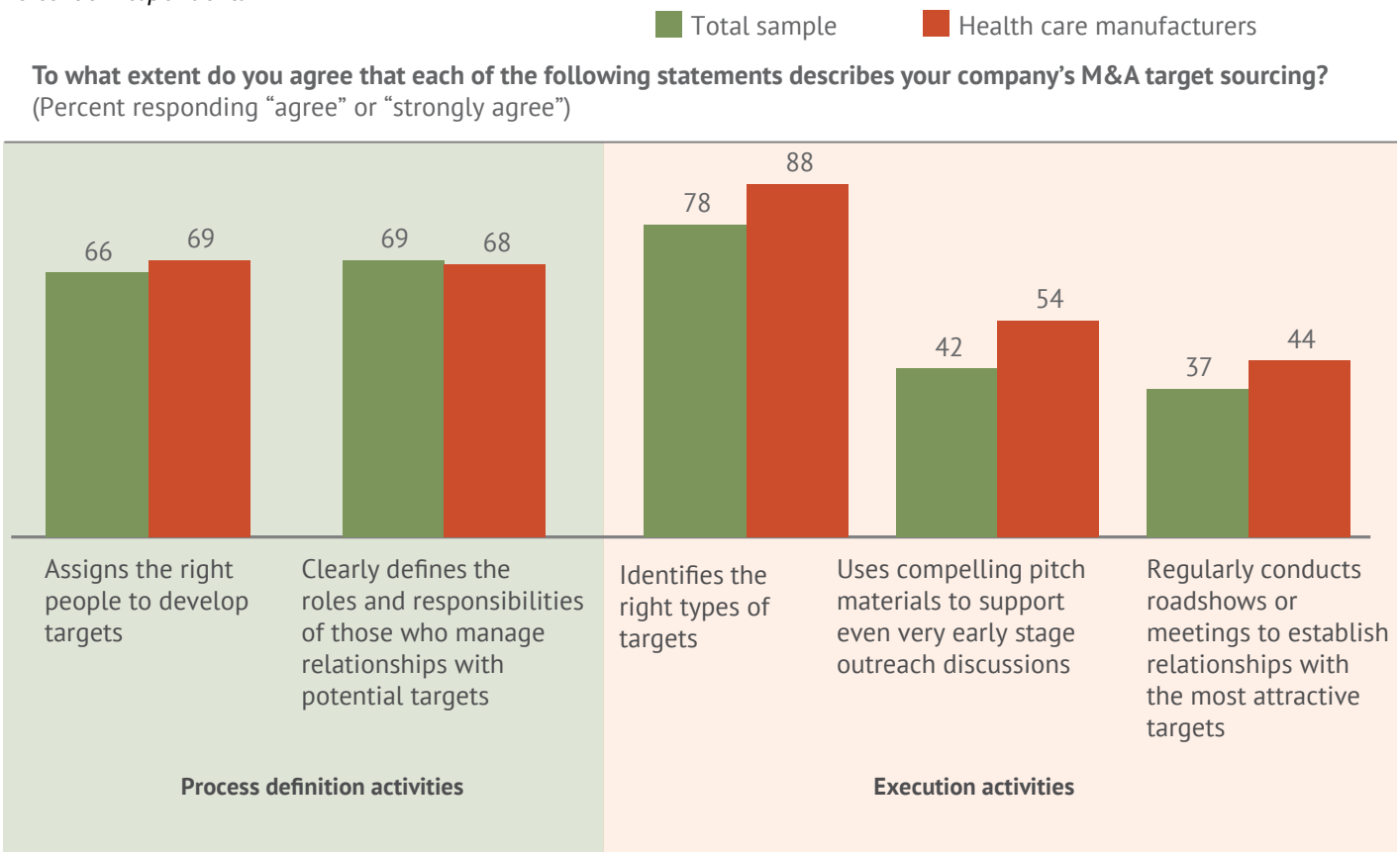
Instead, health care manufacturers can adopt different forms of consistency. One possibility is to develop a set of multiple repeatable processes for specific deal types, such as a company with products on the market, a company with pre-approval products, or a product licensing deal. Such an approach leaves the acquiring company free to pull in suitably qualified experts from across the organization. For each deal type, the company can develop a customizable playbook, with end-to-end M&A processes (including stage gates); descriptions of key roles, deal owners, and cross-functional deal teams; and common tools.

To improve transparency and accountability and build institutional M&A capability, some form of performance feedback is necessary. For M&A teams, the feedback loop will naturally involve an analysis of company or asset performance following integration.

Exhibit 3

Health Care Companies Excel At Identifying And Engaging With Acquisition Targets

Percent of Respondents

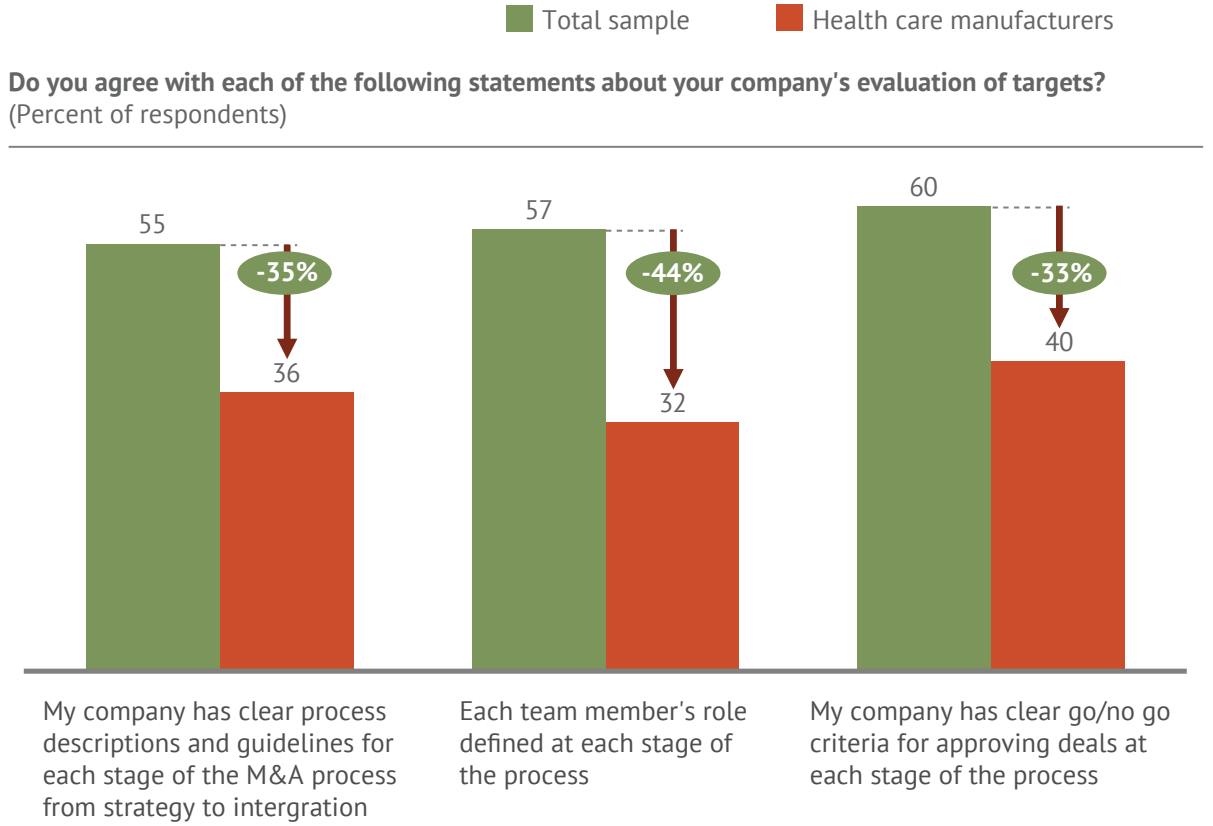


SOURCE: McKinsey

Exhibit 4

Health Care Companies Less Reliant On Standardized Processes And Guidelines

Percent of Respondents



SOURCE: McKinsey

The data from our survey suggest that this area offers health care manufacturers significant scope for improvement. Respondents from the sector were more than twice as likely as the overall cross-industry sample to report not knowing how deals in the past five years had performed relative to plan. Admittedly, the asset-based nature of much health care M&A makes it harder for acquirers to conduct a traditional post-integration analysis of each deal, since many companies include the assets in the base budget of their business. However, companies do need to conduct a retrospective analysis of how a deal has performed relative to the expectations set during the diligence process if they are to consolidate what they learn from individual deals and build their institutional capabilities over time.

CONCLUSIONS

We can expect to see a continuing stream of small M&A deals in health care. Three things will be critical to success: empowering the M&A team to act quickly and pull in expertise from the organization as needed, developing a flexible deal structure and set of guidelines to build up institutional capabilities, and sharpening the company's focus on post-acquisition performance to instill a continuous improvement mind-set in M&A teams.

A#2016800046

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GERMANY: Europe's Go-To Market Changes Rules For High-Risk And Promising Devices

Several recent changes to the German health care system will significantly influence the market access climate for medical device companies working in Europe's largest market. Do they represent an opportunity or a threat for manufacturers accessing the market?

BY BEN MODLEY

- Germany's NUB program, which allows usage of innovative products under a one-year pass-through, has been amended for "especially invasive" products that must undergo an HTA process at the G-BA, the health care reimbursement authority.
- The Trial Regulation – on coverage with evidence development – for promising products in the outpatient sector had a promising start, before quietly coming to a stop. But now it seems to have resumed.
- IQTiG is the latest institute to measure and promote quality in the inpatient sector in Germany. It is early days for the new body, but more quality indicators and some P4P structures are on the horizon, meaning this is definitely something for industry to watch.

Executive Summary >> 52

The medtech industry in Germany is in the midst of the heaviest period of national health care legislation for two decades. Much of it has been spurred by health minister Hermann Gröhe, the CDU and ex-cabinet office minister who assumed the health portfolio at the start of Angela Merkel's third term as chancellor in 2013.

At the same time, the industry across Europe is holding its breath as the proposed Medical Device Regulation (MDR) is hammered into its final shape. This process was made all the more interesting last fall when Germany stood alone in officially objecting to the EU MDR proposal, as reworked by the Council of the EU, based on the lack of consistent standards for notified bodies across the EU. Whatever is decided will likely come into effect in 2019, as things stand at present.

However, of more immediate concern to companies vying for a share of the German medtech market, which expanded by 4.3% in 2014, is the raft of new health and nursing care legislation that came into effect on January 1, 2016, including: a hospital structure reform law, on access to care and inpatient nursing staff; an e-health law, which signals the start of better integration of IT-driven health care; and the final medtech-related piece of the Care Provision Strengthening Act (GKV-VSG), which is described below.

REVISION OF THE INNOVATION-FRIENDLY NUB PROGRAM

For the last decade, Germany has had a very innovation-friendly inpatient reimbursement scheme for premium health care products: the NUB (Neue Untersuchungs- und Behandlungsmethoden) pass-through payments system. Every year, in October, hospitals have been entitled to apply for NUB payments for CE-marked tech-

nologies that are underpaid within the DRG system, without having to file high-quality clinical data.

The DRG Institute, InEK, has had the task of assessing these NUB applications, and has approved them based on cost versus reimbursement considerations – for the most part relying on the CE-marking for safety and efficacy of medical devices. NUB payments are usually available until the product has been integrated into the system of regular DRG payments.

Medical devices have regularly been launched on the German market with data from CE-marking clinical trials, which are often uncontrolled or small-scale. Because in general this is sufficient to trigger the NUB application process, the German hospital sector has been seen as an attractive early "go-to" market. The additional NUB reimbursement allows for market-penetration before the full DRG payments kick in. The time is used for generation of further clinical data until full coverage is secured.

Then, in June 2015, the German parliament adopted the GKV-VSG (see above). This amended the NUB process by among other things introducing an early benefit assessment for "especially invasive" medical devices (under paragraph 137h of the SGB V – Social Law Book V). This legislation links the approval and negotiation of NUBs to the outcome of an official and mandatory rapid health technology assessment (HTA) carried out by the Federal Joint Committee (G-BA, Gemeinsamer Bundesausschuss).

"Less invasive" medical devices and pharmaceuticals/biopharmaceuticals will not be affected by this new legislation, and the NUB process for those products will remain unchanged.

The TAVR Experience

Before we elaborate further on the new NUB process, let us take a real-world look at the market access situation for transcatheter aortic valve replacement (TAVR) products, by way of example.

Edwards Lifesciences Corp.'s *Sapien* device received CE-marking late in 2007 with unique procedure coding already available in Germany upon launch as well as NUB pass-through payments for ten hospitals. Other products followed and were able to use the existing procedure coding and reimbursement. These were based on CE-marking data alone (presumably a small cohort study). Since 2007, we have seen a massive increase in the total number of implanting centers and the volume of procedures performed annually, jumping from ten to almost 50 in 2008, and to 80 in 2009. Since, then the number has remained relatively stable at around 90.

In the early years, annual TAVR procedures in Germany saw growth rates of 100% and above. Starting with a couple of hundred procedures in 2007, the total volume had already reached the 1,500 mark in 2008 – a year that saw a significant increase of implanting centers and successful NUB negotiations. The total amount of procedures grew constantly, surpassing 3,000 in 2009 and reaching 6,000 in 2010 – the year when TAVR reimbursement was integrated into a standard DRG.

All that was based on the CE-marking. After 2010, German TAVR market growth cooled somewhat, but annual growth rates have remained healthy, and mostly above 25%. In 2014, German hospitals performed a total of 13,445 TAVR procedures – a rate of 16.56 TAVR procedures per 100,000 population.

The CE-marking regulatory approval pathway, the different local reimbursement mechanisms around Europe and the differences between EU and US regulatory approvals and reimbursement pathways are themes for further articles.

But all other European markets have been significantly slower at adopting and reimbursing TAVR despite the same regulatory approval pathway. And in the US, it took until November 2011, after solid clinical data from the PARTNER trial, to achieve FDA clearance for the first TAVR device in the narrow indication of inoperable patients (Edwards Lifesciences).

In 2012, the FDA broadened the indication to high-risk patients. The total number of procedures in the US amounted to 26,414 in 2014, according to the US Transcatheter Valve Therapy Registry, roughly 8.28 per 100,000 population (precisely half the rate in Germany; see above).

To gain control over the TAVR market in Germany, the G-BA issued a directive (under §137 SGB V) setting strict quality standards for implanting centers. This has seldom happened in the past, and may be interpreted as a final attempt to restrict the indication and the range of providers who are allowed to use TAVR. The directive came into effect in 2015, with a transition phase until June 2016. Indeed, the history of TAVR's route to

Quick Facts On The German Domestic Market

The April 2014 German federal statistics office (Statistische Bundesamt) report on health care spending noted:

Spending in Germany on medtech products (excluding investment goods and dental implants, but including trade markups) in 2012 totaled €29 billion.

Medtech aids accounted for the largest share (€15.2 billion). Other medtech products totaled €12.8 billion, and wound care €1 billion.

Industry association BVMed says there are some 12,000 medtech companies in Germany, of which 10% have more than 20 staff. They employ 195,000 staff in all. The production value of German-based medtech companies in 2013 was €22.8 billion, up 2.2% on 2012. Domestic sales of medtech products totaled €7.3 billion, and overseas sales €15.5 billion.

uptake in the market may have done much to prompt the introduction of the amended NUB process, which involves the G-BA and its executive arm, the Institute for Quality and Efficiency in Healthcare (IQWiG), and features a more rigorous assessment of clinical data for new technologies.

WHICH DEVICES ARE AFFECTED?

There has been much debate about which medical devices should be affected by the new NUB process. The final version of the law mentions Class IIb and III medical devices, as well as active implantable devices that are of a particularly invasive nature. A lower-level directive from the health ministry, the MeMBV (Medizinproduktemethodenbewertungsverordnung), published in December 2015, details which devices will be affected. They are:

- **Active implantable** medical devices;
- **Class III** (if the mode of action constitutes a significant intervention to the function of organs or the organ system, especially heart, central circulatory system, central nervous system). An intervention is "significant" if there is long-term modification or replacement of the function of an organ (or organ system), or if the medical device has direct contact with the heart, central circulatory system or central nervous system;
- **Class IIb** (if the mode of action is based on influencing organs – especially the heart, central circulatory system, central nervous system – by transmission of energy and/or releasing radioactive substances).

The G-BA is currently updating its rules of procedure to address its new responsibilities. Publication of the update is expected within the coming months. A public discussion to shed further light on the issue was scheduled for March 17.

NEW NUB PROCESSING DETAILS

As to what is known about the updated NUB process, starting October 2016, first-time applications for NUB payments will require timely submission of a value dossier to the G-BA. While the InEK will remain responsible for economic aspects, the G-BA will conduct a rapid health technology assessment and evaluate available clinical evidence.

It is likely that "benefit approved" will be granted only if data are available from high-quality, randomized clinical trials (RCTs) against an active comparator. In the case of suspected bias, the G-BA often downgrades the level of evidence. Expect to see further discussion around this area, since the generation of this level of evidence may not be possible with certain devices.

Medical devices with CE-marking data only may be classified as having "potential benefit." For those procedures, access to (additional) reimbursement under the updated NUB scheme will require further evaluation according to the Trial Regulation, Germany's coverage with evidence development program.

For technologies with potential benefit, the G-BA will commission an impartial scientific institute to plan and conduct an evaluation. Manufacturers and/or distributors will have to cover the overhead costs of the scientific evaluation and its project management, whereas provision of the method including costs for the medical device, are reimbursed through NUB payments. To be eligible to receive a NUB, hospitals must participate in the coverage with evidence development program.

There is an ongoing debate as to whether hospitals may choose to either participate in the core trial, which will likely be an RCT, or in an additional registry.

After the trial phase is completed, G-BA assesses the clinical data produced, publishes the findings and comes to a final decision about whether the benefit of the new method is approved or rejected.

The revision of the NUB program looks like a big threat for the medical device industry. Due to restricted use in a clinical trial setting, indications may remain rather narrow, and broadening them will likely be difficult.

THE TRIAL REGULATION – A TOOL FOR OUTPATIENT INNOVATION

Although the industry was concerned that this legislation would introduce another market access hurdle in the outpatient sector, we had high hopes that the Trial Regulation would offer a shortcut to reimbursement for promising new treatment concepts.

Basically, the Trial Regulation can be seen as somewhat complementing the inpatient NUB program, but in the outpatient sector and in the form of coverage with evidence development. For the first time, this program allowed manufacturers of medical devices to request assessments of innovative outpatient methods. Before the Trial Regulation was available, manufacturers had hardly any opportunity to apply directly for outpatient reimbursement of their technologies.

So, under the Trial Regulation, manufacturers are entitled to request an assessment of new and innovative methods that rely on the use of a medical device and are performed mainly in the outpatient sector. The term "new method" in this context refers to methods that are not yet reimbursed within the German statutory health insurance (SHI) system. This system is not expressly time sensitive either, which means that the time since invention or introduction into the market are not of critical importance.

Upon submission of a value dossier by the manufacturer, the G-BA conducts an initial appraisal and decides if the method under scrutiny has the "potential" to become an alternative to the standard of care.

"Potential" refers to a variety of outcomes, like greater efficacy/effectiveness, better cost-effectiveness, fewer side effects or better medical care. At the end of each year, the G-BA selects which of the methods with potential benefit will actually make it to the trial phase. Following studies, the G-BA decides whether or not to include the new technology in the German catalogue of reimbursable procedures and products for the outpatient sector (the EBM). To date, the G-BA has selected just five technologies in seven indications. Expect the next batch in the coming weeks.

IVD Example

In 2013, the first year that the Trial Regulation was in full effect, my company supported the manufacturer of an innovative IVD through the process. Here is some insight

into what happened, and our verdict on how the Trial Regulation has performed so far.

In the beginning, things went pretty smoothly. We compiled a value dossier featuring HTA-relevant data, including a detailed, technical description of the device, appraisal of the scientific literature and extensive data extraction from trials. We submitted the dossier in mid-2013. Three months later, we received positive notification that the technology would be considered as having potential. In fact, we had delivered high-quality RCT data and had been rather worried that the outcome of the G-BA's assessment would be that the technology is beyond just having potential, and that this route actually had been inappropriate. That would have left the manufacturer without any direct way of applying for reimbursement in Germany.

Early in 2014, we received another notification that the technology would be included in the coverage with evidence development program, and that planning of the study would commence shortly after an initial hearing procedure. We were invited to further comment during the official hearing procedure, as were scientific and professional societies and other stakeholders. We were further granted an informal and confidential consultation session with representatives of the G-BA at their offices in Berlin.

At this point, things took a turn for the strange. We connected the G-BA with the principal investigator of a post-marketing clinical follow-up (PMCF) study at a German university hospital. There was some discussion between them about incorporating the PMCF into the G-BA trial.

And since mid-2014, nothing has happened and the process seems stuck. At first, we were worried that the G-BA may just want to wait until the closing of the PMCF, or thought that ethical reasons might be playing a role, since there was a lot of discussion in the public domain about the technology, including in national newspapers and on TV.

However, because none of the technologies selected under the Trial Regulation have seen any progress and trials did not start until recently, we are currently confident that the whole Trial Regulation has been on hold. We hope to see the program pick up speed again once the updated NUB process is in full effect, since the updated NUBs will to some extent rely on the legal and resource framework of the Trial Regulation.

IQTIG INSTITUTE – A SNAPSHOT

Christof Veit, MD, became the inaugural head of the newly formed IQTiG (Institut für Qualität und Transparenz im Gesundheitswesen – Institute for Quality and Transparency in Healthcare) in January 2015. One year and 80 new staff appointments later, IQTiG has taken over full responsibility for quality assurance in German health care, doing the job previously done by the AQUA-Institut GMBH (the Institute for Applied Quality Improvement and Research in Health Care).

It is assumed that Veit will present his agenda for quality indicators in April 2016, and that the reporting of updated quality indicators may be required by hospitals as early as 2017.

Here is a little background on what the possible future role of IQTiG will be in German health care. Veit has a history in health care QA. A physician by training, he has worked in hospital QA since 1992. From 2007 until his appointment as director of IQTiG, Veit was managing director of the BQS institute (responsible for national quality assurance in German hospitals before AQUA was commissioned with this task).

Further, he was part of an advisory board for the health ministry that did research on quality in health care, quality indicators and especially pay for performance (P4P). He was lead author of a 340-page assessment for the health ministry concerning feasibility of P4P in Germany (*Pay-for-Performance im Gesundheitswesen*, 2012). One of the key messages of that paper is that well-established quality indicators are among the most important factors for reliable and successful P4P structures.

THE TRIPLE VERDICT

There is probably still some way to go before we know the impact of the IQTiG on market access and reimbursement in Germany. Currently, we would rate the new institute not as a threat, but definitely as something to watch. It is likely that we will see an increase in quality indicators and we may see some P4P structures in the coming years in areas that already have well-established quality indicators, like heart valve replacement and knee endoprostheses. In these areas, there are definitely some opportunities for devices with exceptional clinical outcomes and low complication rates.

The Trial Regulation in the German outpatient sector still seems to be more of an opportunity than a threat, but it is definitely nothing to build a business on currently. Though the whole process seems to be on hold, we hope to see some progress again in 2016.

By contrast, the revision of the NUB program looks like a big threat for the medical device industry. Due to restricted use in a clinical trial setting, indications may remain rather narrow, and broadening them will likely be difficult. Though the framework is very different, the result may to some extent resemble the current situation in the US, where CMS reimbursement is restricted to rather narrow, expressly FDA-cleared, indications for innovative and expensive devices.

The overhead costs of a multicenter RCT may be tough to take on, especially for SMEs, and must be taken into consideration when developing a business plan. Although SMEs often support investigator-initiated trials and hence may be used to giving over control of their trials to a third party, this might not hold true for the bigger players who may not be willing to give over control of a clinical study using their technology to an official authority.

On the other hand, additional clinical data concerning patient-relevant benefit over and above CE-marking requirements must be generated anyway to secure reimbursement in most European markets, and in the US. Germany's revised NUB program may allow for the collection of the necessary data under an easily accessible conditional coverage program.

Additionally, under the Trial Regulation, SMEs are entitled to apply for co-funding of study overhead costs through the G-BA of up to 50% of the total costs generally, and up to 70% for orphan disease indications.

Overall, we rate these changes in the German market collectively as "substantial threat with a hint of opportunity."

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MEGA MEDTECH M&A MOMENTUM IN 2015

Medtech M&A activity has been on the rise for several years along with a surge in the number of higher-valued mega-deals, those worth at least $1 billion. Yet a survey of all deals with known values indicates that median deal value has actually declined.

BY ANDREA MANCINI

MEDTECH M&A ACTIVITY HAS BEEN ON THE RISE FOR several years and shows no signs of slowing down. The industry has seen its deals getting bigger and bigger, giving way to a surge in the number of higher-valued mega-deals, or those worth at least $1 billion. For each of the past two years there have been at least 10 mega-mergers, three of which were over $10 billion.

While the exact drivers behind these mega M&As vary for each transaction, there are some common factors inexorably contributing to them all. Consolidation among the now more powerful payers and providers has put a squeeze on the industry, which now faces strong pricing pressure and a transition to a value-based care model. Compounding those strains are the high costs of R&D and innovation, and rising operational expenses, to name a few.

Through strategic and well-planned hefty acquisitions, medtechs – particularly the largest, most established ones – have gained from their targets many efficiencies and synergies resulting in substantial cost savings, while also achieving the scale and full range of product offerings needed to become the leaders in a specific space. And in the process, many have also shed their non-core businesses, enabling them to put all of their might behind their best growth prospects. (*Editor's Note: This survey excludes companies whose core business is in vitro diagnostics.*)

2014: A Tough Act To Follow

The year 2014 was a tough one to beat in terms of medtech mega-merger dollars and industry game-changers. (*See Exhibit 1.*) In that year the sector saw the biggest M&A deal in its history, **Medtronic PLC**'s $47.5 billion acquisition of **Covidien PLC**, which created the second largest medtech, behind **Johnson & Johnson**. The next highest valued transaction that year was Zimmer Holdings' $13.4 billion Biomet buy, from which emerged the leading medtech in orthopedics (**Zimmer Biomet Holdings Inc.**) Including Medtronic/Covidien, there were nine acquisitions worth $84.8 billion. Excluding that deal, however, the total of $1 billion+ medtech acquisitions was a much lower, though still respectable $37.3 billion. (*See Exhibit 2.*)

Exhibit 1

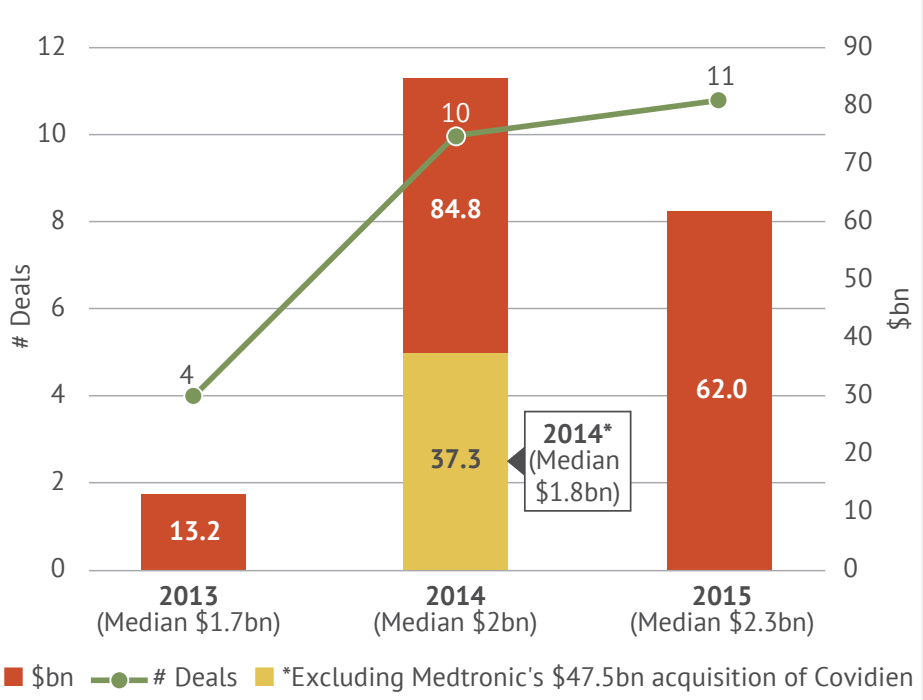
Top Mega Medtech M&A Deals (≥$1bn) In 2014

ACQUIRER	ACQUIRED	DEAL VALUE ($BN)	BUSINESS
Medtronic	Covidien	47.5	Surgical supplies and devices, respiratory and patient care, vascular therapies
Zimmer Holdings	Biomet	13.4	Surgical and implantable orthopedic devices
Becton Dickinson	CareFusion	11.8	Patient safety products, technologies and services

SOURCE: *Strategic Transactions*

Exhibit 2

Medtech M&A ≥$1 Billion



SOURCE: *Strategic Transactions*

The mega M&A momentum rolled right into 2015, when 11 medtech mergers (vs. 2014's 10) had a combined total value of $62 billion. And as was the case in 2014, those deals centered around surgical and patient monitoring supplies and devices. (*See Exhibit 3.*) Their median value was $2.3 billion, just slightly higher than the $2 billion median of 2014's mega-deals, even including the Medtronic/Covidien transaction. (Absent Medtronic/Covidien that median goes down just slightly to $1.8 billion.)

A survey of all medtech mergers with known values, however, paints a somewhat different picture. It shows that although there was an increase in deal volume from 2014 (54) to 2015 (62), the median value declined year over year. In 2014 the median value of a medtech merger, even excluding Medtronic/Covidien, was $188 million. In 2015 that median fell to $155 million. (*See Exhibit 4.*) (*For another look at recent medtech M&A, see "Institutionalizing M&A Excellence In Health Care," this issue.*)

Early in the year and top of the list in terms of dollar value was **Pfizer Inc.**'s February $17.1 billion acquisition of **Hospira Inc.** Although it was mostly a drug play, the deal included Hospira's troubled infusion pump business. (In late 2012 FDA banned imports from one of Hospira's pump manufacturing facilities – that ban was lifted in early 2015 – then in 2014 it told hospitals to stop using Hospira's *Sybiq* system, due to cybersecurity concerns.) Pfizer gained about $800 million in cost synergies, a well-positioned biosimilars pipeline and about 200 injectables, mostly generics, focused on cancer and acute care. (In August the FTC required Pfizer to sell off one of its own and three of Hospira's generics.) At the time of the deal Pfizer stated strongly that it would keep the newly acquired infusion pumps; however, in January 2016 – and after sealing its immense acquisition of **Allergan Inc.** – it announced it is considering divesting them. Industry sources estimate that the selling price would be around $2 billion.

The next largest 2015 medtech acquisition behind Pfizer/Hospira was in May, when **Danaher Corp.** concurrently announced its $13.8 billion acquisition of filtration and purification equipment maker **Pall Corp.**, and its plan to split its businesses into two separate public entities in 2016. That strategy includes the move of its industrial units – focused on testing and measurement equipment, fuel pumps, automation gear and sensors, and the *Matco* brand of tools for mechanics – into one stand-alone company. Danaher's other, life sciences-focused entity, will join Pall's technologies and products with Danaher's life sciences, diagnostics and dental units, as well as its water quality and product identification platforms. Danaher expects the deal to provide the combined companies $300 million in cost savings and to accelerate new product development.

Loss To One, Profit To Another

Divestitures were at the heart of many of 2015's mega medtech deals, which left both buyer and target poised to maximize profits. Large device firms sold off their non-core assets and built up the businesses in which they saw the most growth opportunity. Buyers of the discharged assets had complementary businesses and strategies to increase their revenues.

Case in point: Johnson & Johnson's exit from interventional cardiology in March through its sale of **Cordis Corp.** to **Cardinal Health Inc.** Cordis' well-established brands are focused on coronary and peripheral vascular disease and include diagnostic and interventional devices such as stents, balloons, catheters and vascular closure systems. J&J asserted that the deal would enable the company "to focus on [its] most promising opportunities to help patients and drive growth."

Though the mature brands would not appear to have much revenue growth potential, they appealed to Cardinal because they fit into its physician preference item (PPI) strategy, an effort by Cardinal to provide cost savings to health care providers for products (often traditional ones with little innovation or differentiation) that usually come at a high cost in part due to high physician preference. As part of the PPI initiative, Cardinal leverages its manufacturing capacity and vast distribution channels to offer lower prices than its competitors.

Also last March **Endo International PLC** sold to **Boston Scientific Corp.**, for $1.6 billion in cash, the men's health business of its **American Medical Systems Holdings Inc.** division. Endo divested AMS so it could focus on its pharmaceuticals business, which

Exhibit 3

Mega Medtech M&A Deals (≥$1bn) In 2015

ACQUIRER	ACQUIRED	DEAL VALUE ($BN)	BUSINESS
Pfizer	Hospira	17.1	Infusion pumps, sterile injectables, biosimilar drugs
Danaher	Pall	13.8	Filtration and purification devices
*Dentsply International	*Sirona Dental Systems	13.3	Dental devices
St. Jude Medical	Thoratec	3.5	Cardiovascular/heart assist devices
Exelsior Union (China)	Mindray Medical International	3.3	Patient monitoring, diagnostic imaging
Mallinckrodt	Ikaria	2.3	Neonatal critical care devices
Hill-Rom Holdings	Welch Allyn	2.1	Monitoring and diagnostic devices
Cardinal Health	Johnson & Johnson/Cordis	1.9	Coronary and peripheral vascular disease diagnostic and interventional devices
Greatbatch	Lake Region Medical Holdings	1.7	Surgical devices
Boston Scientific	Endo International	1.7	Urological devices
Mallinckrodt	The Gores Group/Therakos	1.3	Immunotherapy devices for cancer

*Transaction was a merger of equals

SOURCE: *Strategic Transactions*

then comprised just over 80% of Endo's total revenue. It had just acquired the company in 2011 for $2.9 billion, but has since shelled out nearly another billion dollars to settle lawsuits related to defective AMS vaginal mesh products (which aren't part of Boston Scientific's acquisition). While AMS' women's health device sales declined 8% year over year, the men's health unit brought in about $400 million in 2014 sales.

Boston Scientific's acquisition of the AMS business was its first major one since acquiring Guidant back in 2006. The company planned to integrate AMS' portfolio, products to treat urological conditions including benign prostatic hyperplasia, stress urinary incontinence and erectile dysfunction, into its Urology and Women's Health unit, which offers solutions for pelvic organ prolapse, female stress urinary incontinence, abnormal uterine bleeding and kidney stones. Post-acquisition Boston Scientific expects the combined portfolio to be worth about $1 billion in sales and to provide opportunities in innovation and overseas sales growth.

Better Together

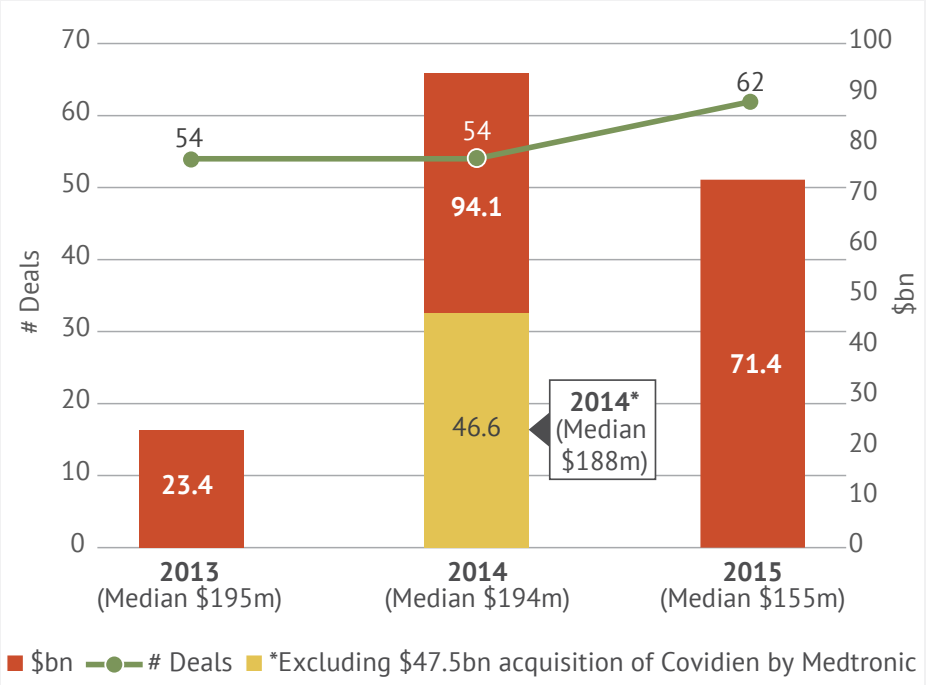
While some medtechs in the mega M&A class of 2015 shed assets and gained complementary ones, a few had deals big enough to establish themselves as leaders in their respective spaces. For other mega-merging medtechs, their newly formed business combinations provided entry into new markets or very well-rounded product portfolios.

In September **Dentsply International Inc.** and **Sirona Dental Systems Inc.** came together via a merger of equals valued at $13.3 billion. The combination, **Sirona Dentsply**, became the world's largest global manufacturer of – and essentially a one-stop shop for – dental products and technologies. Heading into the deal, Dentsply had $2.7 billion in sales from dental consumables including restorative, preventative and prosthetic products, dental implants, and products serving the endodontics and orthodontics markets. Sirona's dental technologies and equipment include drills, panoramic X-ray and chairside CAT systems, plus digital dentistry solutions and imaging systems. The company brought in $1.17 billion in 2014 revenues. Industry observers opine that Dentsply Sirona's mix of dental products and imaging technologies should provide some good potential for growth through innovation.

St. Jude Medical Inc. picked up leadership in left ventricular assist devices (LVAD) and expanded its heart failure portfolio through its $3.4 billion cash acquisition of LVAD market frontrunner **Thoratec Corp.** in June. St. Jude's own core businesses, primarily implantable defibrillators and pacemakers, have had flat to declining sales; the addition of Thoratec will enable it to tap

Exhibit 4

Medtech M&A 2013 - 2015



SOURCE: *Strategic Transactions*

into promising new and emerging markets. The deal was a big bet for St. Jude, which hasn't had a deal nearly the size since 2005, when it paid $1.3 billion for implantable neuromodulation device company **Advanced Neuromodulation Systems Inc.**

Also begging mention is Irish pharma giant and serial acquirer **Mallinckrodt PLC**, which in a five-month span announced two key billion-dollar-plus drug-device acquisitions: private company **Ikaria Inc.** in March ($2.3 billion) and **Therakos Inc.** in August ($1.3 billion).

The driver behind the Ikaria buy was Mallinckrodt's intention to diversify and build out its specialty-branded portfolio, in this case expanding into respiratory neonatal critical care. (Mallinckrodt's main businesses pre-acquisition centered around nuclear imaging and pain management.) Ikaria focused on therapies and delivery systems used in hospitals' neonatal intensive care units. Its key product was *Inomax*, a vasodilator used with ventilator support to treat near-term neonates with hypoxic respiratory failure associated with pulmonary hypertension. Ikaria's terlipressin injection for type 1 hepato-renal syndrome (HRS1) was being evaluated for US approval and was already approved and used outside of the US, including in Europe. Mallinckrodt said it expected to add $150 million of net sales from the deal.

Complementing the Ikaria purchase, Therakos brought to Mallinckrodt an extracorporeal photopheresis (ECP) delivery platform for autologous immune cell therapies. The system is approved in the US for palliative treatment of skin manifestations of cutaneous T-cell lymphoma (CTCL) in patients unresponsive to other treatments. Ex-US, ECP is used in immune-modulating applications against CTCL, for organ transplants and Crohn's disease, and for other conditions. Mallinckrodt expects to expand ECP's use in hospitals, particularly those already using Inomax, as well as to broaden the uses for ECP globally.

A#2016800040

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From: AMAG Pharmaceuticals Inc., SVP, Commercial Ops.
Phone: +33 1 55 42 7878

LEATHER, Alex, MD, PhD
To: Alnylam Pharmaceuticals Inc., General Mgr., Europe & Canada (February)
From: Amgen Inc., VP, Mktg. & Commercial Excellence
Phone: 617-551-8200

LONG, Andrew G.
To: Patheon Inc., SVP, Global Business Controller (February)
From: Fisher Scientific Group, SVP, Global Finance
Phone: 919-226-3200

MANHARD, Kimberly J.
To: Heron Therapeutics Inc., EVP, Drug Dev. (January)
From: Ardea Biosciences Inc., SVP, Regulatory Affairs & Dev. Ops.
Phone: 650-366-2626

MANSURI, Muzammil
To: Sanofi, EVP, Strategy & Bus. Dev. (February)
From: Gilead Sciences Inc., SVP, R&D Strategy & Corp. Dev.
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NEEDHAM, Jr., Thomas E.
To: C4 Therapeutics Inc., CBO (February)
From: Synthesis Capital, Managing Dir.
Phone: 202-421-7994

NORTHROP, Thomas W.
To: Nutra Pharma Corp., Senior Commercial Dev. Officer (February)
From: Tri-State Capital Partners LLC
Phone: 954-509-0911

O'NEIL, Thomas P.
To: Protagonist Therapeutics Inc., CFO (February)
From: Arcadia Biosciences, CFO
Phone: 408-649-7370

PALOMBELLA, Vito J., PhD
To: Surface Oncology, CSO (January)
From: Infinity Pharmaceuticals Inc., EVP, CSO
Phone: 617-714-4096

PHILLIPS, Andrew, PhD
To: C4 Therapeutics Inc., CSO (February)
From: Broad Institute of MIT & Harvard, Senior Dir., Center for Dev. of Therapeutics
Phone: 202-421-7994

PURDY, Sean
To: Espero Pharmaceuticals Inc., VP, Commercial Ops. (February)
From: Arbor Pharmaceuticals Inc., Cardiovascular National Sales Dir.
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NEW AT THE HELM

Konstantinos Alataris
President & CEO
Zosano Pharma

Marie-Louise Bots, SVP
Corporate Development
BioPharmX

Quinton Farrar, VP
Manufacturing & Operations
Velano Vascular

Jason Fisherman, CEO
C4 Therapeutics

Jeff Goater, CFO
Voyager Therapeutics

SHAW, Karen, PhD
To: Amplyx Pharmaceuticals Inc., VP, Biology (February)
From: Hearts Consulting Group, Consultant
Phone: 415-578-3263

SILBER, Christopher J., MD
To: Agilis Biotherapeutics LLC, CMO (January)
From: H. Lundbeck AS, VP, US Clinical Dev. Center
Phone: 214-706-4340

SINGH, Samir
To: Vaxart Inc., SVP, Corp. Dev. & Strategy (February)
From: Principia Biopharma, Bus. Dev. Consultant
Phone: 650-550-3500

TEMPERATO, John
To: Melinta Therapeutics Inc., Pres. & COO (February)
From: Salix Pharmaceuticals Ltd., Head, Sales & Managed Markets
Phone: 203-624-5806

TOU, Mary
To: Alder BioPharmaceuticals Inc., VP, Commercial Strategy (February)
From: Ipsos Healthcare, SVP, West Coast
Phone: 425-205-2900

TSUI, Helen
To: PhaseRx Inc., VP, Finance (February)
From: Dendreon Corp., VP, Corp. Controller
Phone: 206-805-6300

YEE, John, MD
To: Intarcia Therapeutics Inc., VP, Head, Global Medical Affairs, Safety & Ops. (February)
From: AstraZeneca PLC, VP, Head, Medical Affairs, US Diabetes
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IN MEMORIAM

MannKind Corp.
Alfred E. Mann, Chairman Emeritus

DIRECTORS

BONNEY, Mike
To: Global Blood Therapeutics Inc., Director (February)
Phone: 650-741-7700

CLOYD, Mary Ann
To: Bellerophon Therapeutics Inc., Director (February)
Phone: 908-574-4770

FALLON, John A.
To: Exact Sciences Corp., Director (January)
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GREENLEAF, Peter
To: Mirna Therapeutics Inc., Director (February)
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GRIFFIN, Michelle
To: PhaseRx Inc., Director (February)
Phone: 206-805-6300

INGRAM, Robert A.
To: Novan Therapeutics Inc., Chairman (February)
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KEEGAN, Robert
To: Novan Therapeutics Inc., Director (February)
Phone: 919-485-8080

KUWAHARA, Jon
To: Emmaus Life Sciences Inc., Director (February)
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MILLER, Edward D., MD
To: EnGeneIC Ltd., Director (January)
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RIVET, Jeannine
To: Abiomed Inc., Director (February)
Phone: 508-777-5410

ROGERS, Campbell, MD
To: Corindus Vascular Robotics Inc., Director (February)
Phone: 800-605-9635

VAN GORDER, Christopher
To: Abiomed Inc., Director (February)
Phone: 508-777-5410

YETTER, Wayne
To: Espero Pharmaceuticals Inc., Director (February)
Phone: 904-328-2210

ZWICKER, Ian
To: Emmaus Life Sciences Inc., Director (February)
Phone: 310-214-0065

PROMOTIONS

ALATARIS, Konstantinos, PhD
To: Zosano Pharma Corp.
New Title: Pres. & CEO (January)
Previous Title: Pres. & COO
Phone: 510-745-1200

APPLE, Robert
To: Antares Pharma Inc.
New Title: Pres. & CEO (January)
Previous Title: EVP, COO
Phone: 609-359-3020

CZWORKA, Frank
To: Osiris Therapeutics Inc.
New Title: COO (February)
Previous Title: VP, General Mgr., Wound Care
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GOATER, Jeff
To: Voyager Therapeutics Inc.
New Title: CFO (February)
Previous Title: SVP, Finance & Bus. Dev.
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HOOKS, Dale
To: Clovis Oncology Inc.
New Title: SVP, Chief Commercial Officer (January)
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HOUSTON, Michael, PhD
To: PhaseRx Inc.
New Title: CSO (February)
Previous Title: VP, Therapeutics Dev.
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HUINER, Charles
To: Sientra Inc.
New Title: COO & SVP, Corp. Dev. & Strategy (February)
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KEDDIE, Lee
To: CompuMed Inc.
New Title: Pres. & CEO (January)
Previous Title: Co-interim CEO
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KOCMOND, Warren
To: Cepheid
New Title: Pres. & COO (February)
Previous Title: EVP, COO
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PALEKAR, Rohan
To: Avinar Pharmaceuticals Inc.
New Title: Pres. & CEO (January)
Previous Title: Pres. & COO
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PIPER, Brian
To: Medgenics Inc.
New Title: CFO (February)
Previous Title: VP, Finance & Investor Relations
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RICHEY, Jason
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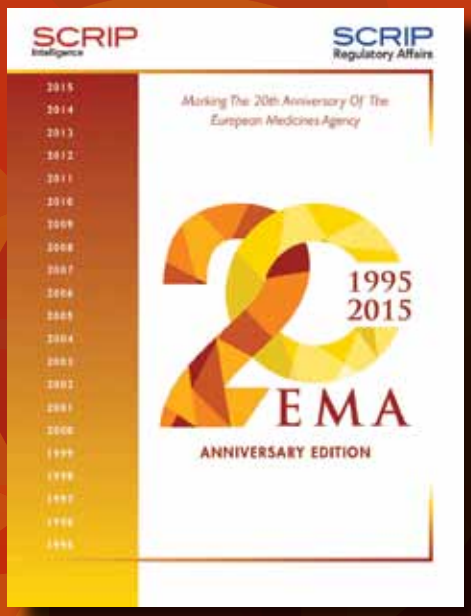

1995
2015
EMA

Marking The 20th Anniversary Of The European Medicines Agency

We commemorate the 20th anniversary with this special report that discusses the EMA's achievements, its shortcomings, and the future of EMA and EU pharmaceutical regulation.

www.PharmaMedtechBI.com/EMA20th

DEALMAKING

This issue's Dealmaking covers deals made:

February 2016

Derived from *Strategic Transactions,* Informa's premium source for tracking life sciences deal activity, the Dealmaking 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.

IN VITRO DIAGNOSTICS

Mergers & Acquisitions

Abbott to pay $56 in cash per share for **Alere**

MedGenome acquires personalized medicine company **Lifecode Inc**

Alliances

Illumina and **10x Genomics** enter into partnership for *Linked-Read* Sequencing products

Qiagen and **10x Genomics** enter into co-development and co-promotion collaboration

Financings

Great Basin Corp. nets $5.9mm in follow-on public offering

Public offering nets $37.6mm for **Quotient**

MEDICAL DEVICES

Mergers & Acquisitions

Medtronic buys **Bellco**

Alcon buys glaucoma device firm **Transcend Medical**

Stryker pays $1.28bn cash to buy **Physio-Control** from Bain

Stryker acquires medical device company **Sage Products** from Madison Dearborn Partners

Stryker acquires **Synergetics USA** neuro assets

Alliances

CryoLife divests *HeRO* assets to **Merit Medical**

Enable Injections and **Flextronics** partner to manufacture wearable high volume injectors

Financings

Acelity proposes $400mm senior notes offering

Sensus Healthcare files for initial public offering

Minimally invasive surgery company **Titan Medical** nets $Cdn11.2mm in overnight offering

PHARMACEUTICALS

Mergers & Acquisitions

Avalanche Biotechnologies and **Annapurna Therapeutics** to merge

Ember reverse merges with public shell to gain OTC listing

Mylan at last acquires **Meda**, paying $9.9bn

Vertical-Trigen Holdings LLC and **Osmotica** merge

Sigmoid Pharma acquires drug delivery technology company **Freund Pharmatec**

Strategia Therapeutics spins out new company **Sola Biosciences**

Alliances

Synlogic selects **AbbVie** as first corporate partner

Achaogen licenses **Trianni**'s transgenic mouse platform

Amgen licenses respiratory antibody to **Genentech**

Hikma to divest rights to five injectable generics to **Amphastar**

Corvidia licenses lead compound from **AstraZeneca**

Premier Biomedical, **Auramedi** form Brazilian JV

Bind, **Synergy** team up on GI cancers

Knight licenses Canadian rights to **Braeburn**'s *Probuphine*

Capsugel, **Pulmatrix** ally in pulmonary therapies

Wuhan Dangdai acquires 19.4% stake in **Cellular Biomedicine Group**

Consort Medical, **Precision Ocular** team up

Merck to sell **Daiichi**'s *Lixiana* in Europe

Eisai gets cancer compound rights from **HUYA**

Eisai and **Piqur** enter trial collaboration agreement for breast cancer therapy

Gavis to divest generic drugs for bacterial infections and UC to **G&W**

Genexine grants EPO license to **Chemo Wanbang**

GSK and **VBI Vaccines** enter into research collaboration

ImmunoGen adds **Merck**'s *Keytruda* to its ovarian cancer trials

ViaCyte gets exclusive license to assets from **Janssen Biotech**

Merus buys three cardiovascular products from **UCB** for £92mm

Pronutria Biosciences secures $42.5mm investment from **Nestle Health Science**

Wanbang gets Chinese rights to **Rockwell**'s ESRD therapies

Financings

Amyris raises $20mm in PIPE

AveXis nets $88.4mm in IPO

BeiGene nets $147mm through initial public offering

Regenerative medicine company **Cesca Therapeutics** secures $15mm strategic investment from Boyalife Group

CytRx enters $40mm loan facility with Hercules; immediately draws down $25mm

Genome editing company **Editas Medicine** nets $101mm in IPO

Mast Therapeutics nets $7.5mm via FOPO

Merus Labs raises $27mm in bought deal private placement

Oxford BioMedica to raise £8.1mm in PIPE

Proteostasis nets $46.5mm in IPO

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

Alliances

Teva and **AbCellera** agree to collaborate for monoclonal antibodies

IN VITRO DIAGNOSTICS

Mergers & Acquisitions
/In Vitro Diagnostics

ABBOTT LABORATORIES INC.
ALERE INC.

Abbott Laboratories Inc. is paying $56 per share (a 50% premium) or $5.8bn to acquire fellow public firm Alere Inc. (Feb.)

Post-transaction, Alere will operate as an Abbott subsidiary. Alere offers tests to diagnose and manage infectious diseases and cardiometabolic conditions, and toxicology products such as rapid analyzer-based tests, visual-read screening devices, laboratory tests, and immunoassay reagents. It will also provide Abbott with benchtop and rapid strip tests. Over half of Alere's $2.5bn in sales are generated in the US, however it also has a growing presence in some markets oversees that can help Abbott further expand internationally. With Alere under its belt, Abbott secures a strong position in the $5.5bn point-of-care testing market and expects its diagnostic sales to exceed $7bn. In mid-2015, Alere sold off its BBI Diagnostics business as part of a reorganization to concentrate on core assets. Concurrent with that transaction, Alere paid $60mm for US Diagnostics, gaining a portfolio of tests for drugs of abuse. Investment Banks/Advisors: Evercore Partners (Abbott Laboratories Inc.); JP Morgan & Co. (Alere Inc.)

MEDGENOME LABS PVT. LTD.
LIFECODE INC.

MedGenome Labs Pvt. Ltd. acquired Lifecode Inc. The acquisition includes all of Lifecode's assets, a 13,000 square foot lab in Foster City, CA, and key employees. (Feb.)

MedGenome currently has the largest privately owned next generation sequencing lab in India and offers genomic research services in the US to pharma and biotech companies in a variety of therapy areas. The Lifecode acquisition will allow MedGenome to expand its genomic offerings using Lifecode's precision medicine in early discovery, research and clinical trials, and more aggressively expand its US customer base. Lifecode is currently offering its initial 52 gene *Pan Cancer Somatic Panel* in the US to a limited number of physicians.

Alliances
/In Vitro Diagnostics

10X GENOMICS INC.
ILLUMINA INC.

Illumina Inc. and 10x Genomics Inc. agreed to co-promote 10x's *Linked-Read* Sequencing products with Illumina's sequencing systems. (Feb.)

10x's microfluidics based solutions are built on their proprietary *GemCode* technology. *GemCode* provides *HiSeq X Ten*, *HiSeq*, *NextSeq* and *Miseq* sequencing users with plug-and-play upgrades at a lower cost. The collaboration will enable phasing, structural variant analysis, de novo genome assembly and remapping of difficult regions of the genome. Simultaneously, 10x entered into another co-promotion partnership with Qiagen NV.

10X GENOMICS INC.
QIAGEN NV

Qiagen NV and 10x Genomics Inc. entered into a collaboration to develop and market next-generation sequencing (NGS), single-cell biology and bioinformatics solutions. (Feb.)

The details of the collaboration include: optimizing Qiagen's sample technologies (including *MagAttract* HMV DNA kit) for use with 10x *GemCode* and *Chromium* systems; leveraging 10x's *GemCode* with Qiagen's single-cell biology portfolio and *QIAseq* NGS solutions; exploring the implementation of 10x's *GemCode* with Qiagen's *GeneReader* NGS system; enabling the processing and analysis of 10x's *Linked-Reads* with Qiagen's bioinformatics solutions; and co-promoting each other's applications including Qiagen's sample technologies, *QIAseq*, and Qiagen Bioinformatics along with 10x *GemCode* and *Chromium* products. Simultaneously, 10x entered into another similar collaboration with Illumina Inc.

Financings
/In Vitro Diagnostics

GREAT BASIN CORP.

Molecular diagnostics company Great Basin Corp. netted $5.9mm in a follow-on public offering of 39.2mm units at $0.16. Each unit consists of one common share and 1.5 Series E warrants (each Series E warrant is equal to one common share at $0.25 strike price for five years). Proceeds will be used to fund R&D, for sales and marketing, for manufacturing of additional analyzers, and to expand manufacturing capacity. Roth Capital Partners served as the placement agent. (Feb.)

Investment Banks/Advisors: Roth Capital Partners

QUOTIENT LTD.

Donor disease diagnostics firm Quotient Ltd. netted $37.6mm through the public sale of 4.44mm ordinary shares at $9. Proceeds will fund ongoing development and commercialization of the *MosaiQ* next-generation transfusion diagnostics platform. (Feb.)

Investment Banks/Advisors: JP Morgan Chase & Co.

MEDICAL DEVICES

Mergers & Acquisitions
/Medical Devices

MEDTRONIC PLC
BELLCO SOCIETÀ UNIPERSONALE ARL

Medtronic PLC is boosting the coffers of its recently formed Renal Care Solutions business through the acquisition of Italian hemodialysis firm Bellco Società Unipersonale ARL. Financial terms were not disclosed. (Feb.)

Medtronic folded its legacy renal access offerings into the new Renal Care Solutions unit, and plans to report revenues from it and Bellco as part of the Minimally Invasive Technologies Group's Patient Monitoring and Recovery division. Bellco (which since 2012 has been majority owned by Charme Capital Partners) offers treatments for renal failure, multiple organ failure, and sepsis. In the chronic care market, products include the *Flexya* dialysis system and other hemodialyzers and hemodiafiltration systems. In acute care, the company sells the *Amplyia* multi-therapeutic system for intensive care, along with extracorporeal filtration systems, and the *Dedyca* ultrafiltration system for congestive heart failure and water overload. Bello also offers devices for the neonatal market, including the *Carpediem* ultrafiltration device.

NOVARTIS AG
Alcon Inc.
TRANSCEND MEDICAL INC.

Novartis AG's Alcon Inc. acquired Transcend Medical Inc., a private developer of minimally invasive glaucoma devices. (Feb.)

Transcend was spun out of ophthalmic device incubator ForSight Labs in 2005, and has since received an aggregate $80mm in venture funding through three rounds from backers including Morgenthaler Ventures, Split Rock Partners, HLM Venture Partners, Canaan Partners, Technology Partners, Latterell Venture Partners Investor Growth Capital, Finistere Ventures, and Kaiser Permanente Ventures. Transcend's *CyPass*--a minimally invasive micro-stent to treat mild-to-moderate glaucoma while preserving conjunctival and scleral tissue--received the CE mark in 2013 and is awaiting FDA approval; the company submitted the final PMA application in October 2015. The device is implanted--at the time of cataract surgery, using the same corneal incision--in the supraciliary space (just below the eye's surface) to improve suprachoroidal aqueous outflow (one of the eye's natural drainage pathways) and reduce intraocular pressure levels. Glaukos, one of Transcend's competitors, also has a minimally invasive glaucoma surgery device known as the *iStent* (approved in both the US and Europe); per a November 2015 settlement for a patent infringement case, Transcend is required to provide Glaukos with a 1%, dollar- and time-capped payment on commercial sales of *CyPass*. Alcon's glaucoma offerings consists mostly of drugs (sold through its Ophthalmic Pharmaceuticals unit), including *Travatan* (travoprost) and *Simbrinza* (brinzolamide/brimonidine tartrate), and up until now, Alcon's only device for glaucoma was the *EX-PRESS*, gained through its 2009 acquisition of Optomol. Like the *Cypass*, the *EX-PRESS* is also a glaucoma filtration device, but the latter requires a procedure in which a piece of ophthalmic tissue is extracted. Following disappointing 2015 results in its eye care division, Novartis announced in late January 2016 that it would restructure Alcon's Ophthalmic Pharmaceuticals division, merging it with its own pharma

business, changing management, and allocating more resources to Alcon's two remaining units: Surgical and Vision Care. The current deal expands Alcon's surgical presence to treat glaucoma without medications.

STRYKER CORP.
PHYSIO-CONTROL INC.

Stryker Corp. is paying $1.28bn in cash to buy **Physio-Control International Inc.**, a developer and manufacturer of critical care monitors, defibrillators, and CPR-assist devices. The purchase price amounts to about 2.5 times the acquired company's 2015 revenues of $503mm. (Feb.)

Formed in 1955 as a division of **Eli Lilly**, Physio-Control has changed ownership a multitude of times over the last 20 years. In 1994, Bain Capital Private Equity bought it from Lilly for a reported $60-70mm, and then **Medtronic** stepped in and purchased it for $538mm in 1998. Medtronic then sold it back to Bain in 2011 for $487mm. Stryker looks forward to incorporating Physio-Control into its Emergency Medical Services division. Physio-Control's offerings include *Lifepak* monitors/defibrillators and automated external defibrillators (AEDs), *Lucas* and *TrueCPR* CPR-assist devices, and data management products including *Code STAT* data review software and the *HealthEMS* patient management system. Physio-Control also brings to Stryker a host of accessories and disposables; none of Stryker's revenue in the past has come from the sale of disposables. The acquisition is the second mega-deal announced by Stryker this month. It also revealed that it will buy **Sage Products** from Madison Dearborn Partners in an all cash transaction for $2.775bn. Investment Banks/Advisors: Citigroup Inc.; Jefferies & Co. Inc. (Physio-Control Inc.)

STRYKER CORP.
SAGE PRODUCTS INC.

Stryker Corp. acquired medical device company **Sage Products Inc.** from PE firm Madison Dearborn Partners for $2.8bn in cash. Madison Dearborn originally acquired Sage back in 2012. (Feb.)

Sage manufactures and distributes disposable medical products in the ICU and MedSurg hospital setting for "never-events" including hospital-acquired infections and other related areas. Specific products target oral care, skin preparation and protection, patient cleaning and hygiene, turning and positioning devices and heel care boots. The transaction includes a future anticipated tax benefit in excess of $500mm. Sage reported FY2015 sales of $430mm (giving the transaction a very high 6.5x revenue multiple). Sage will provide Stryker with a disposable revenue stream and will fit well with the company's Medical division. In another mega-deal announced this month, Stryker is also purchasing **Physio-Control International Inc.** (former unit of **Medtronic PLC** spun-off in 2006) for $1.3bn in cash from Bain Capital. In 2014, Stryker acquired **Patient Safety Technologies Inc.** which has a system for counting surgical sponges to avoid accidentally leaving any inside of patients during procedures. Investment Banks/Advisors: JP Morgan & Co. (Stryker Corp.); Barclays Bank PLC (Sage Products Inc.)

STRYKER CORP.
VALEANT PHARMACEUTICALS INTERNATIONAL INC.
Synergetics USA Inc.

In an all-cash transaction, **Stryker Corp.** acquired **Synergetics USA Inc.**'s portfolio of neurology devices, which had 2015 sales of about $32mm. (Feb.)

Valeant Pharmaceuticals International Inc. bought Synergetics in September 2015, including its ophthalmic division (which in 2015 brought in approximately $42mm, representing most of the company's sales), the area Valeant will likely focus upon now that it's divested the neurosurgery products to Stryker. Synergetics' assets in this area include the *Malis* electrosurgical generator used in use in micro, macro, and endoscopic bipolar cutting, tissue coagulation, and blood vessel sealing; and disposable bipolar forceps such as the *Spetzler Malis* brand, used by neurosurgeons in visualization during tissue coagulation (both are distributed by **J&J**'s **DePuy**'s **Codman** division). Back in 2010, Stryker bought Synergetics' *Omni* ultrasonic surgical aspirator, which is used in neurocranial and neurospinal surgeries; the current acquisition of the remaining Synergetics' neuro portfolio will complement Stryker's Neuro Spine & ENT business, which offers *Sonopet* ultrasonic aspirator tips (for soft tissue and bone dissection) and RF generators for interventional spine procedures.

Alliances
/Medical Devices

CRYOLIFE INC.
MERIT MEDICAL SYSTEMS INC.

Merit Medical Systems Inc. paid $18.5mm in cash for **CryoLife Inc.**'s FDA-approved and CE-marked *HeRO* (*Hemodialysis Reliable Outflow*) graft assets including global marketing rights, customers, intellectual property, equipment, and inventory. (Feb.)

CryoLife will manufacture *HeRO* for up to six months after which Merit takes over. The product generated $7.5mm in revenues for 2015. *HeRO* is the only fully subcutaneous arteriovenous (AV) access graft that can maintain long-term access for hemodialysis patients with central venous stenosis. Unlike traditional AV grafts, *HeRO* has no venous anastomosis. The product consists of an ePTFE arterial graft and venous outflow component. Merit has a complementary portfolio of vascular access and dialysis products and will now be able to better serve end-stage renal disease patients. CryoLife divested the *HeRO* assets to focus on its cardiac surgery products. Just two months ago the firm shelled out $130mm for **On-X Life Technologies** to expand its aortic and mitral valve repair and replacement surgery offerings. Investment Banks/Advisors: Canaccord Genuity Inc. (Merit Medical Systems Inc.)

ENABLE INJECTIONS LLC
FLEXTRONICS INTERNATIONAL

Enable Injections Inc. and **Flextronics International Ltd** agreed to partner for the development and manufacturing of wearable high volume injectors. The two companies will collaborate on the design, development and production of the customized wearable injector systems. (Feb.)

Enable's novel injectors are based on pain-free injection technology that can subcutaneously deliver up to 50 mL doses of high volume and/or viscous biologics, monitor compliance and capture data via Bluetooth, passively warm drugs and automate mixing and reconstitution. The injectors can use any standard vials, cartridges or syringes, and will better facilitate in-home therapy.

Financings
/Medical Devices

ACELITY LP INC.
Kinetic Concepts Inc.

Acelity LP Inc.'s advanced wound care subsidiaries **Kinetic Concepts Inc.** and **KCI USA Inc.** may offer $400mm principal amount of first lien senior secured notes due 2021 through a private transaction to qualified institutional investors. Proceeds would help repay Acelity's existing senior term credit facility (due November 4, 2016), and would also be used for general corporate purposes. (Feb.)

SENSUS HEALTHCARE INC.

Sensus Healthcare Inc. (noninvasive skin cancer treatment) filed for its initial public offering on the NYSE. (Feb.)

Investment Banks/Advisors: Joseph Gunnar & Co.; Neidiger Tucker Bruner Inc.

TITAN MEDICAL INC.

Titan Medical Inc. (robotic minimally invasive surgical systems) netted $Cdn11.2mm ($8.2mm) in an overnight equity offering of 13.4mm units (including 1.7mm over-allotment units) at $Cdn0.90 ($0.66). Each unit consists of one common share and one warrant to purchase one common share at an exercise price of $Cdn1.00 ($0.73) for a five-year period. The company will use the proceeds to build five first-in-human units of the its *SPORT* surgical system. (Feb.)

Investment Banks/Advisors: Bloom Burton & Co.; Roth Capital Partners

PHARMACEUTICALS

Mergers & Acquisitions
/Pharmaceuticals

AVALANCHE BIOTECHNOLOGIES INC.
ANNAPURNA THERAPEUTICS SAS

Avalanche Biotechnologies Inc. agreed to acquire all of the outstanding shares of **Annapurna Therapeutics SAS** in exchange for 17.6mm new Avalanche shares. Post-merger 62.5% of the combined company will be owned by Avalanche shareholders and the stock will continue to trade on the NASDAQ under symbol AAVL. (Feb.)

The acquisition will bring together Avalanche's ophthalmic programs with four new gene therapy programs focused on Alpha1-antitrypsin deficiency, cardiomyopathy associated with Friedrich's ataxia, hereditary angioedema, and severe allergies. The new company will be based in California with Avalanche's CEO retaining his position and Annapurna's CEO taking on the COO role. The transaction has already been approved by both boards of directors and now is subject to approval by Avalanche stockholders. Investment Banks/Advisors: Cowen & Co. LLC (Avalanche Biotechnologies Inc.)

EMBER THERAPEUTICS INC.

Ember Therapeutics Inc. (bone morphogenetic protein 7 (BMP-7)-based therapies) reverse merged with American Home Alliance Corp. a public shell, to gain the latter's OTC listing. The combined public company will retain the Ember name and business. (Feb.)

Less than a year ago, the then mostly metabolic-focused Ember merged with Mariel Therapeutics (now an absorbed Ember division), gaining its osteoarthritis and kidney fibrosis pipeline and BMP-7 assets Mariel had acquired from **Stryker** in 2014. Ember, originally

formed by Third Rock Ventures in 2011, the following year in-licensed a BMP-7 platform from **Joslin Diabetes Center** as well as IP from two other research institutes. BMP-7 has demonstrated in clinical trials the ability to form joint cartilage; inhibit and reverse organ fibrosis in the kidney, heart, and lung due to injury or disease; and modulate glucose metabolism in diabetic-related diseases. Ember's current BMP-7 pipeline contains a Phase IIb-ready candidate for osteoarthritis as well as preclinical compounds in Alport's syndrome (a genetic disease affecting waste filtering capabilities of the kidneys), chronic kidney disease, and other metabolic diseases.

MYLAN NV
MEDA AB

Almost two years after launching two separate (but unsuccessful) hostile bids, **Mylan NV** is taking over publicly traded Swedish spec pharma **Meda AB** for SEK83.6bn ($9.9bn). Mylan will pay $8.5bn in cash (SEK165 ($19.68) per share, an 84% premium) and debt, and issue about $1.4bn in Mylan stock). The deal is subject to 90% of Meda shareholders tendering their shares; stakeholders accounting for about 30% of shares have already accepted the offer. (Feb.)

In April 2014, the Meda board rejected both of Mylan's undisclosed offers (industry reports at the time suggested a price of SEK130/share (a 33% premium)) as well as a second sweetened proposal of approximately SEK145/share, which would have represented a 47% premium and valued the deal at about SEK43.8bn ($6.7bn). Meanwhile, in July 2014 both companies made separate strategic acquisitions: Meda bought private Italian pharmaceutical company **Rottapharm SPA** for $3.1bn (in cash and stock), gaining the latter's prescription drug portfolio, consumer health care offerings (Cx; high-margin drugs that aren't reimbursed by insurance), and a greater emerging markets presence. And Mylan acquired **Abbott Laboratories**' developed markets specialty and branded generics business, which it renamed Mylan NV. In April 2015, Mylan attempted another unsolicited bid to take over OTC and generic pharmaceuticals company **Perrigo Co. PLC** for $28.9mm in cash and stock, but the Perrigo board rejected that offer as well as two other higher bids. (In April 2015 **Teva Pharmaceutical Industries** concurrently launched an unsolicited bid to acquire Mylan in a deal worth $40bn, contingent on Mylan not completing the Perrigo acquisition.) In August 2015, Teva dropped its offer for Mylan in favor of buying **Allergan**'s generics business, and after much back and forth, in November 2015 Mylan finally let its offer lapse to acquire Perrigo. Already reigning as the biggest generics company in the US, Mylan, through the addition of Meda, will be able to increase its global salesforce (particularly in Europe, which boasted 65% of Meda's 2015 sales), expand its specialty brands, create a $1bn global OTC business, and grow its emerging markets presence (especially in China, Russia, the Middle East, and Southeast Asia). In 2015, prescription drugs accounted for 62% of Meda's SEK19.65bn ($2.3bn) in sales, while OTC drugs represented 36%. Meda is primarily focused on branded generics and OTC drugs in mostly the dermatology and respiratory/allergy fields. Top dermatology brands include *Aldara* (imiquimod)--for actinic keratosis, superficial basal cell carcinomas, and genital warts--and *Elidel* (pimecrolimus) for atopic eczema. Respiratory offerings include rhinitis nasal sprays *Dymista* (azelastine/fluticasone) and *Astepro* (azelastine). Meda and Mylan are already partners for *EpiPen* (epinephrine) under a 2010 agreement in which Meda licensed exclusive European rights to the auto-injector. Cardiology, pain and inflammation, women's health, and gastroenterology are among Meda's other therapeutic areas. In addition to in-licensing products from Big Pharmas (such as **J&J**, **Novartis**, and **GSK**) and several other partners, a good part of Meda's portfolio was gained from various acquisitions during 2010-2013, including **Acton Pharmaceuticals Inc.** (respiratory therapeutics), **Jazz Pharmaceuticals**' women's health division, **Antula Healthcare** (OTC), and **Alaven Pharmaceutical** (anemia, women's health, and gastroenterology). The enlarged Mylan/Meda merged branded/specialty, generics, and OTC portfolios--which will be sold in more than 165 countries around the world--will have more than 2k products. Mylan expects the combined company to have annual synergies of about $350mm. Investment Banks/Advisors: Centerview Partners LLC (Mylan NV)

OSMOTICA PHARMACEUTICAL CORP.
VERTICAL-TRIGEN HOLDINGS LLC

Vertical-Trigen Holdings LLC and **Osmotica Pharmaceutical Corp.** through its **Osmotica Holdings Ltd.** entity merged to create a fully-integrated specialty pharmaceutical and generics company. The new company will keep the Osmotica name and be jointly owned by both companies. (Feb.)

The combined company will offer both branded and generic products from Vertical in addition to Osmotica's extended-release formulations (pending regulatory approval). Brian Markison (former executive chairman of Vertical) of Avista Capital Partners (Avista is a part owner in combined company) will be the CEO of the new entity. Vertical currently supplies niche, OTC and prescription products (and generics through Trigen) with a focus on women's health and pain management, while Osmotica uses its proprietary osmotic technology and forms strategic partnerships to develop products. Osmotica has several neurology-based new drug programs in the pipeline.

SIGMOID PHARMA LTD.
FREUND PHARMATEC LTD.

Sigmoid Pharma Ltd. acquired drug delivery technology company **Freund Pharmatec Ltd.** for an undisclosed consideration. The acquisition includes 100% of the Freund Pharmatec entity and all its assets including a state of the art GMP pharmaceutical manufacturing facility and research laboratories. (Feb.)

Sigmoid will gain expanded manufacturing capacity from the Freund *Spherex* and *Granulex* technologies along with various IP assets. Freund will continue its customer-funded research and development programs and will support manufacturing for Sigmoid's pipeline including its late stage *CYCol* (colon-targeted formulation of cyclosporine) program in development for ulcerative colitis. Prior to the acquisition, the two companies already had a long-standing relationship with a shared focus on seamless minicapsule technology. Sigmoid's *Single-Multiple Pill (SmPill)* technology is a versatile delivery system for optimizing the formulation of active therapeutic agents and allows for targeted release at the disease site.

SOLA BIOSCIENCES LLC
STRATEGIA THERAPEUTICS INC.

Pharmaceutical R&D company **Strategia Therapeutics Inc.** spun out its first pharmaceutical company **Sola Biosciences LLC**. (Feb.)

Sola focuses on Strategia's proprietary *Tapboost* technology which controls protein folding and the protein production process. The platform is a significant improvement for targeted protein production including antibodies and Fc-fusion proteins. The company has already established ten material transfer agreements with pharma and biotech companies to use the technology. The technology is expected to decrease the cost of biologics.

Alliances
/Pharmaceuticals

ABBVIE INC.
SYNLOGIC INC.

Under a multi-year deal, **Synlogic Inc.** and **AbbVie Inc.** are teaming up to develop new microbiome therapies for inflammatory bowel diseases including Crohn's disease and ulcerative colitis. (Feb.)

Under the deal, which is its first partnership, Synlogic will identify, characterize, and optimize oral IDB candidates and deliver compounds that have completed preclinical studies. With its expertise in metabolic and inflammatory diseases, AbbVie will then take over clinical development and is responsible for regulatory activities and commercialization. Synlogic uses microbial engineering to develop therapeutic microbes or what it calls synthetic biotic therapies. The company's approach is based on the idea that bacteria can detect physiologic conditions, perform a therapeutic action, and then deactivate. AbbVie was attracted to the technology for its unique ability to address various mechanisms of action with a single bacterium and because of its on/off capability where it can sense and respond. Synlogic was founded in late 2013 by a member of Atlas Ventures and professors from **Boston University** and **Massachusetts Institute of Technology**. The company intends fuel its in-house orphan disease-focused pipeline through outside partnerships that apply Synlogic's synthetic biotics technology platform in broader disease indications. It closed a $34.4mm Series A in 2014 and is currently raising Series B funds.

ACHAOGEN INC.
TRIANNI INC.

Trianni Inc. licensed **Achaogen Inc.** rights to its Trianni transgenic mouse platform. (Feb.)

Trianni's human monoclonal antibody discovery platform is based on a unique chimeric gene segment design and optimized for the expression of human variable domains. Achaogen plans to use the technology to create mAbs aimed at several multi-drug resistant (MDR) bacterial infections. The company is currently focused on antibacterials to treat MDR gram-negative infections.

AMGEN INC.
ROCHE
Genentech Inc.

Amgen Inc. licensed **Genentech Inc.** exclusive worldwide rights to its interleukin-33 antibody inhibitor AMG282, in Phase I for asthma and COPD. (Feb.)

Genentech will be responsible for clinical development, manufacturing, and commercialization. While Amgen doesn't focus on respiratory disease (its key areas include hematology/oncology, cardiology, inflammation, musculoskeletal, nephrology, and neurology), respiratory represents a major segment for Genentech's parent **Roche**, especially after Roche in 2014 bought InterMune and its idiopathic pulmonary fibrosis drug *Esbriet*. In the pipeline, Roche also has a promising candidate lebrikizumab, which targets asthma in patients expressing the periostin protein. Both *Esbriet* and lebrikizumab are forecasted to replenish Roche's respiratory sales when *Xolair*'s US patent expires in 2017. (*Xolair* and

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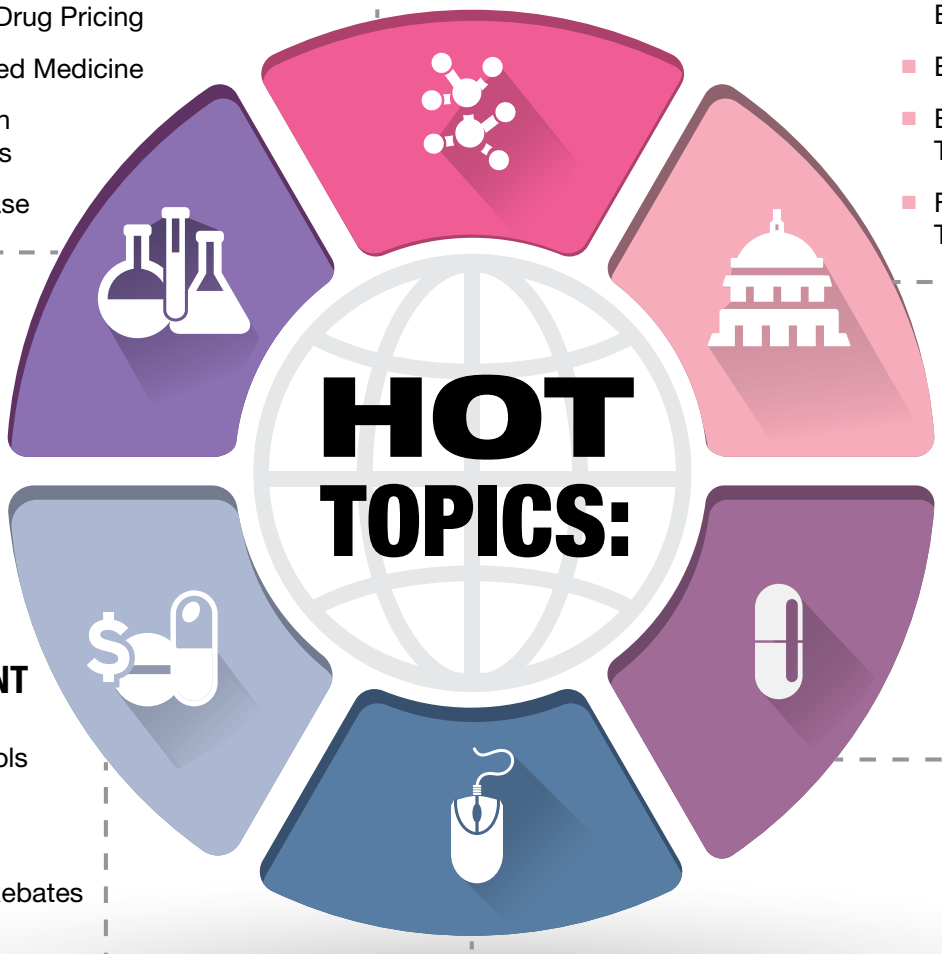

BUSINESS AND R&D

- R&D Reorganization
- Oncology Drug Pricing
- Personalized Medicine
- Companion Diagnostics
- Rare Disease

HOT MEDICAL AREAS

- Oncology
- Hepatitis C

POLICIES ON DRUG REVIEW

- FDA's Breakthrough Designation and Other Expedited Pathways
- Biosimilars
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OTHER FDA ISSUES

- Biopharma's Use Of Social Media
- Generic Drug User Fees

REIMBURSEMENT

- Commercial Formulary Controls
- Federal 340B Discounts
- Medicare Drug Rebates
- Health Reform's Impact On Drugs

MISCELLANEOUS

- Medication Adherence
- Comparative Effectiveness Research

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lebrikizumab each have ties to Tanox, which Genentech acquired in 2007.) Amgen was also testing AMG282, which blocks IL-33 binding to the ST2 receptor, for nasal polyposis (abnormal, noncancerous masses caused by inflammation of the mucous membranes) in Phase I. It's unclear if Roche will continue to pursue that indication.

AMPHASTAR PHARMACEUTICALS INC.
HIKMA PHARMACEUTICALS PLC

Hikma Pharmaceuticals PLC will sell the rights to five marketed injectable generics to **Amphastar Pharmaceuticals Inc.** as an FTC-mandated anticompetitive condition of Hikma's pending acquisition of **Bedford Laboratories** (the US generic injectables subsidiary of **Boehringer Ingelheim** division **Ben Venue**), announced in May 2014. (Feb.)

Hikma's divested injectables include acyclovir sodium for chicken pox, herpes, and other infections; diltiazem hydrochloride for hypertension, angina, and arrhythmias; famotidine for ulcers and GERD; prochlorperazine edisylate for schizophrenia and nausea; and valproate sodium for epilepsy, seizures, bipolar disorder, anxiety, and migraines.

ASTRAZENECA PLC
CORVIDIA THERAPEUTICS

AstraZeneca PLC granted **Corvidia Therapeutics** rights to COR001, a cardiovascular monoclonal antibody project that had previously been under development by AZ's **MedImmune** but re-purposed for out-licensing. (Feb.)

Corvidia, which is developing precision cardiovascular therapies based on functional genomics, will use funds from a concurrent $26mm Series A round to bring the compound into Phase I/II trials for an undisclosed cardio indication. The company was co-founded by Dr. Michael Davidson, former CMO of Omthera Pharmaceuticals, which AZ acquired back in 2013. Additional Corvidia co-founders include Drs. Rahul Kakkar and Matt Devalaraja, both of whom were at AZ's Emerging Innovations unit prior to Corvidia and had a hand in the re-purposing of COR001.

AURAMEDI FARMACEUTICA LTD.
AURAMEDI-PREMIER BIOMEDICAL JV
PREMIERE BIOMEDICAL INC.

Premier Biomedical Inc. is setting up a joint venture with **Auramedi Farmaceutica Ltd.** in the latter's home country of Brazil. (Feb.)

The companies signed a letter-of-intent back in October 2015 to explore the possibility of a JV. Now that the deal is final, Auramedi plans to invest $6mm in the JV to fund facilities to manufacture, distribute, and sell Premier's drugs and devices in Brazil and throughout South America. Premier's portfolio spans various therapy areas including breast cancer, fibromyalgia, neuropathy, atherosclerosis, and muscular dystrophy. Auramedi was created to develop treatments for dermatology, oncology, and rare diseases. The firms will also collaborate to use Premier's extracorporeal technology to find a treatment for the current Zika epidemic as well as Dengue viruses. A third party had estimated Premier's annual sales in South America at $400mm by 2020.

BIND THERAPEUTICS INC.
SYNERGY PHARMACEUTICALS INC.

Bind Therapeutics Inc. is partnering its *Accurin* technology with **Synergy Pharmaceuticals Inc.**'s uroguanylin analogs in an effort to create new treatments for gastrointestinal cancers. (Feb.)

Developed with Bind's *Medicinal Nanoengineering* platform, *Accurins* are polymeric nanoparticles that can remain in the bloodstream for a longer period of time to allow for controlled-release delivery of the therapeutic directly to the diseased cells or tissues without affecting healthy areas. The firms seek to develop *Accurins* that incorporate Synergy's uroguanylin analogs, targeting the guanylate cyclase-C (GC-C) receptors expressed on GI tumors. (Uroguanylin is a naturally occurring GI peptide and activator of the intestinal GC-C receptor.) Following proof-of-concept, Bind and Synergy plan to expand the deal to enhance the potential effect of uroguanylin-based *Accurins* by incorporating therapeutic payloads.

BRAEBURN PHARMACEUTICALS SPRL
KNIGHT THERAPEUTICS INC.

Knight Therapeutics Inc. licensed exclusive Canadian rights to **Braeburn Pharmaceuticals Inc.**'s *Probuphine* (buprenorphine implant), which is awaiting US approval for opioid addiction. Under a 2012 agreement with **Titan Pharmaceuticals** (the implant's original developer), Braeburn holds exclusive North American rights for the later of a 15-year period, or patent expiry. (Feb.)

Probuphine is designed using Titan's *ProNeura* continuous drug delivery technology (a solid matrix consisting of ethylene-vinyl acetate combined with a drug substance), to which Braeburn also holds rights. Implanted subdermally, *Probuphine* is capable of providing sustained and continuous release of buprenorphine--an active ingredient approved for opioid dependence--for six months. The company says this method may improve patient compliance versus sublingual and buccal formulations that require daily self-administration. Following its initial NDA submission for *Probuphine* in October 2012, the FDA issued a complete response letter requiring additional efficacy data, so in August 2015 Braeburn resubmitted a revised NDA. In January 2016 the FDA voted 12 to 5 in favor of approving *Probuphine*, with a target agency action date of February 27, 2016. According to *BioMedTracker*, it has an 88% likelihood of approval. Although Knight has been an active in-licenser in neurology recently--penning deals with **Antibe** (anti-inflammatory and pain), **Origin** (diabetic pain), **Synergy** (neuropathic pain), and **NeurAxon** (migraine)--this is its first foray into drug addiction treatments.

CAPSUGEL
PULMATRIX INC.

Pulmatrix Inc. licensed **Capsugel** exclusive rights to manufacture clinical trial and commercial batches of candidates developed using Pulmatrix's *iSPERSE* (*inhaled Small Particles Easily ReSpirable and Emitted*) dry powder technology. (Feb.)

Capsugel will use its expertise in spray drying process development, scale-up, and commercial manufacturing. Pulmatrix's *iSPERSE* enables pulmonary delivery of drugs with high efficiency, dose reproducibility, and flow-rate independence. Under the collaboration, Capsugel will initially fulfill manufacturing needs for Pulmatrix's clinical trials in cystic fibrosis, and eventually produce next-generation pulmonary therapies at commercial scale.

CELLULAR BIOMEDICINE GROUP INC.
WUHAN DANGDAI SCIENCE & TECHNOLOGY INDUSTRIES

Wuhan Dangdai Science & Technology Industries (through its **Dangdai International Group Co. Ltd.** subsidiary) acquired a 19.4% stake in **Cellular Biomedicine Group Inc.** in a deal worth $43.13mm (2.27mm shares at $19 per share; a 37% premium). (Feb.)

Cellular Biomedicine has already received $5mm up front in exchange for 263.2k shares issued to Dangdai, with the remaining funds expected by April 2016. The company is developing cell therapies for degenerative and cancerous diseases and will benefit from Dangdai's large direct sales force in China. Cellular Biomedicine will use the proceeds for its long-term clinical trials in stem cell indications and in multiple CART trials.

CONSORT MEDICAL PLC
Aesica Pharmaceuticals Ltd.
Bespak Europe Ltd.
PRECISION OCULAR LTD.

Consort Medical PLC, through its **Bespak Europe Ltd.** and **Aesica Pharmaceuticals Ltd.** units, has allied with start-up retinal disease firm **Precision Ocular Ltd.** (Feb.)

Bespak will contribute its expertise and capabilities in device development and manufacturing, while Aesica adds knowledge in manufacturing and filling. The agreement is designed to develop, scale-up, and industrialize Precision Ocular's therapeutics and drug delivery system. Precision's system can target and access small spaces in the eye and deliver the therapeutic agent to tissues involved in retinal diseases. Concurrent with the agreement, Consort contributed £3.3mm to Precision's £13.5mm Series A financing and will get representation on the start-up's board. Following its investment, Consort will hold a 13.7% equity stake in Precision.

DAIICHI SANKYO CO. LTD.
Daiichi Sankyo Europe GMBH
MERCK & CO. INC.

Daiichi Sankyo Europe GMBH (the European marketing arm of **Daiichi Sankyo Co.**) chose **Merck & Co. Inc.** to sell its once-daily anti-coagulant *Lixiana* (edoxaban) in 13 European countries, where Daiichi does not have a market presence. (Feb.)

Merck will sell the drug in Bulgaria, Croatia, Czech Republic, Denmark, Finland, Hungary, Iceland, Norway, Poland, Romania, Slovakia, Slovenia, and Sweden. *Lixiana*, a Factor Xa inhibitor, was approved by the European commission in June of last year for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors (such as congestive heart failure, hypertension, an age of 75 or older, and prior stroke or transient ischemic attack). It is also approved to treat and prevent recurrence of deep vein thrombosis and pulmonary embolism. *Lixiana* is marketed in the US as *Savaysa*, but carries black box warnings in that country that don't apply in Europe. In Europe, the drug's steepest competition will come from **Bayer**/**J&J**'s Factor Xa inhibitor *Xarelto* (rivaroxaban). Other oral anti-coagulants sold there include **Boehringer Ingelheim**'s *Pradaxa* (dabigatran), and **Pfizer**/**Bristol-Myers Squibb**'s *Eliquis* (apixaban).

EISAI CO. LTD.
HUYA BIOSCIENCE INTERNATIONAL LLC

Eisai Co. Ltd. licensed exclusive rights from **HUYA Bioscience International LLC** to develop and sell the HDAC inhibitor HBI8000 in Japan, South Korea, Thailand, Malaysia, Indonesia, the Philippines, Vietnam, and Singapore. (Feb.)

HUYA originally licensed global rights (excluding China) to the compound from **Shenzhen Chipscreen Biosciences** in 2007; it has been approved in that country as *Epidaza* (chidamide) for relapsed or refractory peripheral T-cell lymphoma (a type of non-Hodgkin's lymphoma) and is currently in development for vari-

ous solid and blood tumors. Eisai is responsible for an up-front payment, milestones of up to $280mm, and royalties. HUYA will complete HBI8000 development in Japan (where the project was recently granted orphan drug designation) for PTCL and adult T-cell leukemia-lymphoma and Eisai will commercialize it there for these specific indications; Eisai additionally has rights to develop and commercialize it in the licensed territories for other indications including solid tumors. HUYA will manufacture and supply to Eisai.

EISAI CO. LTD.
PIQUR THERAPEUTICS AG

Eisai Co. Ltd. and **Piqur Therapeutics AG** are working together to evaluate the combination of Piqur's Phase II PQR309 together with Eisai's marketed *Halaven* (eribulin) as a treatment for triple-negative breast cancer. (Feb.)

PQR309 is a PI3 kinase/mTOR inhibitor in Phase II trials for solid tumors and lymphoma, while *Halaven*, a tubulin inhibitor, is marketed for breast cancer and liposarcoma and in trials for a variety of other cancers including soft tissue sarcoma and non-small cell lung cancer (Phase III), and prostate, bladder, lung, and colorectal cancers (Phase II). Eisai and Piqur will look at the combo in a Phase I dose escalation safety and tolerability study in locally advanced or metastatic HER2-negative and triple-negative breast cancer, followed by a Phase IIb study in advanced or metastatic triple-negative breast cancer. Studies are expected to commence in early 2016; an expansion to Phase III and additional studies in other indications is also possible.

G&W LABORATORIES INC.
GAVIS PHARMACEUTICALS LLC
LUPIN LTD.

Gavis Pharmaceuticals LLC will sell the rights and assets (including manufacturing technology) affiliated with generic doxycycline monohydrate capsules and generic mesalamine capsules to **G&W Laboratories Inc.** no later than ten days after closing its pending acquisition by **Lupin Ltd.** (Feb.)

The FTC is requiring Gavis to divest these assets due to the anticompetitive nature of the current Lupin acquisition as it now stands (the merger would have combined two of only four companies marketing such products). For the next two years, Lupin will supply G&W with the finished product. The products are currently marketed to treat bacterial infections (doxycycline) and ulcerative colitis (mesalamine). Back in 2015 G&W acquired numerous products and a manufacturing facility from **Teva Pharmaceutical Industries Ltd**.

GENEXINE INC.
FOSUN INTERNATIONAL LTD.
Shanghai Fosun Pharmaceutical Group Co. Ltd.
Shanghai Chemo Wanbang Biopharma Co. Ltd.

Genexine Inc. granted **Shanghai Fosun Pharmaceutical Group Co. Ltd.** division **Shanghai Chemo Wanbang Biopharma Co. Ltd.** exclusive rights to develop and sell the long-acting erythropoietin GXE2 (EPO-hyFc) in China (excluding Hong Kong, Macau, and Taiwan). (Feb.)

GXE2 is in Phase II trials, and is being co-developed by Genexine and partner **Green Cross** under a 2006 collaboration. (Due to Chinese regulations, development in China will have to start over from preclinical studies, which the companies anticipate commencing next year.) The compound is available for semi-monthly and monthly dosages as a treatment for anemia due to chronic kidney disease and chemotherapy. Genexine is eligible for up to $44.5mm in development and sales milestones, plus royalties.

GLAXOSMITHKLINE PLC
GlaxoSmithKline Biologicals SA
VBI VACCINES INC.

GlaxoSmithKline Biologicals SA is evaluating **VBI Vaccines Inc**'s *LPV* platform in a new research collaboration. GSK has the option to negotiate an exclusive license to the platform. Financial terms were not disclosed. (Feb.)

The *LPV* platform uses a proprietary formulation and process which encloses and protects the antigen in a vaccine or biologic. This enables development with greater stability and preserved potency. Proof of concept studies have been completed on a number of targets.

IMMUNOGEN INC.
MERCK & CO. INC.

ImmunoGen Inc. and **Merck & Co. Inc.** entered into an trial collaboration to investigate the combination of Merck's marketed immunotherapy *Keytruda* (pembrolizumab) with Immunogen's mirvetuximab soravtansine for ovarian cancer. (Feb.)

Immunogen is studying mirvetuximab--a folate receptor antagonist--in a Phase Ib/II trial named FORWARD II, which studies the compound in combination with other anticancer agents. Merck will supply *Keytruda* for inclusion in FORWARD II; it is an anti-PD-1 mAb marketed for melanoma and non-small lung cancer and in a variety of trials for solid and blood cancers including renal, bladder, head and neck, breast, colorectal, lymphoma, and myeloma. Following FORWARD II, the companies have the option to extending the collaboration to include a Phase III trial.

JOHNSON & JOHNSON
Janssen Biotech Inc.
VIACYTE INC.

Janssen Biotech Inc. licensed **ViaCyte Inc.** exclusive rights to the assets of its BetaLogics group, including intellectual property in the area of metabolic diseases (including diabetes). (Feb.)

Through the deal, ViaCyte gets 145 issued patents (15 in the US) to add to its own 215-strong patent portfolio and 565 pending patent applications (ViaCyte has 145 pending). Like ViaCyte, BetaLogics has been working on a stem cell-derived therapy for diabetes. ViaCyte is developing the first pluripotent stem cell-derived islet replacement therapy for Type I diabetes. Its Phase I/II VC01 incorporates the company's *PEC01* human pancreatic progenitor cells with the *Encaptra* drug delivery system. Back in August 2014, **Janssen R&D LLC** got the option to exclusively license VC01 following initial clinical trials. But now, rather than take the option, Janssen decided to hand over ViaCyte the BetaLogics IP to have a better chance of bringing a stem cell treatment for diabetes to market.

MERUS LABS INTERNATIONAL INC.
UCB GROUP

Merus Labs International Inc. paid £92mm ($134mm) to purchase three cardiovascular products from UCB Group. Together the acquired assets brought in £34mm in sales in the last 12 months. (Feb.)

UCB gets the once-daily controlled-released angina therapies *Elantan* (isosorbide mononitrate) and *Isoket* (isosorbide dinitrate), and a transdermal nitroglycerine angina patch *Deponit*. The products are sold in 20 European countries (plus Mexico, South Korea, and Turkey) and are expected to generate an additional $22mm in annual EBITDA for Merus. The deal gives Merus an entrance into the cardiovascular space; the company's existing products are for conditions including thromboembolic diseases, urinary urgency and incontinence, dry mouth and dry eye associated with radiation or Sjögren's syndrome, C. difficile infection, and symptoms of menopause.

NESTLE SA
Nestle Health Science SA
PRONUTRIA BIOSCIENCES INC.

Pronutria Biosciences Inc. (products for amino acid imbalances) secured a $42.5mm investment from **Nestle Health Science SA**. (Feb.)

The proceeds will be used to advance the company's platform to develop late-stage clinical candidates in various indications. Pronutria was founded within VentureLabs at Flagship Ventures and has received prior funding from Fidelity and Gurnet Point Capital. The company raised $39mm in its Series C round ten months ago and has raised over $112mm to date. Pronutria is developing a new way to develop proteins that can deliver therapeutic doses of amino acids to the bloodstream and its lead drug PN107 is being developed for sarcopenia (muscle loss).

ROCKWELL MEDICAL INC.
FOSUN INTERNATIONAL LTD.
Wanbang Biopharmaceuticals Ltd.

Rockwell Medical Inc. granted **Wanbang Biopharmaceutical Co. Ltd.** exclusive rights to sell two of its end-stage renal disease (ESRD) therapies in China. (Feb.)

Included in the deal are *Triferic* (soluble ferric pyrophosphate), an iron absorption stimulant that treats anemia in ESRD patients on dialysis, and *Calcitriol* (Vitamin D), to treat and manage hyperparathyroidism and hypocalcemia, also for dialysis patients. Wanbang will pay up to $39mm in up-front fees and development and regulatory milestones to become the exclusive distributor of the products for an initial term of ten years. (An additional ten years could be tacked on based on the satisfaction of annual minimum purchase requirements.) Wanbang is responsible for all costs (development, regulatory, and marketing) for both products, and will also pay additional costs if it decides to pursue development of *Triferic* for other indications. Rockwell will manufacture and supply both products to Wanbang throughout the deal term.

Financings
/Pharmaceuticals

AMYRIS INC.

Amyris Inc. (biosynthetic production processes for drug manufacturing) raised $20mm in a private placement of unsecured promissory notes (13.50% annual interest) due May 15, 2017 to existing investors led by Foris Ventures LLC, with participation from Biolding Investment SA and Naxyris SA. The company also issued warrants for 2.9mm common shares. (Feb.)

AVEXIS INC.

Gene therapy biotech **AveXis Inc.** (mostly rare neurological genetic diseases) netted $88.35mm its initial public offering on Nasdaq of 4.75mm shares at $20, the mid-point of its anticipated $19-21 range. (Feb.)

Investment Banks/Advisors: BMO Financial Group; Chardan Capital Markets; Goldman Sachs & Co.; Jefferies & Co. Inc.

BEIGENE (BEIJING) CO. LTD.

Cancer drug developer **BeiGene (Beijing) Co. Ltd.** netted $147mm through its initial public offering on the Nasdaq exchange of 6.6mm American Depositary Shares (representing 85.8mm ordinary shares) at $24 per ADS. (The company originally hoped to sell 5.5mm ADSs for between $22-24 apiece.) (Feb.)

Investment Banks/Advisors: Cowen & Co. LLC; Goldman Sachs & Co.; Morgan Stanley & Co.; Robert W. Baird & Co. Inc.

CESCA THERAPEUTICS INC.

Cesca Therapeutics Inc. (autologous cell-based regenerative medicine) secured a $15mm strategic investment from the Boyalife Group in order to repay outstanding senior secured convertible debentures and retire associated Series B Warrants. The investment is composed of $2.5mm in new common shares at $0.17 per share and $12.5mm in senior secured three year convertible debentures. The interest on the notes accrues at 22% per annum and the transaction also includes five year warrants to purchase 80% of the shares sold to Boyalife Group at $0.40 per share. (Feb.)

CYTRX CORP.

Cancer therapeutics company **CytRx Corp.** entered into a $40mm long-term loan and security agreement with Hercules Technology Growth Capital, and immediately received an initial $25mm. CytRx will use the funds for precommercialization activities and manufacturing of its lead project aldoxorubicin (Phase III as a second-line treatment for soft tissue sarcoma). The second tranche of $15mm will be available on or before December 31, 2016 if positive Phase III aldoxorubicin data is received and a clinical trial of second candidate based on the company's *LADR* (*Linker Activated Drug Release*) technology is initiated. (Feb.)

EDITAS MEDICINE INC.

Editas Medicine Inc. netted $101mm in its IPO of 6.8mm shares (including full exercise of the 885k overallotment option) at $16 per share. Proceeds will be used to fund the company's trials for LCA10 (Leber Congenital Amaurosis type 10; genetic progressive form of blindness), for preclinical studies with the candidate under its **Juno Therapeutics** collaboration (entered into in May 2015), and for expansion of platform technology. (Feb.)

Investment Banks/Advisors: Cowen & Co. LLC; JMP Securities LLC; JP Morgan & Co.; Morgan Stanley & Co.

MAST THERAPEUTICS INC.

Mast Therapeutics Inc. netted $7.5mm through the follow-on public offering of 29mm units at $0.275. Each unit consists of one common share and one five-year warrant to purchase a share at an exercise price of $0.42. Proceeds will help in ongoing development of Phase III-ready vepoloxamer in sickle cell disease and vepoloxamer (Phase II-ready) and Phase II AIR001 in heart failure. Money will also fund regulatory, manufacturing, and pre-launch activities for vepoloxamer in the sickle cell indication. (Feb.)

Investment Banks/Advisors: Maxim Group LLC; Roth Capital Partners

MERUS LABS INTERNATIONAL INC.

Specialty pharmaceuticals company **Merus Labs International Inc.** raised $27mm in a bought deal private placement of 14.25mm subscription receipts (each subscription receipt will convert into one special warrant which is convertible into one common share) at $1.90 per receipt. The proceeds will be used for prospective acquisitions of four pharmaceutical products in a key European market and will be held in escrow until that time. (Feb.)

OXFORD BIOMEDICA PLC

Oxford BioMedica PLC plans to raise £8.1mm ($11.5mm) in a private placement of 128.4mm new ordinary shares at 6.3 pence ($0.09) per share (10% discount) to both new and existing investors. The placement agents are Jefferies and WG Partners. Proceeds will be used for working capital and to fund the product pipeline in lentiviral vector manufacturing-related technology. Oxford plans for OXB102 for Parkinson's and OXB202 for corneal graft rejection to enter into Phase I/II clinical studies within the next year and is currently in IP out-licensing discussions. (Feb.)

Investment Banks/Advisors: Jefferies & Co. Inc.

PROTEOSTASIS THERAPEUTICS INC.

Proteostasis Therapeutics Inc. (developing therapies for cystic fibrosis and neurodegenerative and orphan diseases) netted $46.5mm in its initial public offering of 6.25mm common shares at $8. The company had planned to sell 3.85mm shares between $12-14 each. (Feb.)

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

EQUIPMENT & SUPPLIES

Alliances

/Research, Analytical Equipment & Supplies

ABCELLERA BIOLOGICS INC.
TEVA PHARMACEUTICAL INDUSTRIES LTD.

Teva Pharmaceutical Industries Ltd. and **AbCellera Biologics Inc.** have entered into a collaborative research agreement in which AbCellera will apply its high-throughput single cell antibody platform for the discovery of monoclonal antibodies. The company recently entered into another antibody discovery collaboration with **Merck** to generate antibodies against an undisclosed target. (Feb.)

In return AbCellera will receive an upfront payment, research payments, and undisclosed downstream milestones. The company's technology enables the discovery of rare antibodies with defined specificity and functional activity against difficult membrane protein targets. The technology isolates single antibody-secreting cells in nanoliter-volume chambers for fast detection and combines flexible assay formats with enhanced sensitivity.

IN VIVO
THE BUSINESS & MEDICINE REPORT

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IN VIVO: The Business & Medicine Report [ISSN 2160-9861] is published monthly, except for the combined July/August issue, by Informa Business Intelligence, Inc., 52 Vanderbilt Avenue, 11th floor, New York, NY 10017. Tel: 888-670-8900 (US); +1-908-547-2200 (outside US); Fax: 646-666-9878.

Subscriptions cost $2,630 (online and print) per year. Office of publication, The Sheridan Group, 66 Peter Parley Row, Berlin, CT 06037. Postmaster: Send address changes to Informa Business Intelligence, 52 Vanderbilt Avenue, 11th floor, New York, NY 10017.

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PUBLISHED MONTHLY

"The Gold Sheet"

PHARMACEUTICAL & BIOTECHNOLOGY QUALITY CONTROL

SEPTEMBER 2015

Vol. 49, No. 9

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Quality metrics honeymoon ends
After two years of collaborating with industry on potential quality metrics, FDA finally makes a proposal and industry objects to the whole idea. Game on ..... cover

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FDA Quality Metrics Proposal Sparks Objections, Disarray

Bowman Cox bowman.cox@informa.com

Industry's anxieties about the pharmaceutical quality metrics guidance FDA drafted in July boiled over in an Aug. 24 meeting at FDA's Silver Spring, Md., headquarters.

Groups for brand and generic drug makers, so often at odds in Washington, agreed on one point: FDA has no authority to make their members report quality metrics data.

But industry was unable to agree on much else about FDA's quality metrics proposal. Pharmaceutical manufacturing science groups differed with each other on whether to report the data by site or by product. Active pharmaceutical ingredient manufacturers split evenly on who should report API data, API firms or drug product firms. And generic drug firms demanded that FDA make their contract manufacturers report metrics directly to the agency, only to acknowledge upon questioning that they had misgivings about this position and would be reconsidering it the next day.

Support – and resistance

About the only thing certain by the end of the meeting was that, as much as industry has embraced FDA quality metrics, it was prepared to resist them.

Every industry representative who spoke assured FDA that their organizations supported the quality metrics initiative, or aspects of it anyway, but none appeared anxious for it to get underway. Many argued that it didn't apply to their members, or shouldn't, or at least it shouldn't until later, or only when they wanted it to.

And many claimed they were just trying to protect FDA from the deluge of data that the agency must not have realized it was requesting.

One group, the International Society for Pharmaceutical Engineering, believes, based on experience from Wave 1 of its quality metrics pilot (*"Lessons from ISPE Quality Metrics Pilot: Start Small and Be Aware of Costs" – "The Gold Sheet," June 2015*), that FDA has significantly underestimated the burden of complying with the draft guidance.

Genentech/Roche quality VP Diane Hagerty said ISPE member companies are particularly concerned about "the anticipated costs for firms to adjust internal IT systems and incorporate additional review and retention of data to support this program, as well as to support the intention that has been stated, that FDA would very likely be looking to verify this data upon inspection."

The main theme that FDA heard from the commenters, Russell Wesdyk, acting director of the Office of Surveillance in the agency's Office of Pharmaceutical Quality, said in his closing remarks, was "a request for a phased or risk-based approach to implementation."

The bottom line is this: Now that FDA has taken the quality metrics idea it has been discussing with industry manufacturing science and quality experts for the past two

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EXECUTIVESUMMARY

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A Road Map To Strategic Drug Pricing

BY ELLEN LICKING AND SUSAN GARFIELD

Current pricing practices create conflict between drug companies and other health care stakeholders, fostering a negative reputation for the biopharmaceutical industry and a slowdown in growth. Because products come to market with clinical trial data and not real-world evidence, stakeholders may see them as having "potential," not "proven", value at the time of launch. As a result of this evidentiary divide, many products already enter the market with a "value gap." To accelerate the shift to proven value and bridge the value gap, biopharma companies should consider multi-stakeholder collaborations aimed at co-creating data to support innovative pricing models. EY's qualitative pricing methodology helps companies understand which products will derive the greatest benefit from innovative pricing models, enabling a proactive and systematic approach to pricing decisions.

SUMMARY OF ARTICLE FROM PAGE 20

ANGLE Targets A Rich CTC Niche In Liquid Biopsy

BY ASHLEY YEO

UK-based ANGLE is aiming to shift clinician and industry sentiment away from the view that the easy collection of viable cancer cells from blood on a regular basis for analysis cannot be done. Its liquid biopsy system, Parsortix, is a disruptive technology that can be used to collect all types of cancer cells in all types of cancer, and could be used as a companion diagnostic in the future. ANGLE has high hopes that its cell harvesting technology will win acceptance from clinicians who have hitherto been using tools that are both more expensive and have greater limitations. It also aims to partner with as many companies as possible, both medtech instrument companies and pharma partners that are developing new drugs. Now with its first (research use) sales completed, the company sees 2016 as a year of KOL news, progress toward regulatory clearance and awareness-raising at some of the world's key cancer forums, ahead of future clinical application launches.

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Institutionalizing M&A Excellence In Health Care

BY SPRING LI, MATTHEW VAN WINGERDEN, ANKUR AGRAWAL AND RUTH DE BACKER

The need for innovative technologies continues to be the main driver for pharma and medtech M&A deals. Mega-mergers may grab the headlines, but the health care industry's smaller deals are equally important and we can expect to see a steady stream of them going forward. To maximize dealmaking success, McKinsey advises health care companies to follow the examples of peers in other industries and systematize their M&A processes by implementing better consistency, transparency and accountability.

SUMMARY OF ARTICLE FROM PAGE 30

Germany: Europe's Go-To Market Changes Rules For High-Risk And Promising Devices

BY BEN MODLEY

The medical technology industry in Germany is in the midst of the heaviest period of national health care legislation for two decades. The changes include an amendment to the innovation-friendly NUB program that allows usage of originative products under a one-year pass-through for "especially invasive" products. These must now undergo an HTA process at the G-BA, the health care reimbursement authority. Elsewhere, the Trial Regulation (on coverage with evidence development) for promising products in the outpatient sector has had a promising start, before quietly coming to a stop. But now it seems to have resumed. Finally, a new institute to measure and promote quality in the inpatient sector in Germany has been set up. It is early days for this new body, but more quality indicators and some pay-for-performance structures are on the horizon, meaning this is definitely something for industry to watch. Overall, the new rules represent a mix of threat and opportunity.