IN VIVO

THE BUSINESS & MEDICINE REPORT

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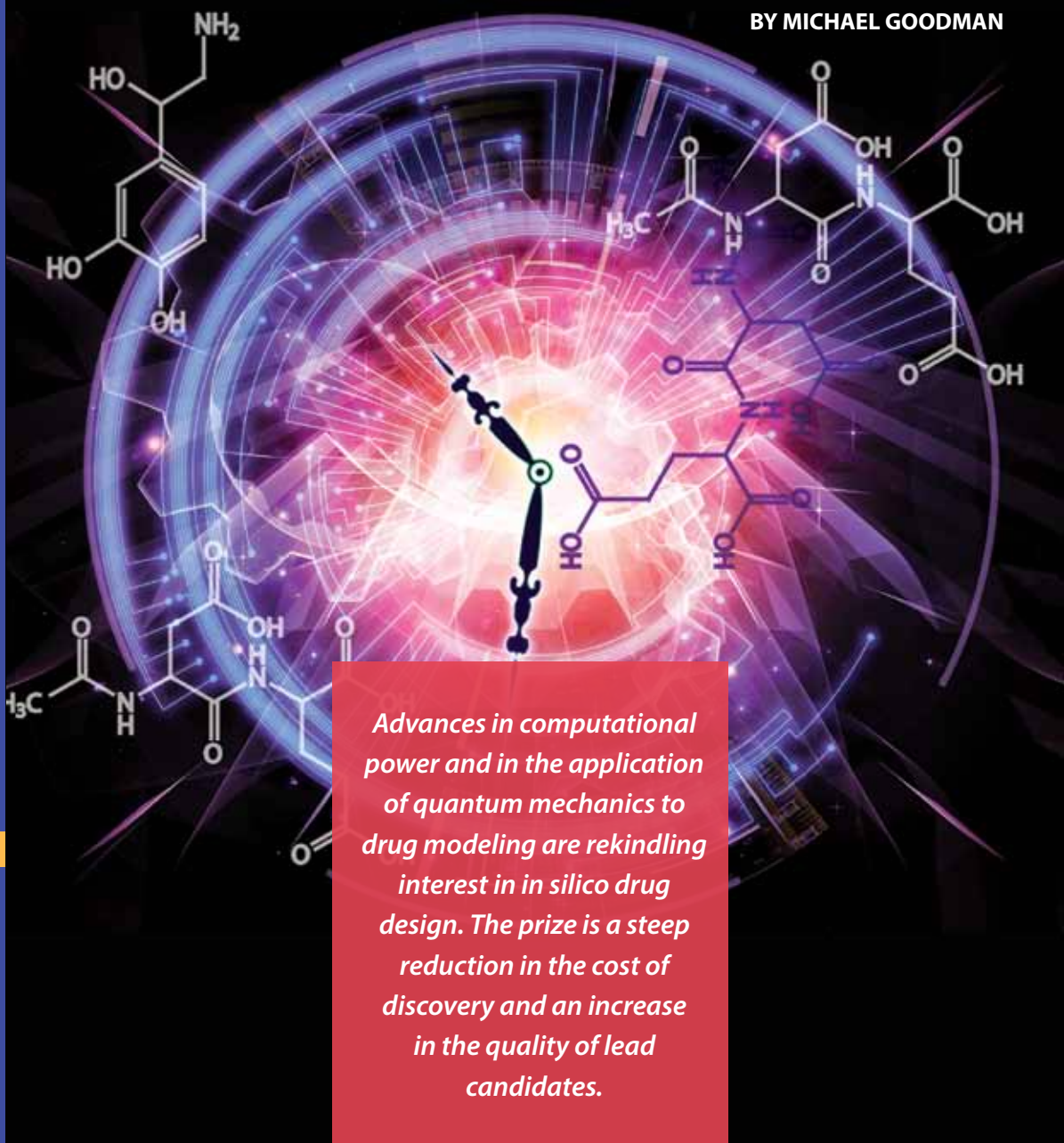
INSIDE

In Silico Drug Design: Finally Ready For Prime Time?

BY MICHAEL GOODMAN



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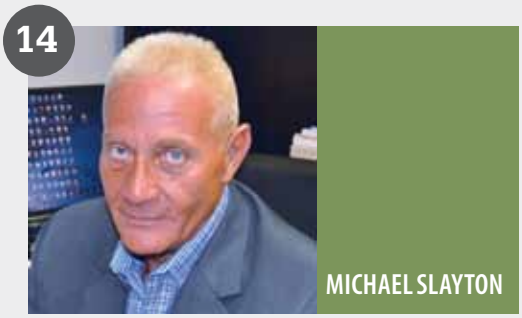

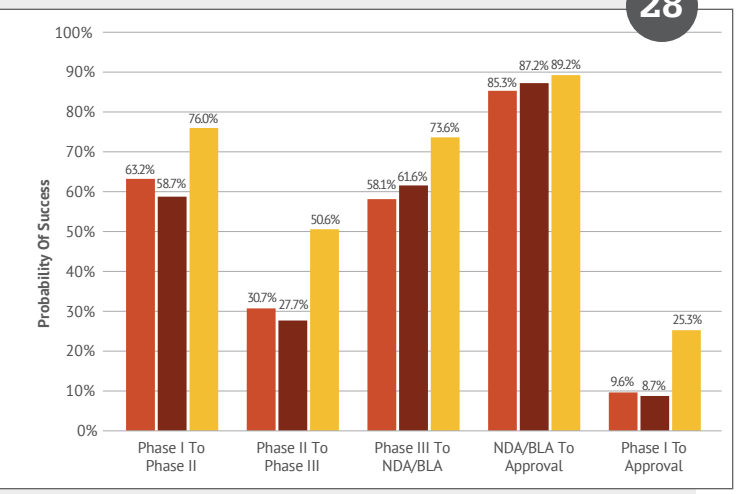

Rare Disease Candidates Outperform

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JUNE 2016

EXCLUSIVE ONLINE-ONLY

Growing Established Pharma Products: Three Strategic Imperatives

Sarah Rickwood, Adam Weston and Denis Kent

Who's Running The Trials?

Nancy Dvorin

■ Deals In Depth

An overview of biopharma, medtech and diagnostics dealmaking in April 2016

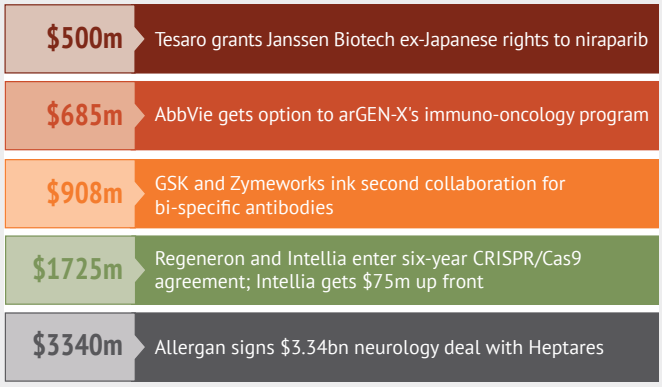
■ Device/Diagnostics Quarterly Dealmaking Statistics, Q1 2016

Amanda Micklus and Maureen Riordan

■ Emergings

START-UP Previews

Start-Ups Across Health Care:
Profiles of Ariste Medical, BioDirection, Cardialen and Homology Medicines



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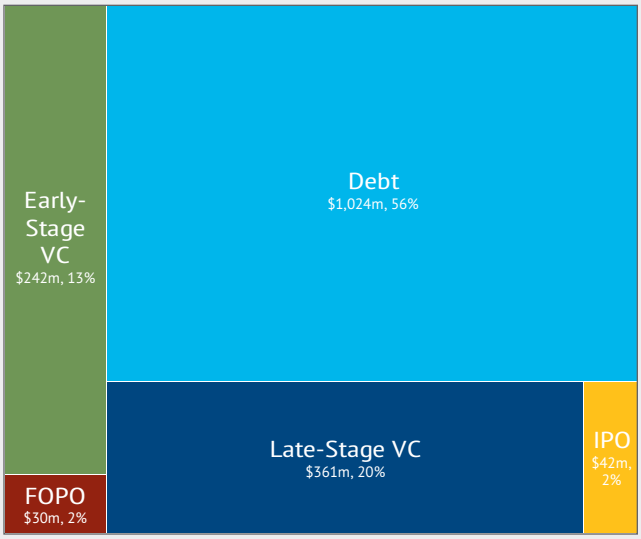
Top Alliances In April 2016



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Biopharma M&A

SHIRE'S ORNSKOV MAPS OUT FUTURE PROSPECTS POST-BAXALTA MERGER

Shire PLC CEO Flemming Ornskov, MD, could perhaps be forgiven for sounding like the cat that finally got the mouse when commenting on the June 3 completion of the company's combination with **Baxalta Inc.**, creating "the global leader in rare diseases with the number one rare diseases platform based on both revenue and pipeline programs." Gaining Baxalta also gives Shire strength in hematology and immunology and boosts its leading position in angioedema, enzyme replacement therapy, endocrinology and gastrointestinal diseases.

In an interview with *In Vivo*'s sister publication *Scrip* in early June Ornskov said that "as a combined group we'll be able to cover more technologies now, and that's particularly true in rare diseases, where we'll be able to focus on a vast array of illnesses, be that in the neurological area, the ophthalmic field or the hematological area or more typical genetic protein-based conditions."

He said the Baxalta deal increases the combined company's scale in R&D and should generate stable cash-flows that can be invested in fresh partnering to expand pipeline prospects. "We already have a large number of partnerships with commercial entities and academics. And with Baxalta we get the opportunity to be located in the innovative hub of Cambridge [MA] . And the company will throw off $6 billion in cash, which will allow us to repay debt, but also allow us to make significant investment in-house and for partnered R&D," the CEO said.

Through the combination, Shire expects to deliver double-digit compound annual top-line growth, with more than $20 billion in annual projected revenue by 2020 and about 65% of total annual revenues generated by its rare disease products. The marriage was sealed a week before the deal closed, when shareholders of both companies voted in favor of the transaction. Initially launched as a hostile bid in mid-2015, Shire's acquisition of Baxalta was agreed upon in January at a price of roughly $32 billion, in a transaction that will leave Shire owning 66% of the combined company and Baxalta 34%.

Ornskov, who has led Shire since 2013, outlined during Shire's first-quarter results presentation in April the planned "inverted pyramid approach" for integrating acquired companies – the Baxalta deal and the recent buyout of **Dyax Corp.** being the two largest acquisitions in the company's history. In the inverted pyramid approach, he explained, customer-facing services are affected the least, including retaining salesforce and patient-support personnel. Shire will prioritize preserving the expertise within Baxalta's manufacturing organization, and will strive to preserve clinical expertise in R&D and to make a top priority of innovative projects targeted at unmet medical needs.

COMBINED PIPELINE TO BE ASSESSED

Asked whether management would now be re-evaluating Baxalta's presence in biosimilars and oncology, Ornskov said everything in the combined group's pipeline was now going to be assessed, but no decisions have been made yet and the collective R&D team will meet in mid-June to begin that process. "Baxalta brings to us enormous expertise in manufacturing and technical operation, augmenting that of Shire, so naturally it allows us to participate, if we wanted to, in biosimilars. What we're going to do now is look at everything within the combined portfolio – both things that come from Baxalta and things that come from Shire – and prioritize. We won't be able to do everything going forward," he said. "And if there are areas we can't focus on, then there's different ways of dealing with that, such as partnerships or external funding, but no decision has been made."

He noted that Shire now has more than 50 programs in clinical development, with a balanced mix of early, mid and late-stage projects. "So we have enough to choose from and want to ensure we have enough resources to focus on the essential projects that we have," the CEO said.

That evaluation process could in the longer-term see Shire re-evaluate its presence in the ADHD market. The group's key ADHD asset remains *Vyvanse* (lisdexamfetamine dimesylate), which is continuing to grow in the US, particularly in the adult ADHD market, and which is rolling out slowly outside of the US. The US franchise was boosted by the addition of a binge-eating indication in early 2015 which helped raise the overall growth rate in 2015 to 20%.

"When I came in as Shire CEO in 2013, there was a bit of gloom overhanging the ADHD franchise in terms of growth prospects, notably the pediatric market, so the team put an increased focus on the adult market, which is now the fastest growing part of the market," Ornskov noted, adding: "There's a lot of room still in that franchise and any decision on that franchise would be centered around whether we can add additional, longer-acting compounds.

He said the company has big hopes for its longer acting SHD465, which works in ADHD for up to 16 hours and will be submitted to the FDA later this year. "So there's a lot going on in that space and it's too early to make a decision about the longevity of that franchise, but so far the picture is very positive."

Ornskov, a physician by training, played down concerns voiced by some analysts over Shire-Baxalta's prospects for retaining a market leadership role in hemophilia as novel new therapies loom, notably **Chugai Pharmaceutical Co. Ltd.**'s hemophilia A treatment emicizumab (ACE910/RG6013/RO5534262), which is currently in a Phase III multinational study program. Instead, he welcomed the competition, while noting that Baxalta is positioned with its own pipeline of novel agents including a once-weekly factor VIII therapy BAX826, which analysts believe could launch in 2020. "Baxalta has a wide array of products in this area and will just be stimulated by new entrants and it will continue to have a leadership position there," he added.

Partnering and bolt-on acquisitions of promising compounds will also be part of the new company's strategy. But Ornskov expects more emphasis to be placed on in-house R&D going forward. "The model that Shire has is a mix where external innovation has been a bit more prioritized than internal innovation.

Now we have the opportunity to increase our R&D base to also focus a bit more on internal innovation, but I am agnostic with regards to where the compounds come from, whether it's home-grown or an externally acquired compound," he said.

The enlarged R&D group will continue looking at compounds in various stages of development. "One of the key strengths that this combined company will have is that with our depth of expertise in crucial areas – clinical development, clinical operations, regulatory process and product development and manufacturing – it makes us a partner of choice to help compounds navigate clinical development and bring it over the finish line and into the marketplace."

But another big acquisition is not in the cards. "We will continue to look for acquisitions at the product level so that we can continue to bring innovative medicines to patients, but after this Baxalta merger we will not be in the business of big deals. But, we will continue to be in the business of partnerships and business development," Ornskov said.

He did show interest in the product offerings and scientific focus of one company - **Intercept Pharmaceuticals Inc.** – but declined to comment on media reports that the company was a target. Intercept's novel therapy *Ocaliva* (obeticholic acid) recently was approved in the US to treat primary biliary cholangitis (PBC), but it also is in development for the much larger indication of non-alcoholic steatohepatitis (NASH).

"I will not comment on Intercept's being a potential takeover target, but will say how pleased I am that they have been a trailblazer in an area that often has scientific interest here at Shire. We have two rare disease compounds – SHP625 and SHP626 – [and] SHP626 is being investigated in NASH, where there is a significant opportunity and I hope Shire can continue to contribute in this area," he said.

CONFIDENT DEAL POSES NO TAX RISK

Ornskov also played down potential risk that the Baxalta transaction will trigger a tax obligation for Shire. He said Shire and its tax counsel are confident that a merger with the proposed cash consideration of $18 per Baxalta share will not jeopardize the tax-free status of the Baxalta spinoff from **Baxter International Inc.** "The Shire team has gotten all the relevant tax information and options that are needed to ensure we can bring this over the finish line correctly, so I remain confident. We've answered all the relevant questions and done all the relevant diligence that we need to do," he said.

With the Baxalta deal done, the focus should shift back to the advancement of Shire's pipeline. *Scrip* asked Ornskov which assets he gets most excited about and he pointed to lifitegrast for dry eye disease. "Lifitegrast has a special place, in my view, and has a lot going for it, such as phenomenal clinical trials, innovative mode of action, good safety profile and [it] addresses a market with significant unmet need and is in late stages of review at the FDA. It's had lots of ups and downs, like most innovative products – it never goes in a straight line," he said. The company's guidance is for lifitegrast sales of more than $1 billion by 2020. Some analysts believe shares in Shire could be given higher ratings with the expected US approval on July 22 for its dry eye therapy, and potentially mark a first step toward a broader ophthalmic franchise.

Ornskov said the general opinion regarding the Shire/Baxalta merger "has had its ups and downs – like lifitegrast – but people eventually came around to our thinking. The support this deal got from our shareholders is also testimony of the merger's innate logic. There are still skeptics out there, but I'm sure the group's pipeline will speak for itself."

A#2016800120

By Sten Stovall

This article is adapted from Scrip. In Vivo *brings selected complementary coverage from sister publications to subscribers.*

Medtech M&A

ZIMMER BIOMET BUYS LDR TO BOOST SPINE REVENUE GROWTH

The world's second-largest orthopedic device firm **Zimmer Biomet Holdings Inc.** is making its biggest move since Zimmer and Biomet came together in 2015 with a $1 billion acquisition of spine-device specialists **LDR Holding Corp**.

At $37 per share, Zimmer Biomet will pay a 64% premium above LDR's last closing share price before the deal was announced on June 7. Zimmer Biomet is paying the high price because it expects that Austin-based LDR will instantly put it in a leading position in the rapidly growing cervical disc replacement and minimally invasive spine surgery markets.

"This transaction is about accelerating Zimmer Biomet's growth in Spine, which is the largest musculoskeletal market with a value of approximately $10 billion," Zimmer Biomet CEO David Dvorak said during a June 7 conference call. "We see significant opportunities for Zimmer Biomet in this segment, where we currently have a small presence of only 5% of global market share. Our strategy is to drive growth both organically and inorganically, with a focus on differentiated innovation within the fastest-growing segments, complemented by a specialized sales force."

Currently, Zimmer Biomet's Spine division markets a wide variety of hardware and biologics for spine surgery, but it does not offer anything like LDR's *Mobi-C* cervical disc replacement, the only artificial cervical disc approved by FDA for both single- and two-level disc replacement.

LDR CEO Christophe Lavigne added: "With Zimmer Biomet, we will have the size, resources and talent to leverage the combined portfolio and expand our leadership position in the [cervical disc replacement] market, delivering long-term value to health-care providers and their patients."

This is Zimmer Biomet's third acquisition of 2016. In March, Zimmer Biomet completed the acquisition of Colorado-based **Ortho Transmission LLC**, which makes transcutaneous osseous integrated skeletal implant technology that complements Zimmer Biomet's ongoing collaboration with the US Department of Defense on prosthetic limbs. And on May 16, Zimmer Biomet closed a deal for Arizona-based **Cayenne Medical Inc.**, which markets devices for knee, shoulder and extremity soft-tissue repair and reconstruction. Terms of both the Ortho Transmission and Cayenne deals were not disclosed.

COMPLEMENTARY PRODUCT LINES

"There is essentially zero overlap in the product portfolio," Dvorak said. "These highly proprietary unique offerings that LDR brings are going to be cross-sellable right into our distribution channel on the legacy Zimmer Biomet side and vice-versa, and that's going to be powerful," Dvorak said.

Driven by near-30% year-over-year growth in sales of Mobi-C, LDR recorded 9.7% total revenue growth in the first quarter of 2016, including 15.4% growth in the US.

In addition to Mobi-C, LDR has it *MiVO* line of minimal-implant-volume surgery devices. Although revenues from that division have been shrinking lately because the company is putting its limited resources into Mobi-C, the firm says it has eight MiVO product launches planned for the next three years to revive that business. For example, LDR announced on June 2 the first implants of the *ROI-C* titanium-coated cervical cage with the proprietary *VerteBRIDGE* in-line plating technology for optimizing a minimally invasive surgical technique. FDA cleared ROI-C in December 2015.

LDR will become part of Zimmer Biomet's Spine & Craniomaxillofacial division, led by Adam Johnson, who is group president of the Spine, Dental, CMF and Thoracic unit. During the June 7 call, Johnson said LDR currently only sells to about 52% of spine surgeons in the US; the combination with Zimmer Biomet, he said, will help bring Mobi-C and MiVo technologies to more surgeons, while adding LDR's 68 sales reps to Zimmer Biomet's sales force.

A#2016800119

By Reed Miller

This article is adapted from The Gray Sheet. In Vivo *brings selected complementary coverage from sister publications to subscribers.*

DEALS OF THE MONTH

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

TOP ALLIANCES: CIGNA PAYS IF PCSK9S PERFORM

Cigna Corp., a leader in outcomes-based reimbursement, has signed value-based contracts for the two PCSK9 inhibitors on the market for high cholesterol. Cigna's contracts with **Amgen Inc.** for *Repatha* (evolocumab) and with **Sanofi/Regeneron Pharmaceuticals Inc.** for *Praluent* (alirocumab) are independent of each other, but share the same objective: if patients taking the drugs aren't able to reduce their LDL-C levels at least as much as clinical trial participants did, the drugmakers will discount the products more steeply than the rebates already negotiated.

TOP FINANCING: HOMOLOGY BANKS $43 MILLION FOR GENE EDITING

5AM Ventures and ARCH Venture Partners led a $43.5 million Series A round for **Homology Medicines Inc.** Helmed by CEO Arthur Tzianabos, PhD, and other ex-Shire executives, Homology will pursue gene editing and gene therapy using vectors derived from naturally occurring human adeno-associated viruses, an approach that the start-up thinks confers advantages over competing technologies.

TOP M&A: QUINTILES AND IMS COME TOGETHER

CRO **Quintiles Transnational Holdings Inc.** has agreed to merge with health care data giant **IMS Health Inc.** in a deal worth $9 billion. Although billed as a merger of equals, IMS Health shareholders will own 51.4% of the combined company, to be called Quintiles IMS Holdings, which will have a market cap close to $18 billion.

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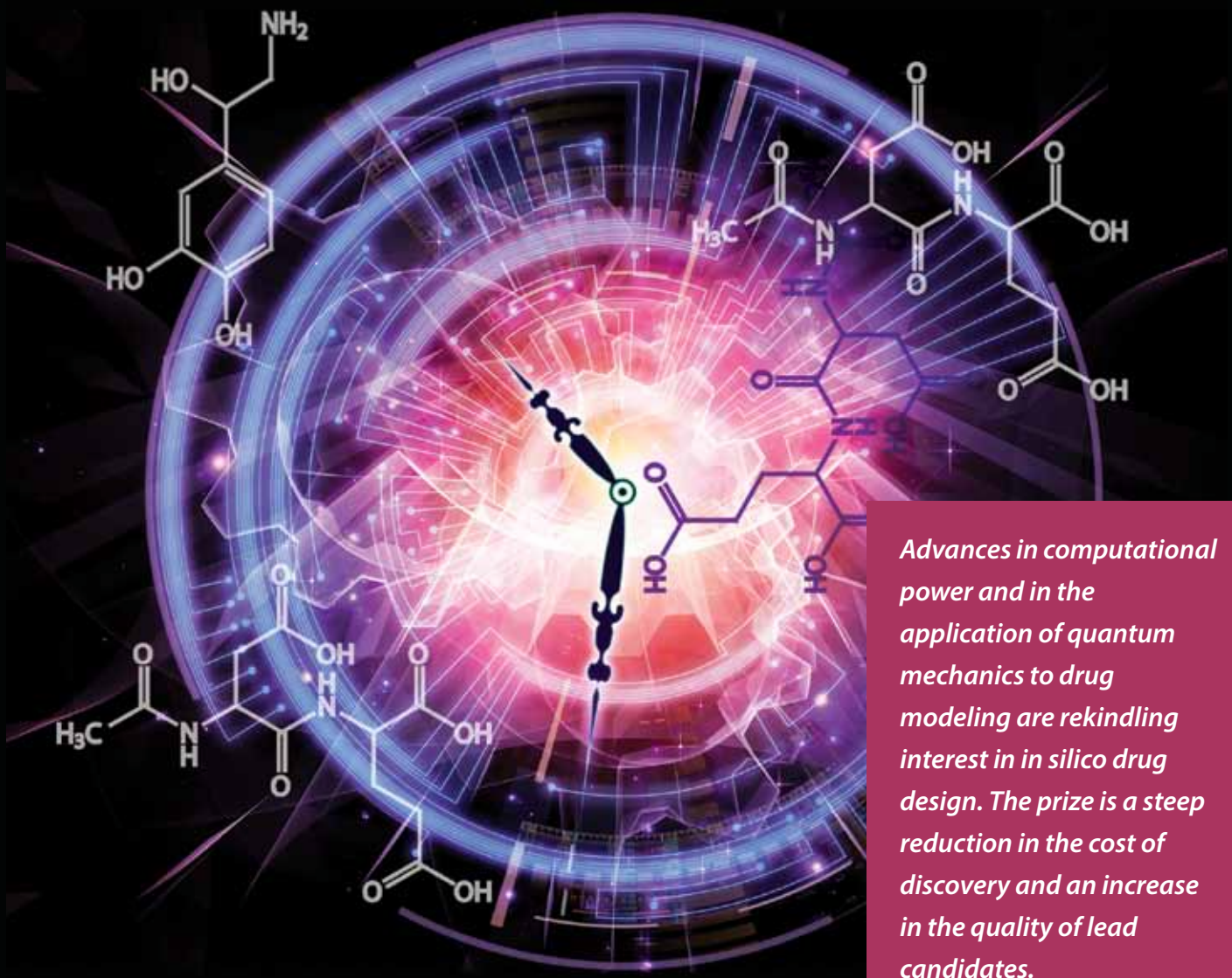
In Silico Drug Design: Finally Ready For Prime Time?

BY MICHAEL GOODMAN



Advances in computational power and in the application of quantum mechanics to drug modeling are rekindling interest in in silico drug design. The prize is a steep reduction in the cost of discovery and an increase in the quality of lead candidates.

- After decades of disappointment, improvements in computing power are allowing researchers to generate virtual compound libraries and apply the insights of quantum mechanics to the modeling of ligand/receptor interactions.
- The benefits include novel chemical matter, higher affinity hits, and lower-cost drug design than was possible using high-throughput screening.
- Observers see the new physics-based computational chemistry as potentially the most powerful of several new technologies in the discovery toolbox.
- Several companies have entered the field, including Nimbus Therapeutics and Verseon. Each has a portfolio of early-stage compounds, but different approaches to how they access their platform.

Executive Summary >> 52

Building on improvements in the price-performance of computing power and on early efforts to incorporate principles of physics in the modeling of ligand/receptor interactions, a few pioneering companies like **Nimbus Therapeutics** and **Verseon Corp.** are pushing the boundaries of computational drug design.

Kenneth M. Merz, PhD, director of **Michigan State University**'s Institute for Cyber-Enabled Research, and former head of Pharmacopeia Inc.'s Center for Informatics and Drug Discovery, says that the introduction of quantum mechanics into computational drug design, primarily to develop quantitative structure-activity relationships, began 50 years ago. "It really took off when DuPont got involved in the 1980s," he says.

But lack of computing power, and the inability to accurately model the behavior of molecules in the presence of receptors, has held back the field. Also, high-throughput screening (HTS), which had its origins in the late 1980s as the preferred technology for natural product screening, was widely adopted in the industry in a short time. Along with combinatorial chemistry, which enabled the generation of libraries of compounds to screen, these technologies dominated drug design, which we define as the process for generating lead candidates.

But HTS is an expensive, time-consuming technology. The "hits" that result from it may be potent, but may also turn out to be toxic, or have poor solubility and bioavailability. A basic shortcoming of HTS is that only already synthesized compounds are available for screening. Combinatorial chemistry yields a relatively small pool of drug-like compounds against target proteins. Corporate compound collections typically have about four to six million distinct compounds, a small swath of the drug-like chemical space that could potentially be synthesized. And the presence of analogs and variations on core chemical structures means that corporate collections are not very chemically diverse.

Attempts to make discovery more efficient by scaling these processes (e.g., faster HTS, larger chemical libraries) have not reversed the industry's diminishing returns from research. The promise of computational drug design informed by physics is that it will explore a larger region of the accessible chemical space, producing high-quality, novel chemical matter that is potent and highly selective at a fraction of the cost of the old lead discovery paradigm.

"The promise of computational drug design informed by physics is that it will explore a larger region of the accessible chemical space, producing high-quality, novel chemical matter that is potent and highly selective at a fraction of the cost of the old lead discovery paradigm.

The old paradigm at best led to an approximation. "Now we have the tools to accurately quantify how a drug interacts with its binding site," says Rosana Kapeller, MD, PhD, chief scientific officer of Nimbus. She believes that may be the tipping point that industry and investors have been waiting for.

THE APPLICATION OF PHYSICS TO COMPUTATIONAL DRUG DESIGN

MSU's Merz notes that to accurately calculate protein/ligand binding affinity, two things are needed: one must fully sample the relevant configuration space, and one must accurately calculate the energies involved.

The configuration space refers to the various conformational positions that a ligand can assume in a binding pocket. Both ligand and receptor typically alter their conformations to bind to one another. Adityo Prakash, CEO of Verseon, refers to these changes as the "bend, flex, vibration and twist" of ligand and receptor. The changes in conformational positions throughout the binding process must also be modeled. A virtual compound library might consist of several million distinct compounds plus many more millions of conformational positions.

The energies to be modeled – and here's where quantum mechanics come in – include solvation (the presence of water as a bulk medium), electrostatics, hydrogen bonding, and van der Waals forces (a general term defining the attraction of intermolecular forces between molecules).

The need to simulate the interaction of a ligand with a target in an aqueous medium, although computationally intensive, is straightforward: the human body is about 60% water. The presence of water may also alter the electrostatics of a ligand/receptor system.

"If you have a 10,000-atom protein, you have a few hundred Dalton of molecular weight drug that you're trying to design," says Prakash, "and you have tens of thousands of water molecules leading the interaction. At the heart of it, it's quantum mechanics that's guiding all of these interactions."

More recently, the need to model the displacement of discrete water molecules trapped in the binding pocket of the active site has been solved. These bound waters can negatively impact the binding affinity of the system. "If you pick a ligand that can displace that water," says Kapeller, "it can increase the affinity of the ligand for that receptor 10-fold, 100-fold, or 1,000-fold."

Hydrogen bonds are important to ligand/receptor binding but are difficult to model. Both Verseon and Nimbus (via strategic partner **Schrödinger LLC**) have developed low-cost methods of modeling hydrogen bond energies.

THE PROCESS OF COMPUTATIONAL DRUG DESIGN: A NEW PARADIGM

Companies at the forefront of physics-based *in silico* drug design have similar discovery procedures. Nimbus and Verseon both begin

VERSEON CORP.

www.verseon.com

HQ: 48820-100B Kato Road
Fremont, CA 94538

FTEs: 50

Global Infrastructure: Silicon Valley; contract resources in India, China

Financing: Founders, Robert Karr, John Leonard, Neil Woodford

Company Model: Computational platform is organic; three founders are physicists

Portfolio/Status: Antithrombotic/preclinical (lead candidate), plasma kallikrein inhibitor/preclinical, non-VEGF angiogenesis inhibitor/preclinical

Corporate Status: LSE/AIM: VSN

with a library of virtual compounds.

Verseon's Molecule Creation Engine (VMCE) generates large numbers (c.10^8) of virtual, drug-like and synthesizable compounds per program. Prakash says, "This enables us to explore a completely novel chemical space." The VMCE provides each compound with synthesis guidelines, a kind of recipe for manufacture. Moreover, it can generate a cluster of closely related variants to prevent the entry of single agents into the downstream discovery process.

Nimbus takes a different approach. Rather than designing a library per program, it has worked with its strategic partner Schrödinger to create a virtual library of commercially available drug-like compounds that have been curated to have the right physiochemical and drug-like properties. It also contains fragments. To this it adds proprietary libraries that it accesses through licensing agreements or via its own internal efforts over the past six years.

In terms of the target being structurally enabled, Kapeller prefers targets that already have compounds bound to it. "This can teach us quite a bit about it," she says. Nimbus' targets to date are biologically validated, but unprecedented in the clinic. It avoids emergent biology. Prakash takes a less risky approach for his initial projects, avoiding historically challenging targets for well-established, clinically validated ones.

The next step is to assess this virtual library *in silico* against a disease-causing target. Ligand/receptor interactions are modeled and in an iterative process winnowed down into smaller and smaller subsets of hits prioritized by binding affinity. This is the heart of the new paradigm – the accurate modeling of these interactions.

Large virtual libraries require a significant number of computational calculations. Prakash claims that Verseon's Molecule Modeling Engine (VMME) performs more than 10^{11} compute operations per tested compound against a target, capturing all conformational changes and energies that determine binding affinity. Since brute force sampling is not feasible, sophisticated optimization algorithms are generally employed to explore the search space and, if possible, find the best molecular configurations for the system by ignoring unfavorable binding states and thereby lowering the computational load.

Both companies do their computing across a cloud. Verseon uses a dedicated private cloud, whereas Nimbus uses a cloud and 50,000-core cluster through its partner Schrödinger. Prakash says Verseon is planning to build a new cluster that will run at a peak speed of one petaflop.

Virtual compounds that are predicted by the platform to bind strongly with the target are then synthesized in the lab and put through a battery of biochemical assays – what Nimbus calls its "primary assay" – and further biological characterization.

Prakash stresses that Verseon's downstream lab processes – the *in vivo* biology – are seamlessly integrated with the computational front-end. Kapeller holds that computational tools for the *in vivo* lead optimization stage have not kept up with the technology used in ligand/receptor modeling. "We need technology that is more predictive of ADME and ADMET properties. Metabolism is key. Are there toxicities present? Schrödinger has been spending a lot of time to get us out of the muck of lead optimization."

Computational chemistry based on the insights of physics appears to have solved most of the problems of potency and selectivity. In fact, compounds that are advanced via computational drug design to *in vivo* testing so far appear to stand a better chance of passing than hits derived from HTS. But metabolism, toxicity – these are not known *a priori*.

Merz likens drug design to a vast funnel. "At the top are the *in silico* methodologies where you've got billions of compounds. The computational methods can help you whittle that down to a million compounds, then down to a thousand. At the bottom of the funnel, other aspects come into play: is it soluble? Is it bioavailable? Will it survive the first pass through your liver? Is it toxic? Will your hair fall out?"

At Nimbus, Kapeller says they've had some success using data as a predictive tool. "We iterate everything with data, so we're very comfortable that whatever they predict is what we are seeing. That speeds up the process over time, and we can translate that across multiple programs."

DEGREES OF VALIDATION

Industrial *in silico* drug design based on insights from physics has been validated to varying extents and by several routes.

Verseon was founded in 2002 by three physicists who had earlier founded a video compression start-up called Pulsent Corp. After a few years, Prakash and his co-founders went around showing their computational discovery platform to people like Robert Karr, MD, former SVP of R&D at Pfizer and John Leonard, MD, former chief scientific officer and SVP of R&D at Abbvie. "Those men threw hundreds of test cases at us," says Prakash, "where they knew beforehand what binds to a particular protein." In a typical test, they selected a drug and a target and challenged the platform to predict how they would bind. In each case, they already knew the outcome. And in each case, the platform's prediction matched the experiment.

Karr and Leonard were convinced. Both men sit on Verseon's scientific advisory board and were among the early outside investors in the company. Steven Chu, PhD, former US Secretary of Energy and a Nobel physicist, also sits on Verseon's scientific advisory board. As Verseon's portfolio progresses through clinical proof-of-concept, the company will likely rely on the data that its candidates generate to validate its platform.

Verseon has a portfolio of three preclinical assets. Its lead program – an anticoagulant for cardiovascular indications with a unique chemical structure that has been shown in animal models to substantially reduce the risk of bleeding – is in IND-enabling studies. (*See "Verseon Claims Major Move In Drug Design, Will Enter Clinic Within A Year"* — "The Pink Sheet" DAILY, *September 15, 2015*.)

Nimbus is structured as an LLC holding company that houses each program in a c-corporation. When the asset-centric LLC holding structure enters into a transaction with a buyer, it can follow one of three typical paths. One path involves an equity investment and/or an option to acquire, and allows the clean, value-maximizing sale of individual drug programs. This was the case with Nimbus' early deals with **Monsanto Co.** and **Shire PLC**. A more recent deal with **Genentech Inc.** for an IRAK4 inhibitor was a more straightforward licensing deal. (*See "Potent Selectivity: Nimbus Entrusts IRAK4 Program To Genentech"* — "The Pink Sheet" DAILY, *October 20, 2015*.) But the most recent transaction with **Gilead Sciences Inc.** for the allosteric acetyl CoA carboxylase (ACC) inhibitor for the treatment of non-alcoholic steatohepatitis (NASH) was an acquisition of Nimbus' subsidiary Nimbus Apollo (the c-corp) for $400 million up front plus earnouts. (See *"Gilead Increases NASH Emphasis With Pickup Of Nimbus ACC Inhibitor"* — "The Pink Sheet" DAILY, *April 4, 2016*.)

The validation of Nimbus' discovery methodology is primarily commercial; three big biotechs did their due diligence and ponied up for the unique products of its computational platform.

WHAT LIES AHEAD?

If physics-based computational drug design produces drug candidates that prove themselves in the clinic, then several factors will determine its place in industrial drug discovery.

The benefits are clear:

- Novel chemical matter around which strong patent protection can be claimed.
- Significant cost and time-savings. Kapeller claims that, "For most programs, we can get from a computer-generated hit to a lead series in four to six months."
- More potent and selective leads than can be generated by HTS.

Steve Hall, PhD, general partner at Lilly Ventures, sits on multiple boards including those of Nimbus Therapeutics and **Numerate Inc.**, a machine learning-based drug design specialist. Although he is clearly enthusiastic about the advances brought by computing power and insights from physics, he sees a current landscape where many companies have moved away from HTS and are employing medium-throughput screens based on target families (GPCRs, kinases). "I don't see it replacing HTS; rather, it's very much a matter of using the right tool for the right job," he says. Hall envisions a future where several technologies will co-exist. But as he himself notes, computational chemistry may be the best bet for generating novel chemical matter.

Although much about their respective platforms and procedures is similar, it is the differences between Nimbus and Verseon that may determine the business models of drug design start-ups as well as point the way for the widespread integration of computational drug design into industrial discovery.

For instance, staff composition and the way each company accesses computational and physics expertise have trade-offs. Verseon built its platform over a period of 12 years. Its founders are physicists with extensive computational experience. The company has hired in staff with expertise in chemistry, clinical development and biology, and moreover relies on CROs for laboratory work – mostly synthesis – in India and China.

Nimbus instead has staffed the company with veteran drug hunters, and relies on its strategic partner Schrödinger for the computational platform and related expertise. Nimbus does not get off-the-shelf technology in the arrangement; rather, Schrödinger – an equity backer that participates in exits and milestones – works closely with Nimbus to solve its challenges in real time.

Hall, who has spent time as an executive in multiple pharma labs, recalls in the past having one computational chemist supporting three to five different projects. "Contrast that with the Nimbus-Schrödinger relationship where the ratio is almost reversed: multiple computational scientists working on a single Nimbus project."

Although it is too early to say which staff model produces the best platform and uses it for the best result, the answer may turn on the benefits of external access to the platform versus an organic solution.

Prakash is adamant that the "outsider" status of Verseon's three co-founders – physicists and mathematicians, not drug industry insiders – allowed them to bring a new perspective to the fundamental challenges of drug discovery. With the guidance of its scientific advisors, the company was able to build a homegrown, proprietary computational platform that confers potential economic advantages and performance benefits.

Rosana Kapeller argues that Schrödinger "is in the engine room with us," participating in project team meetings and target

NIMBUS THERAPEUTICS LLC

www.nimbustx.com

HQ: 784 Memorial Drive
Suite 100
Cambridge, MA 02139

FTEs: 22

Global Infrastructure: Uses distributed R&D model with workers worldwide. CRO network in China, India, Germany, France

Financing: Founded by Atlas Venture & Schrödinger; later, Pfizer Venture Investments, Lightstone Ventures, Bill Gates, SR One, Lilly Ventures, undisclosed investors. Most recent round a $43 million Series B in 2015

Company Model: Computational platform and ongoing expertise provided via Schrödinger; FTE staff weighted toward drug hunters

Portfolio/Status: Novel fungicide/in crop field trials (partnered); ACC inhibitor/Phase II ready (sold); IRAK4 inhibitor/preclinical (partnered); Tyk2 inhibitor/discovery; Kras inhibitor/discovery; STING modulator/discovery

Corporate Status: Private

selection. Rami Farid, PhD, president of Schrödinger, sits on Nimbus' board. The two companies are aligned to a common goal. She feels that the Verseon model is basically split between scientists developing technology and scientists doing drug discovery. "They have to spend a lot of time and money doing both. This creates push and pull – where do resources go when money is tight?"

The intensely cross-disciplinary nature of *in silico* drug design raises other challenges. Physicists, computational chemists, medicinal chemists and mathematicians do not necessarily speak the same language. Kapeller recalls being stunned in the early days to learn that computational chemists and medicinal chemists don't talk to one another. "Med chemists say, 'Knowing what to synthesize is an art and I have experience.' The computational chemist looks at everything in an analytical, quantifying way, yet without help they come up with a compound that can't be synthesized in the real world." Nimbus, she says, has solved this problem, but it's one that could delay the wider adoption of computational chemistry.

The two companies also differ in their approach to target risk. As noted above, Nimbus takes on targets with well-validated biology in animals and humans, but which are not validated in the clinic. Verseon has chosen well-established, clinically validated targets for its initial three programs. But Prakash expects to take on more target risk in the future. "I don't want to design the perfect drug for the wrong target early on," he says. Both companies, in so far as they generate novel structures, take on chemistry risk.

> "Computational chemistry based on the insights of physics appears to have solved most of the problems of potency and selectivity.

Gilead's ACC compound for NASH, which is Phase II ready, is the most advanced compound to emerge from the new physics-based computational chemistry. Verseon, after spending 12 years building its platform, has only recently emerged from stealth mode. It expects to file an IND for the lead anticoagulant program by year's end. According to Merz, if these programs are successful, and they are followed up with other successful programs, industry might accelerate the integration of the new discovery paradigm into R&D, especially if it can demonstrate time and cost savings. Hall suspects that most big pharmas currently have licenses to Schrödinger's software, although the extent to which its technology is being applied at Nimbus is unique.

Further improvements in compute power, in the sophistication of algorithms and in access to high-performance cloud computing will increase the attractiveness of the new, physics-based paradigm for designing drugs. As the enabling technologies continue to fall into place, allowing researchers to run more complex calculations, the quality of Nimbus' and Verseon's programs, and those of other start-ups that enter the field – the data they generate – will help determine the direction that the new technology takes, and its rate of uptake.

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Guided Therapy Systems Keeps Options Open On Tissue Regen Device

Guided Therapy Systems CEO Michael Slayton has a history of medtech innovation, with a primary focus on diagnostic and therapeutic ultrasound applications. He tells In Vivo about the 22-year engineering journey that has led him and the company he founded to the cusp of market launch of a non-invasive tissue regeneration device for musculoskeletal injuries.

BY ASHLEY YEO

- Disruptive technologies do not come along very often but Guided Therapy Systems' handheld ITU-based imaging and tissue repair device is one that appears to fit the bill.
- The first groups of US clinical trials are well underway ahead of regulatory filing later this year, but the US will not be the global launch market.
- GTS' CEO Michael Slayton has a firm idea of who would be the ideal partner to go to the market with, and has the simple goal of making this happen.
- The company has selected two prevalent musculoskeletal conditions to start with, but there are many that could follow, including drug delivery, for a product that is so far without a direct competitor.

Executive Summary >> 52

Scalpel or sound wave to treat musculoskeletal and sporting injuries? Mesa, AZ, medical device innovator **Guided Therapy Systems LLC** (GTS) claims it has developed a revolutionary method of treating conditions like plantar fasciitis, epicondylitis and tendon injuries that is superior to laser, radiowave or other energy delivery devices.

Revolutionary, because the product, *Actisound*, introduces intense therapeutic ultrasound (ITU) guided by ultrasound imaging in a device that offers a quicker, safer, cheaper way of non-invasively repairing tissue. Its action enables concentrated energy deposition to occur deep inside skin tissue, which initiates the healing response and stimulates tissue growth, all without breaking the skin.

This novel therapy is set to enter a lucrative market. To give an idea of the potential territory at stake, Medtech Insight's report "US Markets For Sports Medicine Products" notes that of the 200 million adults who participate in non-work-related sports or recreational activities in the US, nearly 5 million receive medical treatment for sports injuries including sprains/strains, dislocations/fractures, knee injuries, shoulder injuries and muscle/tendon tears every year.

In 2013, combined sales of sports medicine products in the US totaled about $13 billion, of which conservative care products accounted for 81% of sales. Combined US sales of sports medicine devices are expected to increase at a compound annual growth rate of 3.5%, reaching nearly $15.5 billion in the year 2018.

Before founding GTS in 1994, CEO and chief technical officer Michael H. Slayton, PhD, was VP of advanced development at Daimler Benz subsidiary **Dornier Medizintechnik GMBH**. He has developed dozens of commercially successful products, of which Actisound is the latest.

GTS restructured in 2004, with **Ardent Sound Inc.** becoming the commercial manufacturer of diagnostic ultrasound imaging

devices, and GTS incubating new commercial opportunities for its ITU platforms. Although Slayton originally developed the technology for the destruction of non-resectable liver tumors, GTS found its early opportunity in aesthetics, creating **Ulthera Inc.**, the only energy-based technology with an FDA indication for non-invasive tissue lift, in 2004. **Merz North America Inc.** bought Ulthera for $600 million in 2014. (*See "Going More Than Skin Deep Into Merz's Ulthera Acquisition" — IN VIVO, November 2014.*)

GTS expanded into the consumer skin care market with the founding of **Xthetix Inc.** in 2006. In 2011, Xthetix was acquired by a Fortune 100 consumer products company, which is currently partnering with GTS to bring these devices to the over-the-counter, home-use market.

Now, Slayton and GTS hope to position Actisound as a major solution in tissue repair, first in the private sector and later in the public sector, upon being reimbursed.

In Vivo: ***How disruptive is the technology that you are developing for soft-tissue repair?***

Michael Slayton: That's difficult to say, as very disruptive technologies do not come along very often. What we're trying to do is repair soft tissue. We're not trying to get something into the body – not yet anyway – we simply help the restorative or rejuvenative mechanism of the tissue. The Actisound intense therapeutic ultrasound [ITU] device non-invasively creates small incisions/lesions – small zones of thermal injury – that restart and enhance the production of endogenous growth factors in connective tissue. In short, the immune system responds faster when there is an area that is repairable.

It works by encouraging natural soft-tissue repair cascade and peaks inflammation. Next, the fibroblasts migrate into the targeted area, leading to the formation of collagen. Then there is maturation and a remodeling phase in which the new collagen converts into fibers, and formation of collagen fiber cross-linkage in the final stage of the repair process. The final stage is the formation of new musculoskeletal tissue and the repair of the damaged organ. The idea is we try to repair things that don't need open surgery, and if we do things right, it's curative not a palliation.

How far have you progressed with trials of the technology?

We have been involved in three trials to date, two of which are fairly complete. We selected plantar fasciitis [PF] and epicondylitis, as they are prevalent conditions.

The first trial, at the University of Arizona, was in PF, which affects 10% of the US population. It was double blinded and sham controlled. We recruited 50 people and have already published the results of what from our point of view was a very successful trial under principal investigator Dr. Daniel Latt [MD, PhD], an orthopedic surgeon and professor at the University of Arizona Medical School. We used chronic patients – we did not involve people with acute injuries – who had had PF for 12 to 18 months: it was hurting a lot and/or they couldn't walk. The disease becomes chronic as there's not enough blood supply going through the MS tissues – it's poorly perfused. We had an over-80% repair rate within 12 weeks post-treatment – an over-80% repair rate is statistically significant and is testament to a disruptive device.

The second trial is in 30 people with epicondylitis [tennis elbow].

Michael Slayton, PhD

We are working toward completing it at The CORE Institute, Phoenix, Arizona. It was conducted to explore the success of ITU technology on lateral epicondylitis, which affects up to 3% of the population (the prevalence of chronic problems caused by overuse in tennis players can be as high as 40%). The efficacy rate – in what is a much smaller muscular structure – is about the same as we saw in the PF trial: 83% of the first 18 patients reported improvement in elbow pain when ITU technology was applied. They also showed significant improvement in daily function. (*See Exhibit 1.*)

We are now starting a third trial, in 30 people, at University Foot and Ankle Institute in Los Angeles, which is also in PF. We are doing this one in order to get the numbers up for the regulatory submission. We want to avoid any uncertainty there. Regulatory submissions have become pivotal; it's no longer enough to make something that works, but FDA usually looks favorably on well-designed trials that have more than 50 to 100 people and a good safety profile. The trial schedule is six months, and there will be a further month to gather the data together – so it will be completed within this year.

What setting are you targeting for use of the device?

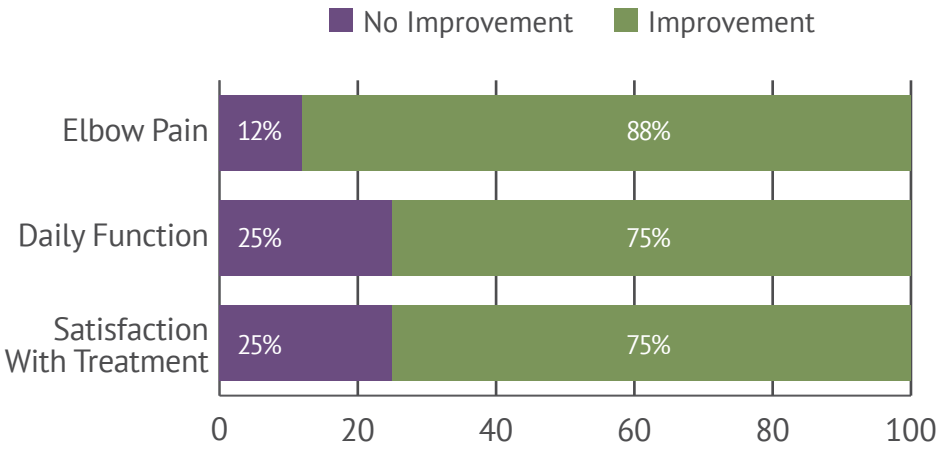
Our primary market is orthopedic surgery. We plan to introduce Actisound into the professional setting – for the most part the non-hospital setting. The primary market is orthopedic surgeons and podiatrists; the secondary market is GPs and secondary providers. At the top of the pyramid are the people who feel comfortable and know what they're doing. There are no user/skill issues to worry about. It is a relatively simple device. It doesn't have to be "idiot-proof," but we've built in precautions and a safety valve such that the damage that could be created is minimized to a point where it's not a regular concern at all. Basically, it's a turn on/off device, which the user moves up and down the damaged area.

What size is the market you are addressing?

An ITU markets study – compiled by McKinsey for J&J [**Johnson & Johnson**] – reveals a market that's very large: over 18,000 potential users/practitioners in the US alone. Normally, double the US market to get an approximation of the worldwide market. If we get 5% to 10% penetration – which is a moderate goal – we'll be in pretty good

Exhibit 1

CORE Trial Results



SOURCE: GTS

shape. The most valued commodity for any physician is their time, and that's the simplicity of using this device: the procedure takes just a few minutes.

Current practice, for acute injuries, is to use conservative treatment – that is, special shoes, ice, stretching and strength training, or advice about staying off the leg. After a few months, it usually eases up, but it may or may not heal. The problems start when it doesn't heal. Tenotomy is then usually brought into play – a minimally invasive technique of using needles to create a lesion. For the most part it works. The alternative is shock wave therapy, but that is marginal and works in, say, only 30% to 40% of cases. It's not bad, but then again it's not very good. After you've exhausted all of those options, the patient basically has to face the fact that they're living with a chronic injury.

ITU can penetrate safely through tissue and deliver precisely targeted heating while sparing intervening tissue, unlike with lasers, microwaves or radio frequency. ITU technology is a cost-effective, fast and relatively pain-free treatment that leads to reduced pain and inflammation within two to three days, and soft-tissue injury repair within 12 weeks.

Actisound is being tested on ligaments, tendons and muscle, and apart from PF and lateral epicondylitis, initial indications include Achilles tendon and patella tendon injury.

What is the regulatory plan for the device?

We may be a US-based company, but we're not starting with FDA. We're starting with the CE mark. We have several CE-marked products. We also have extensive FDA experience, but FDA changed dramatically last year: the straightforward path for substantial equivalence has been made less easy – now you have to file an IDE, and the FDA needs to confirm the protocol.

How will you move Actisound into the market?

There are two ways to get into the market. The first can be likened to "selling your soul" – basically going to a major company and giving them the product and the regulatory package. They sometimes move you to one side, to take greater control, do some of their own work on it over a couple of years, and if there's enough movement, it hits the market big time.

The second route is to go with SMEs, which generally don't have time to sit on a product. If it's too big for them to handle, they might get bought out. The majors want the success, but they also want the risk to be taken out, even if they have to pay a premium. Our goal is simple: to get to the market and make the product available. In my experience, if something works, it usually finds its way to patients.

We're preparing to go ahead with the device this year. Depending on what we hear from customers, we'll go one way or the other – either direct sales or via a partner. That will be a matter of tactical approach.

As to public sector reimbursement, is that in the plan yet?

The device is not very expensive, and reimbursement is not a major factor at this point, but it would be, up ahead, if we were to go with a company the size of a Stryker or DePuy – which is quite possible. The strategics, with their dedicated departments, have more "oomph" than we would have as far as reimbursement is concerned. Reimbursement tends to become a big part of a selling strategy when capital-intensive and extensive procedures are involved. In those cases, without reimbursement, you can't move. Fortunately, we're more dynamic than that, and reimbursement for us is important, but not critical.

What category of partners are you looking for as you move toward market launch?

Not necessarily just distributors. We have several strategies "on the leash" at this point. They say: finish it; give us the package and we'll go from there. But we don't want to be dependent on somebody giving us a letter of intent and then saying they need six months to figure things out.

If we had the alternative of a small company that combines manufacturing with a distributorship in, say, Ireland or the Czech Republic, we'd go with that. You have to keep a range of options or basically you become subservient to whomever.

As to manufacturing, we can manufacture in the US ourselves at present, as the volumes are not yet huge. But I'm convinced that eventually we'll go for manufacturing in Europe if we start with Europe – about that there is no question in my mind.

Ideally, we would opt for a technically astute partner – regardless of size (within reason) – whom we can rely on. And we are only at the first clinical applications. Just looking at musculoskeletal, there is jumper's knee, shoulder tears, etc. There are so many things we can fix that it simply boggles the mind. And later, we'll have drug delivery too. I want this treatment to become pervasive.

> "There are so many things we can fix that it simply boggles the mind. And later, we'll have drug delivery too. I want this treatment to become pervasive."
> – Michael Slayton, PhD

You have experience in Germany: will that be the starting point in Europe?

We have several relationships in Germany – and I also worked for Dornier in the past – so it's not an unknown territory. But the borders are blurred in Europe, and it's not as geographically well-defined as it used to be. Germany is not necessarily the answer for the whole of Europe – it is part of Europe. We would not be focused on Germany to the exclusion of France and the UK, say. We also have contacts in the Czech Republic, France, the UK and other countries. If we were to opt for the distributor route, it's an arrangement that usually covers several countries. We might also consider going the "big" route, and teaming up with US tax inversion companies that are now headquartered in Europe – and maybe use one or two of them for Europe. We've already started to talk to small/medium-sized companies in the $50 million to $100 million sales range – and even those up to $200 million. We are trying to see who has the right level of hunger that matches our expectations. At the risk of sounding trite, you have only one chance to make the first impression.

Why has such a compelling technology taken this long to get to the market?

It will be 12 to 18 months still before we hit the market. Good things that are disruptive or somewhat disruptive usually take time to get to the market – they need to be proven. Incremental improvements, of, say, 20% to 30% better than what is already available are relatively easy. Physicians are conservative by nature – the most conservative section of the population that I've ever known – and for good reason! But by the time a product has been approved, you'd have had a couple of thousand users vouching for how good it is.

And we're also aware that big companies don't always move fast. A look at the successful projects that we've steered in the past shows that what dictates the pace is not the technology itself, but the marketing and sales. It can take years for those groups to get something on the market.

The hope is that we can be more in charge of timings – dictate the pace more and "nudge" the market if that is needed. A company will want the technology sometimes simply to avoid competitors getting it, or if their business can be improved by the addition of the technology. If we don't have a big company taking it over, we will try to nudge it.

It is not yet in general use, and won't be until after regulatory approval, but people in the know have heard about the technology at conferences and in publications. These are the people who lead our trials – the people of note.

What are the next stages for Actisound as it progresses to market?

For us, we must finish the clinicals, start the pre-production runs – which are already underway – and we need to start the submission. It has to take its course – and we want to do it right. We're talking about more sophisticated technology, with drug delivery potential that combines medication and energy sources, so it has to sit on a base of good solid clinical practice, and that's what we're going for.

We're investing heavily into this, and as we said, we've been doing this for the better part of 22 years. But as to investment, we've learned our lesson by now. We used to do deals with VCs, but we no longer want to be dependent on outside sources of any kind. We're in a position to invest in ourselves, so we do, and that gives us a control over timings. It gives us a bit more control over what we own rather than always having to look over our shoulders.

As to our sales model, I don't see any departure from the traditional model. And looking at price, we'll review the results, clinical possibilities, and the patient population. The price is defined by the cost of goods, and will probably be set at what the market can bear. A broad guess would be in the $25,000 to $35,000 range.

We see Actisound as an affordable, effective, and logical patient-centric technology. We don't have a competitor at this point – there is no effective non-invasive alternative on the market that allows doctors directly to treat soft-tissue injuries without breaking the skin – but that does not concern me. I simply want people to know about the innovation we've developed for the musculoskeletal space, and athletic sector in particular, and I want them to consider adopting it. I want people to know about this technology that we've been working on for so many years. We're a small company that has done some interesting things, and this latest one is very worthwhile, as far as I'm concerned.

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

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To Outperform In Pharma, Go Deep – Not Broad

The world's most successful pharma companies aren't winning on the basis of absolute scale; they succeed instead thanks to their leadership in a few clearly defined product categories. That approach delivers outsized returns, while helping firms navigate a changing health care landscape where payers and providers increasingly demand evidence of treatment efficacy.

BY NILS BEHNKE, MICHAEL RETTERATH AND TIM VAN BIESEN

- Category leaders are those firms that employ a common set of capabilities to develop products that serve a defined set of end-users and often exist within a common competitive class. The products are bought using a common purchasing process managed by common stakeholders.
- The key to understanding category leadership is to view categories through the eyes of the customer – patients, prescribing physicians and payers.
- Current industry trends play to the strengths of category leaders. Payers and providers are demanding evidence of efficacy, creating new hurdles for drug approval, and category leaders are the best positioned to deliver compelling evidence.
- The rise of drugs prescribed by specialists instead of primary care physicians also favors pharma companies with deep networks and strong relationships within the specialty.

Executive Summary >> 52

Key innovation, commercial strength and profitability in pharma are all closely linked to category leadership, analysis by Bain & Co. shows. Based on research over several years, Bain has found that companies that produce a higher share of revenue from category-leading positions have operating margins 13 percentage points higher than those that do not. Category leaders also achieved a success rate in Phase III clinical trials 27 percentage points higher than non-category leaders and peak sales from newly launched drugs are 36% higher. The combination is a powerful one, creating significant long-term competitive advantage. (*See Exhibit 1.*)

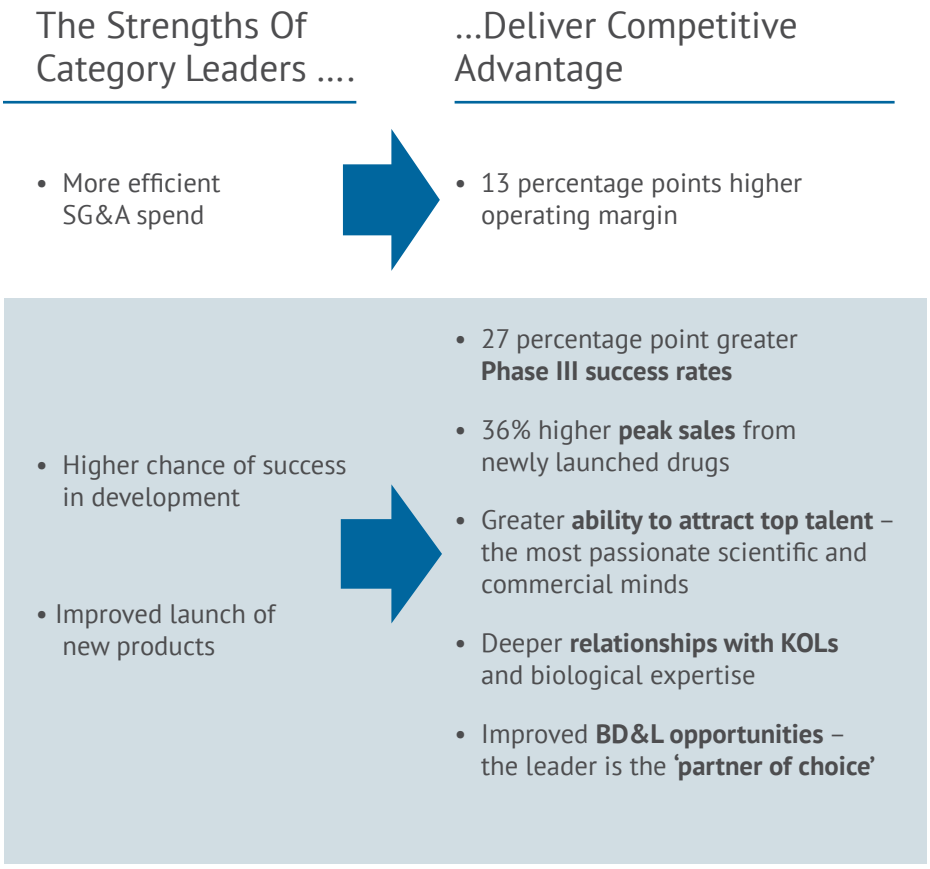
Why? Category leaders have a better understanding of the dynamics and evolution of the category. That's a built-in competitive advantage. Their product and regulatory divisions develop greater expertise and better insights into market needs, helping push innovations to market faster. They have greater ability to attract top talent and benefit from privileged access to all stakeholders in the category, including patients, key opinion leaders and clinical trial partners. Category leaders also have more resources to invest in product development, commercialization and acquisitions. And their ability to identify the best assets better and faster often gives them priority access.

Powerful industry trends play to the strengths of category leaders. Payers and providers are developing more sophisticated buying behaviors. Increasingly they are demanding evidence of efficacy, creating new hurdles for drug approval. Category leaders are the best positioned to deliver compelling evidence. The rise of drugs prescribed by specialists instead of primary care physicians also favors players with deep networks and strong relationships within the specialty.

Of course when it comes to winning, nothing trumps true innovation. But the bar for real scientific breakthroughs keeps rising. By concentrating on a category, companies enhance their ability to innovate and increase the odds of their success. The FDA approved 67% of category leaders' NMEs in Phase III, compared with 40% for non-category leaders. (*See Exhibit 2*). Category leaders also are bet-

Exhibit 1

Innovation, Commercial Strength, Profitability Linked To Category Leadership



SOURCE: Bain & Co.

ter positioned to identify and help create new pharma categories in adjacent fields – because they have privileged access to all stakeholders in the category, better insights into unmet needs in the market, and better access to new assets and technologies. As Goldman Sachs noted in a September 2014 equity research report, "five years down the road we could envision companies shifting to disease-based powerhouses that focus on only one or a few disease areas … this model would allow for focus and innovation."

DEFINING CATEGORY LEADERSHIP

The definition of category leadership is critically important, and in our experience it is often misunderstood. A category is not just a product or technology platform. Nor is it a function of how companies are organized, for example, around therapeutic areas. Rather, a category is a group of products developed from a common set of capabilities and they are bought using a common purchasing process managed by common stakeholders. These products serve a defined set of end-users and often exist within a common competitive set.

In practical terms, the key to understanding category leadership is to view categories through the eyes of the customer – patients, of course, but also prescribing physicians, clinicians and payers. Category leaders have built a sustainable competitive advantage in a category, often by nurturing strong connections with customers and by using commercial insights to inform highly effective investments in R&D. Serving similar customers with similar technology helps develop strong capabilities.

To better understand the relationship between category leadership and value creation in pharma, we analyzed a dataset of 1.2 billion Medicare Part D prescriptions using prescriber overlap as a proxy for shared customers, cost and capabilities. We found that the US prescription market breaks down into at least 22 different customer-based categories that differ significantly from traditional therapeutic and disease areas. (*See sidebar, "Customer-Based Therapeutic Categories."*)

Our analysis also found that that leading category positions are highly predictive of profitability and value creation, measured in terms of total shareholder returns. To capture and track this trend, we created a Category Leadership Index (CLI) score. The CLI score is the revenue-weighted average of a company's relative market shares (RMS) in the categories in which it competes.

The CLI score showed a strong correlation between operating margins and weighted average RMS across the major pharma categories, using data from 2013. (*See Exhibit 3.*)

Category leaders benefit from scale economies in their category through significantly lower sales and general and administrative expenses. Even more striking, late-stage development programs from category leaders (RMS >0.75) were more than twice as likely to result in regulatory approval as similar programs from followers ($p = 0.01$).

That's partly because they picked the right molecules in earlier stages and partly due to a better understanding of the disease. Category leaders also typically design better clinical trials, with a keener understanding of what's possible from a regulatory perspective and what payers value most when deciding on reimbursement.

HOW CATEGORY LEADERSHIP WORKS

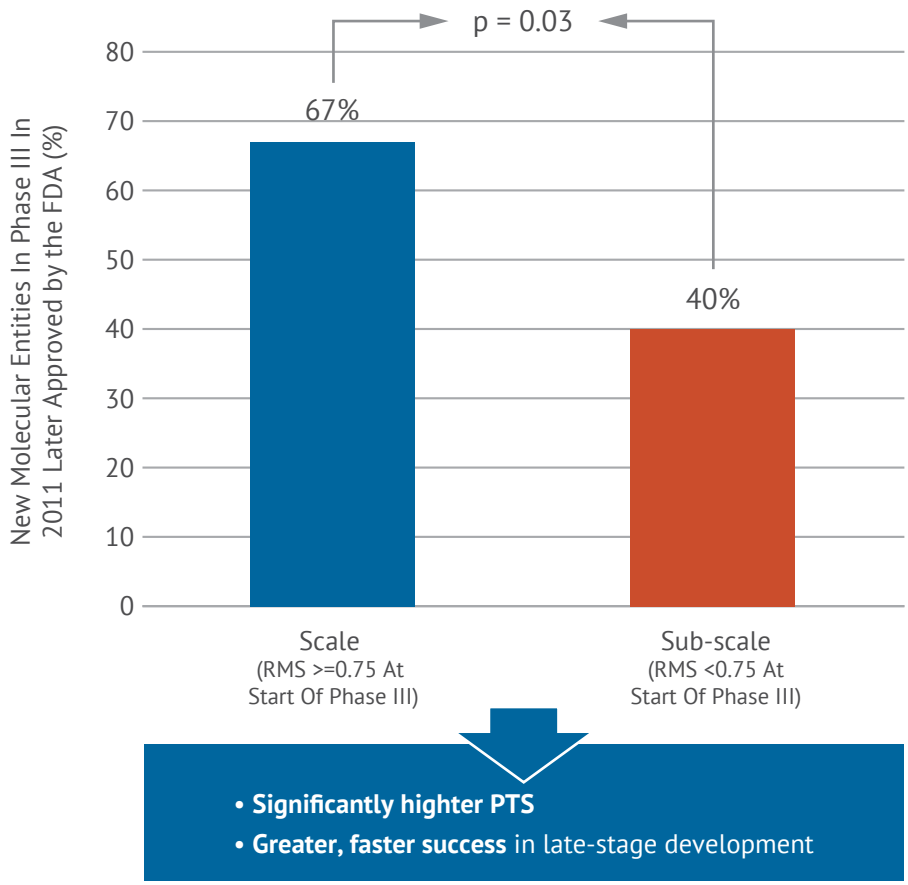
The pharma industry's leading long-term value creators refute the widely held assumption that serendipitous innovation is the key to success in pharma. They have prospered despite industry-wide trends such as declining R&D productivity and the demise of the primary care blockbuster model.

Most of these companies have focused on achieving leadership within specific categories rather than pursuing scale across the industry as a whole. Several, including Roche in oncology and Novo Nordisk AS in diabetes care, generated at least 50% of their revenues from one category. In two cases – Biogen Idec in neurology and Celgene Corp. in oncology – more than 90% of revenues came from a single category.

Category leaders are better positioned to deliver big breakthroughs as well as incre-

Exhibit 2

Category Leaders Innovate More, Have Better R&D Success Rates



SOURCE: Bain & Co.

CUSTOMER-BASED THERAPEUTIC CATEGORIES

Bain found that the US prescription market breaks down into at least 22 different customer-based categories that differ significantly from traditional therapeutic and disease areas.

- Cardiology
- Dermatology
- Dialysis
- Endocrinology
- Geriatrics
- Gynecology
- Hepatology
- HIV
- Inpatient infectious disease
- Neurology
- Oncology (treated as one category for the *In Vivo* analysis)
- Ophthalmology
- Pain medicine
- Primary care
- Psychiatry
- Pulmonology
- Retina
- Rheumatology
- Transplant medicine
- Urology
- Vaccines
- Orphan diseases

mental innovation because they are better able to match ongoing product innovations to market needs and communicate their value to stakeholders (payers, physicians, patients). Our data also show that category leaders earn higher rates of advocacy from customers and key opinion leaders, based on measures like the Net Promoter Score (NPS), Bain's key metric for customer loyalty. NPS tracks critical touch-points in the customer experience and helps companies harness that feedback to develop promoters who buy more, stay longer and recommend products and services to others. They also benefit from superior launch performance. In a study measuring average sales two years after launch between 2000 and 2010, category leaders' products averaged sales of $500 million compared with an average $400 million for products from subscale players.

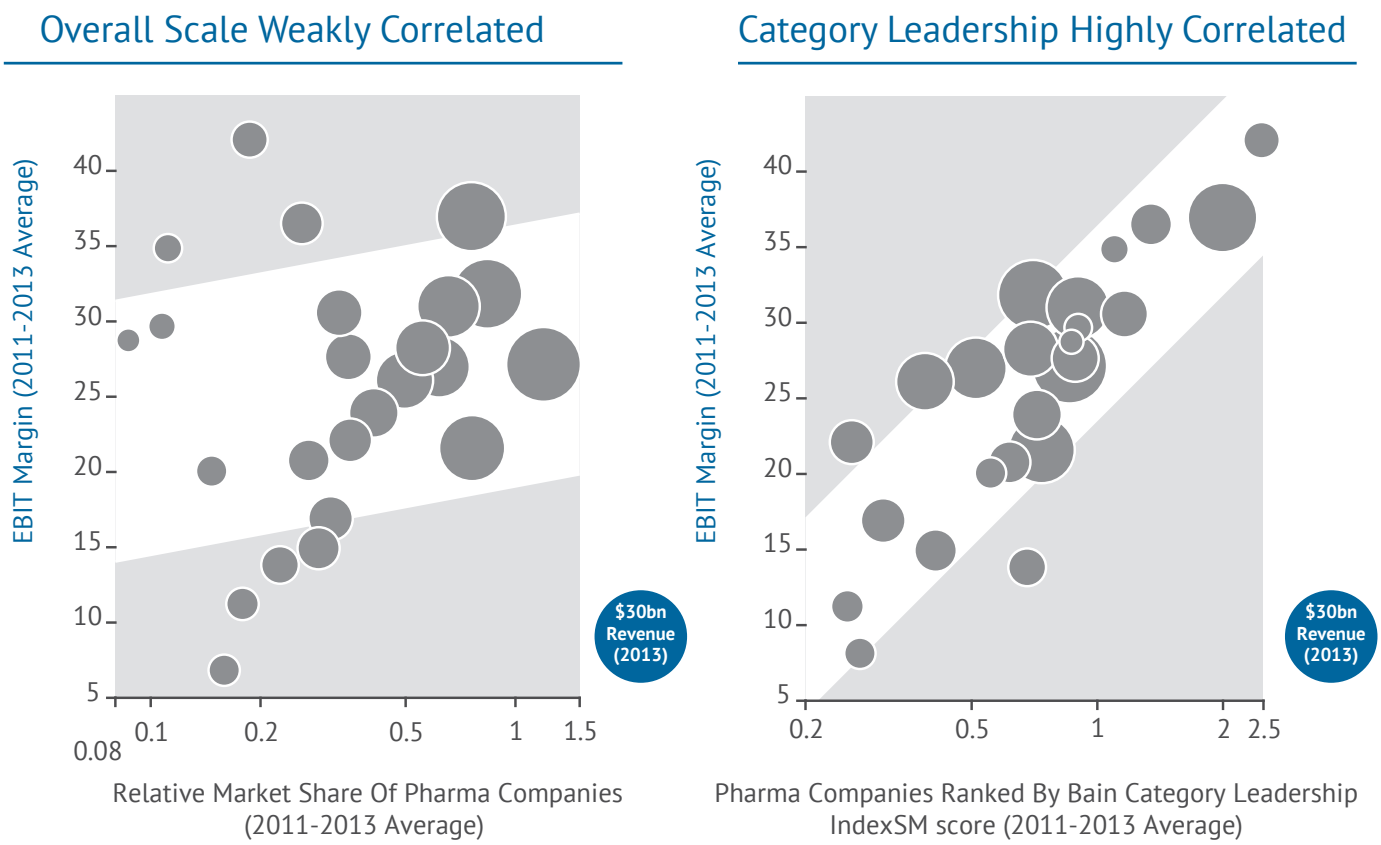
Category leaders often get an earlier look at potential deals and can build deeper valuation insights based on their knowledge and experience. Category leaders typically have the perspective and wherewithal to place a higher value on assets, which in turn raises the profile of their dealmaking and partnerships. In late-stage development, category leaders attract the best scientific and clinical talent, are better able to identify and screen out inferior assets, and typically design better clinical endpoints and economic models.

When commercialization kicks in, category leaders again demonstrate advantages, with generally superior insights to guide marketing choices and both scale and quality in the infrastructure of their field forces, which can provide a cost advantage for incremental assets in a category. Their relationships with and access to key customers – key opinion leaders in a category, as well as payers, clinicians and patient bases – provide an additional edge.

Category leaders have privileged access to all stakeholders in the category. As a result, they are typically faster to spot unmet customer needs and deliver solutions, often at the intersection of science and marketing. **Gilead Sciences Inc.**, for example, built its success in HIV/AIDS therapies on the insight that a lower pill burden and fewer side effects were the keys to fostering better adherence in HIV patients and improving long-term outcomes. Gilead is now transferring its capabilities across product areas in virology by developing combination products for hepatitis C.

Exhibit 3

Category Leadership More Correlated With Profitability Than Overall Scale



Note: Includes branded pharmaceutical segments only; Bain Category Leadership IndexSM score is the revenue-weighted average of a company's relative market share in the categories in which it plays; category defined as overlap in prescribers, market access and development.

SOURCES: Bain & Co.; Company reports

Better insights on customer needs and improved understanding of endpoints leads to better asset sourcing and development, enabling category leaders to move from strength to strength and build sustainable advantage. Bain's 2015 "Front Line of Healthcare Report" underscores this point; this national survey of 632 physicians across specialties and 100 hospital procurement administrators in the US found that physicians are most likely to recommend the leader in a category and view that company as the innovation leader.

Category leaders benefit from greater growth opportunities because they are quick to spot emerging categories and invest in them. **Genentech Inc.**'s breakthrough B-cell technology was first used in treating Hodgkin's lymphoma. Deep understanding of the biological mechanisms underpinning the B-cell technology allowed the company's scientists to apply their learnings from oncology in two adjacent fields and develop breakthrough products to treat rheumatoid arthritis and multiple sclerosis, with opportunities to build leadership in these categories as well.

THE PATH TO CATEGORY LEADERSHIP

As the pressure on growth and profits rises, pharma companies are reevaluating where to play and what it takes to win. One of the biggest organizational challenges is overcoming the traditional communication gap between R&D and commercial teams. A category view helps achieve corporate alignment by moving away from the industry's traditional R&D focus and redefining key markets through a customer lens.

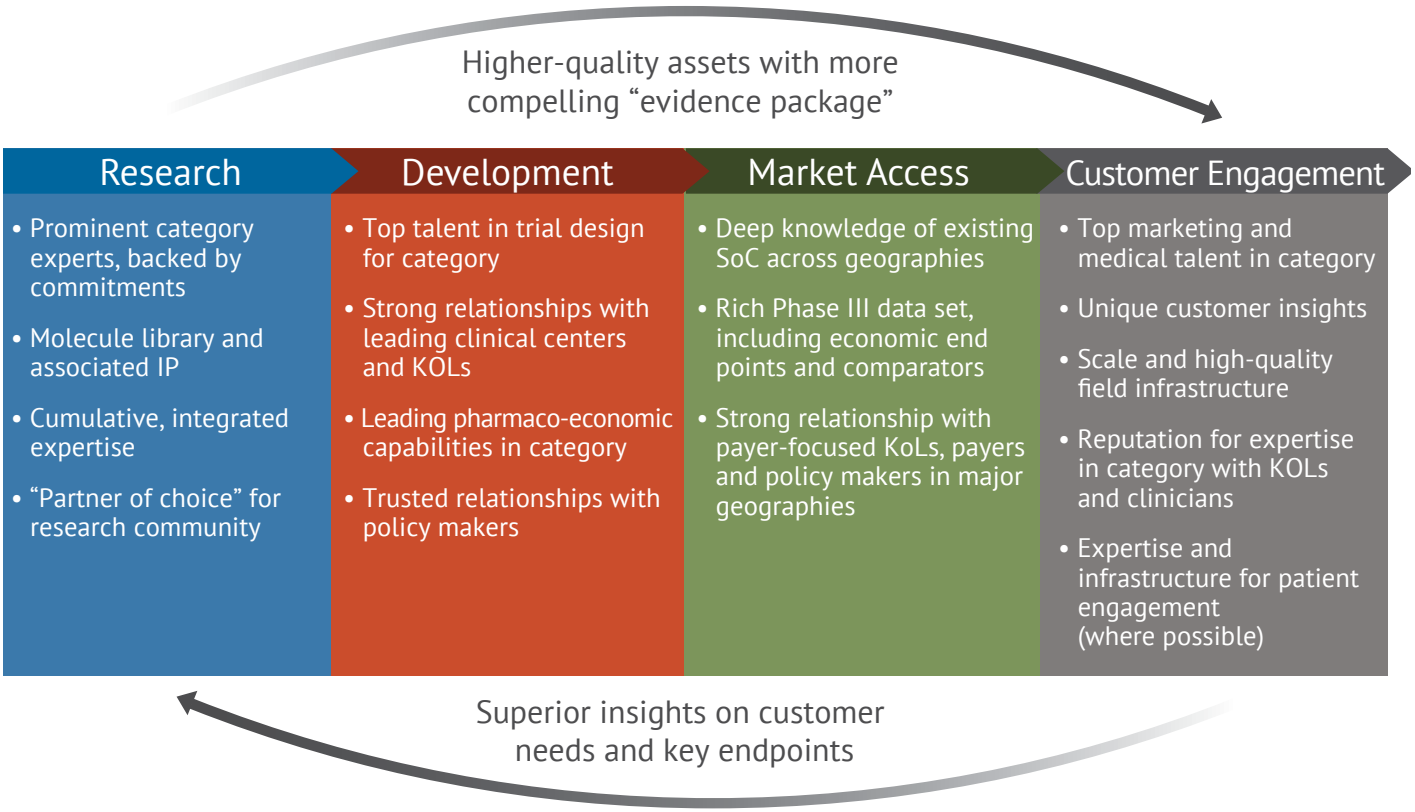
Three key steps can help companies map out a portfolio strategy to become a category leader. **The first one is understanding the category's dynamics and attractiveness**, including its size and growth potential, unmet market needs, the level of innovation and the intensity of competition. What are the benefits of leading in a given category and what factors are critical to success?

Step two focuses on the point of departure – the company's current capability and its ability to win in a given category. How is the company positioned? Do its assets differentiate it from competitors? What are the company's core capabilities in the category, including both "hard" and "soft" capabilities? Finally, how do the firm's assets and capabilities align with the key success factors in target categories? Gilead first developed partnership capabilities so it could team up with firms that had the assets it needed to make a combination treatment for HIV. Later, the company learned to develop all of the components in-house.

Once a company has a solid understanding of a category and the company's relevant

Exhibit 4

A Virtuous Circle That Increases Odds Of Winning



SOURCE: Bain & Co.

assets and capabilities, **it can plot a path to leadership**. This might include buying, selling or swapping assets to bolster its position and free up capital. It might also include designing a new operating model to ensure a sharp focus on the pursuit of category leadership.

FINANCIAL MARKETS PRIZE FOCUS

Financial markets recognize the value of focus; they know that promising assets are not fully valued when the owner is not a category leader. As a result, more companies are pursuing M&A deals to help them achieve category leadership.

The 2014 asset swap between **Novartis AG** and **GlaxoSmithKline PLC** (GSK) left both companies with stronger positions in their target markets: Novartis in oncology, GSK in vaccines and consumer health. GSK's CLI score increased by nearly 9% as a result of the deal, share prices of both companies rose by 3% to 6% following the deal announcement and market cap increased by $6 billion each. (*See "GSK Vaccines: Injecting Visibility"* — IN VIVO, *May 2016.*) Other examples include **Bristol-Myers Squibb Co.**'s sale of its diabetes division to **AstraZeneca PLC**, Novo Nordisk's exit from immunology and AstraZeneca's sale of its rare disease assets to Sanofi's **Genzyme Corp.** division.

Category leaders also are a preferred partner for smaller biotech companies searching for an alliance to commercialize their assets. Celgene built a leading network of biotech start-ups to expand its oncology pipeline, acquiring six companies since 2002 and building strategic alliances with several others.

Category leadership is the single most important opportunity for pharma companies to build long-term profitability and shareholder value. It can help companies to define the business areas they want to be in tomorrow and grow successfully. Leaders benefit from a virtuous circle in the value chain that increases their odds of innovating and winning. (*See Exhibit 4.*) Once on top, companies can build multiple leadership engines by extending core capabilities to adjacent categories.

The biggest risk is taking no action. Pharma companies still operate in a high-margin environment. As a result, they often focus on defending their positions rather than doing things differently. Current leaders face a particular dilemma: move too early and risk losing attractive cash flows from established business models; move too late and risk being overtaken by emerging competitors.

Although bigger may be better in some industries, the dynamics of the pharma industry are changing. Depth, not breadth, will be the key to success in the coming decade. Developing the leading value proposition within a category leads to superior clinical results and sustainable economic returns. That's a future worth investing in.

A#2016800103 IV

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Medtech Uptake Drive Shows France's European Leadership Aims

Somewhat puzzlingly, one of Europe's major national medical device markets is not generally viewed by manufacturers as the huge opportunity that it should surely represent. But matters may now be changing in the wake of a new cross-governmental drive to make adoption and reimbursement easier.

BY CORINNE LEBOURGEOIS

- France is a major medical device market globally, and in Europe is beaten only by Germany in terms of size, but medtech manufacturers often find it hard to fully exploit the potential opportunity.
- To tackle the root causes of this, a high-level group of ministers has agreed to put in place a series of new laws in a bid to create the conditions that encourage device manufacturers to look favorably on France as an innovation launch market.
- The Forfait Innovation, an initiative to speed innovative devices to market, has not yet been the success that was hoped, but that may well change as the new joint ministerial plans come into effect.
- Once the simplified market access processes are in place, companies in the market will need to respond by adapting and providing the right data for registration purposes.

Executive Summary >> 52

Since the introduction of the Forfait Innovation in summer 2015, the French authorities have continued their attempts to accelerate market access for innovative medical devices by further simplifying procedures. (*See "Reimbursement Unraveled: Will New French Medtech Innovation Plans Hit The Spot?"* — Medtech Insight, *July 2015*.)

Even though France is the second-largest European market, in recent years it has not been seen by device manufacturers as a market of choice for launching innovative devices because the reimbursement process has been perceived as too complex and lengthy. Industry has long argued for new procedures that positively impact both market access and the development of local industries.

France has a long history of developing truly ground-breaking medical devices and changing treatment pathways as a result. Cardiac valves, percutaneous cardiac valves, hip and shoulder prostheses, shoulder arthroscopy devices, laparoscopy procedures and spinal implants are just a few examples.

The local medical device manufacturer landscape is composed mainly of start-ups and small and medium enterprises (SMEs), which constitute 94% of the industry. They operate in a fast-moving, competitive environment, but are often hampered by administrative issues and "red tape."

But now, health minister Marisol Touraine, economy and industry minister Emmanuel Macron, and state secretary for research and education Thierry Mandon, have joined forces to make the conditions for entrepreneurs easier and to reduce administrative times in a bid to help innovators survive and adapt in this fast-evolving industry.

Several new laws are being targeted, specifically to cover IP, company funding, clinical trials and reimbursement. SNITEM, the French medical technology industry association, has been instrumental in securing

the changes, and has been working closely with the authorities to ensure they happen. And in Courbevoie, northwest Paris, on March 31, SNITEM brought all industry stakeholders together, including Macron and Mandon, at its second Innovative Start-Up Day, where the new laws and procedures were presented to a large audience of start-ups and SMEs.

In addition, Professor Jean-Yves Fagon, vice president of CEPS (Comité Economique des Produits de Santé, *see below*), was earlier this year appointed as minister for health care innovation (*délégué ministériel à l'innovation en santé*). Fagon, who dropped his CEPs duties after a brief transition, has a mission to focus on facilitating simple, fast and seamless exchanges among all stakeholders, namely patients, health care professionals, manufacturers, the government administration and health care establishments.

This new drive to facilitate market access for innovative devices illustrates the French government's determination to be a major player and thought-leader in the European medical devices arena.

BUILDING ON THE FORFAIT INNOVATION

In June 2015, the Haute Autorité de Santé (HAS), France's health care quality regulator, announced the creation of the Forfait Innovation, a mechanism designed to expedite the market introduction of innovative devices.

This procedure enables manufacturers to secure temporary reimbursement and funding while collecting additional clinical or economic data, in French centers, with which to confirm the medical or economic interest of the device/procedure. But almost a year after its launch, the mechanism is still only slowly taking off.

Professor Jacques Belghiti, president of CNEDiMTS (HAS' national committee for evaluating medical device technologies) has confirmed that to date just three medical device dossiers have been appraised under Forfait Innovation. Why is this? It has been felt that the eligibility criteria are too narrow and file preparation is difficult and time-consuming for those working in a start-up or SME environment.

But now, with new procedures and a relaxation of the framework being discussed, manufacturers are being actively encouraged to set up meetings with the Forfait Innovation team to determine if their devices meet the eligibility criteria.

> MDR reinforces the need for clinical evidence, which will make the CE mark more challenging, but may make reimbursement easier because the quality of the clinical data will be better and more aligned with the reimbursement requirements.

CNEDiMTS generally has the task of assessing both the service expected or delivered (Service Attendu/Service Rendu – SA/SR) by the device or procedure, and the medical benefit/added value for the patient (ASA/ASR). The committee was very active in 2014, says the HAS 2014 annual report (issued July 2015). It received 247 submissions and issued 195 appraisals with the mean review time of 86 days. The device or procedure was considered to deliver a sufficient service (SA/SR) in 167 cases.

To demonstrate added value, companies need to define a benchmark and explain where their target device is positioned, compared with the benchmark, on an added value scale of 1 to 5 (where level 1 is a "major improvement vs. the benchmark," and thus the highest added value, and level 5 is of "no added value").

In 2014, devices/procedures fell into the category of no added value (level 5), compared with benchmark, in 68% of cases. Another 15% were assessed as level 4, 7% as level 3, 8% as level 2 and only 2% were graded as level 1 (major improvement vs. the benchmark). This represented a slight improvement compared with the previous year, when 98% of devices/procedures were graded as level 4 and 5, 2% as level 3 and 0% at levels 1 and 2.

SHIFT IN GRADING LEVELS

This shift toward levels 4, 3 and 2 may be due to the change of reimbursement strategy among manufacturers. If a manufacturer can prove that the added value of its device is superior to a benchmark, and if this medical benefit is validated by the CNEDiMTS when it issues an appraisal, then it has a strong case when negotiating on device prices with the CEPS. The manufacturer can base its discussions on the recognized medical benefit and use the leverage in the subsequent economic discussion.

The CEPS sets the price and the tariff for the whole country. It is under high pressure by the finance ministry to reduce health care costs, and this of course has repercussions on drug and device prices. In 2014, the CEPS achieved a cost reduction of €80 to €90 million ($89 to $99 million) by decreasing device prices, according to the CEPS 2014–2015 annual report (issued in October 2015).

At the same time, drug price decreases allowed savings of about €900 million. "In total, the contribution the CEPS makes to balancing out the accounts of the national sickness fund [Assurance Maladie] amounted to almost €1.8 billion in 2014," according to Dominique Giorgi, former president of the CEPS.

CEPS experienced a difficult year in 2015, with substantial delays in reviewing submissions; the total review time reached 420 to 450 days. This compares with average application processing times in 2014 of 317 days (quicker by nine days than in 2013). The newly elected CEPS president, Maurice-Pierre Planel, has put much focus on managing the situation with the result that everything should be back on track by the end of 2016. Indeed, as of May 2016, the committee has been able to begin performing new assessments again.

At the time of writing (May 2016) another important piece of news is that CNEDiMTS has announced the completion of its review of certain specific categories of devices, namely implantable cardioverter defibrillators (ICDs) and intracranial stents. Biological cardiac valves are still under evaluation. As of today, all devices belonging to these categories must be logged on a positive list, the

liste intra-GHS, before they can be purchased by hospitals.

From now on, manufacturers must file a submission to CNEDiMTS and wait for a positive appraisal, which allows the device to be included on the *liste intra-GHS*. The submission mainly requires a summary of technical specifications, clinical evidence, vigilance data and target population information. To assist manufacturers with the submission, the HAS has published a guideline document, the *Guide fabriquant, Intra-GHS*, published in January 2016.

EU UPDATE

As *In Vivo* goes to press, hopes are high that the EU Medical Device Regulation would be finalized by the end of June 2016 and ready for publication by the year-end. The final scheduled "trilogue" meeting of the European Commission, Council of the EU and European Parliament on May 25 agreed on the text (and that of the sister EU IVD Regulation), but many outstanding final touches – minor and major – are still needed.

The MDR reinforces the need for clinical evidence, which will make the CE mark more challenging, but may make reimbursement easier because the quality of the clinical data will be better and more aligned with the reimbursement requirements (demonstration of clinical effectiveness instead of only clinical performance). It will be very important for companies to be proactive and define the reimbursement strategy up front, together with the clinical strategy.

THE GOAL: SIMPLIFIED MARKET ACCESS IN FRANCE

In conclusion, the French authorities have realized that they should simplify the market access process if they want French patients and hospitals to benefit from innovation whether it comes from local industry or from abroad. Numerous actions are already in place and more will come. It is up to companies in the market to adapt and provide the right data. If they do, then registration will be more straightforward and speedier.

In the coming months, we hope to see the specific category of devices that covers "innovative implantable medical devices used for less than 30 days" being eligible for reimbursement. As of today, this category is excluded from reimbursement in France.

Corinne Lebourgeois (clb@medcpartners.com) *is a Managing Director of MedC. Partners, a Cheseaux, Switzerland-based medtech consultancy, which she co-founded in 2005 to support the market access strategies – including reimbursement, marketing and pricing – of SMEs and start-ups.*

A#2016800113

COMMENTS: Email the editor: *Nancy.Dvorin@Informa.com*

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Clinical Trial Success Rates Still Dismal, But Certain Sectors Outperform

The high risk-high reward nature of drug development is a constant challenge to pharma. Informa's Pharma Intelligence teamed up with BIO and Amplion to provide an update on clinical development success rates from 2006 to 2015, including a new analysis on trials incorporating patient selection biomarkers.

BY AMANDA MICKLUS

HIGH-PROFILE FAILURES IN THE DRUG INDUSTRY can break a company. In immuno-oncology, one of the hottest areas in drug development, **Aduro Biotech Inc.** – a fairly young firm, founded in 2008 through the merger of Triton and Oncologic – had high hopes for GVAX Pancreas, a whole tumor cell vaccine that secretes granulocyte-macrophage colony stimulating factor in an effort to prompt the immune system's attack on the cancer. (Aduro licensed GVAX from BioSante [now part of **ANI Pharmaceuticals Inc.**] in 2011.) The candidate advanced to Phase IIb and was being tested in combination with CRS207 (a proprietary attenuated strain of Listeria that expresses human mesothelin, also from Aduro) in the ECLIPSE trial, but failed to meet its overall survival endpoint in the third-line setting for pancreatic cancer, actually posting a shorter median overall survival time compared with CRS207 alone or chemotherapy. Aduro's shares took a hit, dropping 20% at closing on the day of the announcement in May 2016. The company is still going to be evaluating a triple combination of GVAX, CRS207 and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) in the ongoing STELLAR trial. Aduro has other GVAX vaccines in the pipeline, too, but the pancreatic cancer candidate is its lead, and potentially is closest to market. Likewise, **Celldex Therapeutics Inc.**'s *Rintega* (rindopepimut) vaccine was another high-profile casualty. In March 2016, an independent data safety and monitoring board (DSMB) stated that Rintega would not reach statistical significance for overall survival in patients with newly diagnosed EGFRvIII-positive glioblastoma with minimal residual disease in the Phase III ACT IV study. The DSMB determined that, following an interim analysis, the control arm of generic temozolomide outperformed Rintega, and Celldex terminated the study. (*See "Celldex At A Loss To Explain Why Brain Cancer Vaccine Rintega Failed Phase III"* — "The Pink Sheet" DAILY, *March 7, 2016.*) The news sent Celldex's stock value into a tailspin, dropping more than 50% after the DSMB's determination, and the share price hasn't recovered since.

Results like these are all too common in the pharmaceutical industry, and are especially troubling given that R&D expenses by big pharma, presumably the largest group invested in drug development, have grown at a compound annual growth rate of 4% over the last 10 years (from 2006 to 2015), averaging $6 billion per company in 2015, according to *Datamonitor Healthcare* analysis. While getting a drug through the approval process is only one hurdle in a product's life cycle – increased payer restrictions and reimbursement issues present further challenges – advancing a medicine through the clinical pipeline and getting cleared by the FDA is the first critical step. High-profile failures can destroy a business, reduce investor confidence and have a potential trickle-down effect, causing other biopharma drug developers to abandon certain areas of research. Understanding clinical success rates can help reaffirm strategic therapeutic area development plans, formulate and negotiate terms of deals, and prioritize R&D efforts, especially in light of the expense and lengthy time of clinical trials. In a new, comprehensive analysis, Informa Pharma Intelligence's *Biomedtracker*, the Biotechnology Industry Organization (BIO) and Amplion, which provides intelligence on the clinical biomarker landscape, have updated data from a 2014 study on clinical development success rates and likelihood of approval, shifting the dataset to the current 2006–2015 10-year period and expanding the universe of drugs evaluated. (*See sidebar, "Success Rates In Clinical Trials: Methodology."*) The new results show that the chance that a drug entering Phase I is approved is slightly lower than before, 9.6% versus 10.4% from the 2003–2011 dataset in the 2014 study. Clinical trials that used selection

biomarkers to include or exclude patients yielded a success rate three times higher than that of trials without biomarkers. And the success rate for rare disease candidates in Phase I is three times better than that of drugs for chronic, highly prevalent conditions.

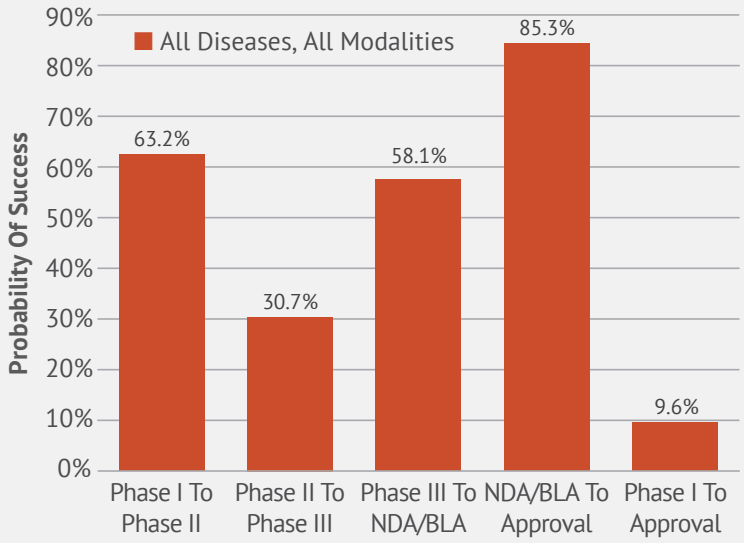
Less Than 1-In-10 Chance Phase I Drug Gets Approved

There is less than a 1-in-10 chance that a compound entering Phase I will get cleared by the FDA, according to the updated results. Based on a dataset of 9,985 phase transitions occurring in 7,455 clinical drug development programs, the compounded probability of progressing from Phase I to US FDA approval, also known as the likelihood of approval (LOA), is only 9.6%, compared with the 10.4% from the previous study. Conventional wisdom might suggest that the odds of advancing from phase to phase improve as the drug moves through the pipeline. In actuality, that's only somewhat true. (*See Exhibit 1.*) Individual phase transition success rates were calculated by dividing the number that advanced to the next phase by the total number of advanced and suspended drug candidates.

Consistent with previous studies of drug development phase transition success, Phase II success rates were far lower than any other phase at 30.7%. As this is generally the first stage where proof-of-concept is deliberately tested in human subjects, Phase II is also the point in development where sponsors must decide whether to pursue large, expensive Phase III studies and may terminate development for multiple reasons including commercial viability. Phase I and III rates were substantially better than Phase II. Phase I yielded the highest success at transitioning on among the clinical phases, 63.2%. Because Phase I is typically conducted for safety testing and is not dependent on efficacy results for candidates to advance, the high success rate among the clinical phases is not surprising. The Phase III rate of 58.1% was not that far behind. This is significant, as most company-sponsored Phase III trials are the longest and most expensive to conduct – roughly 35% of all R&D spending is allocated to the Phase III stage, according to the Pharmaceutical Research and Manufacturers of America. The highest success rate of the four development phases overall was the NDA/BLA filing phase at 85.3%.

Exhibit 1

Clinical Development Probability Of Success By Phase, 2006–2015



Note: Chart displays success rates for all diseases and modalities.

SOURCE: Biomedtracker | Pharma Intelligence, 2016

With The Lowest Phase I LOA, Oncology Candidates Are Tripping Up In Phase III

When breaking down the figures into 14 main disease areas – those that had more than 100 total transitions from Phase I to NDA/BLA approval – nearly all the therapy areas perform above the 9.6% LOA average. (*See Exhibit 2.*) Products in the hematology field yielded a 26.1% LOA from Phase I, the highest in the group. A large portion of hematology transitions came from hemophilia, anemia due to chronic renal failure, blood protein deficiencies, thrombocytopenia and hemostasis. Some of these indications even had overall LOAs that surpassed 50%. This more than offset the weaker hematology success rates that were observed in venous thromboembolism and neutropenia. The neurology, cardiovascular, psychiatry and oncology categories all underperformed the Phase I LOA of 9.6%. In fact, hematology's 26.1% LOA was five times that of oncology's 5.1%.

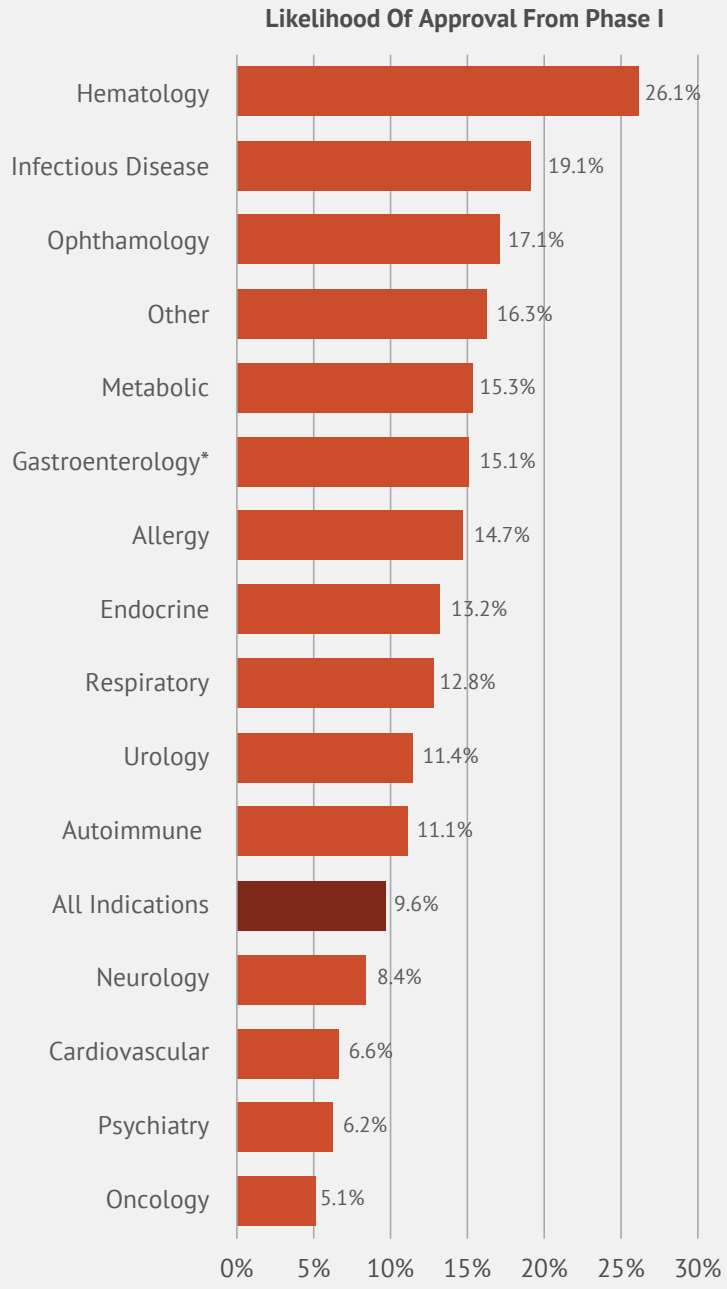
The oncology dataset stands out, featuring the highest number of total advanced and suspended drug candidates at 3,163, and accounting for 31% of the 9,985 total transitions. For these reasons, this disease category is a significant factor in bringing down the overall industry LOA. The Phase III stage appears to be where oncology drugs face the highest hurdles. Oncology Phase III success was 23% lower than non-oncology indications. Further, it's the products for solid tumors, especially pancreatic, ovarian, gastric, and head and neck, that have the lowest chances of advancing – only 34.2% of the drug programs in solid tumors cancers were deemed sufficiently successful to file an NDA/BLA with the FDA, compared with the 52.6% success of hematologic cancer candidates in Phase III, led by multiple myeloma, acute lymphoblastic leukemia and chronic myeloid leukemia. All hope is not lost in oncology, however. The recent successes in immunotherapies and advancement of new drugs in this class indicate that there will be improvements in LOAs. Further, the large increases seen in progression-free survival and overall survival also allow for smaller trial designs to reach statistical significance.

Biomarkers Improve Clinical Success

Biomarkers have the potential to greatly improve efficiency of drug development. Their use, to either include or exclude patients from clinical trials, began taking off once the human genome had been sequenced. But adoption is slow: only a small proportion (5%) of the total phase transitions in the 2006–2015 study incorporated a biomarker for patient selection. Still, for the pharma

Exhibit 2

Hematology At Front Of Pack, Oncology Last – Phase I LOAs By Therapy Area



*Gastroenterology does not include irritable bowel disease.

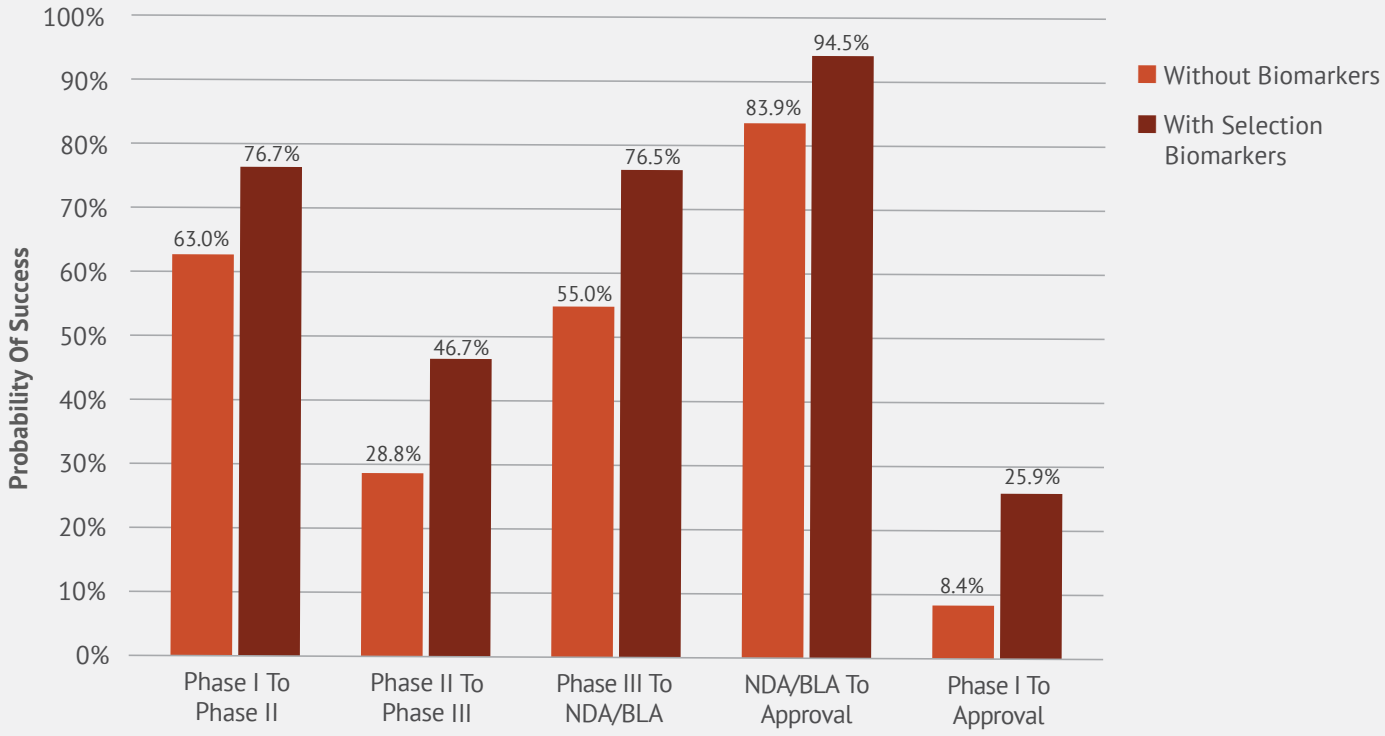
SOURCE: Biomedtracker | Pharma Intelligence, 2016

industry, biomarker stratification has paid off, improving the chances of moving candidates through the pipeline to approval.

Based on an analysis using Amplion's BiomarkerBase, reconciled with data from Biomedtracker, success rates in studies in all four phases were much higher for programs incorporating selection biomarkers compared with those that did not, especially at the Phase III stage. The benefit from selection biomarker use raises the LOA from Phase I to a 1-in-4 chance versus about 1-in-10 when no selection biomarker was used. In other words, there was a three-fold higher LOA from Phase I for biomarker-based programs than non-biomarker programs, 25.9% versus

Exhibit 3

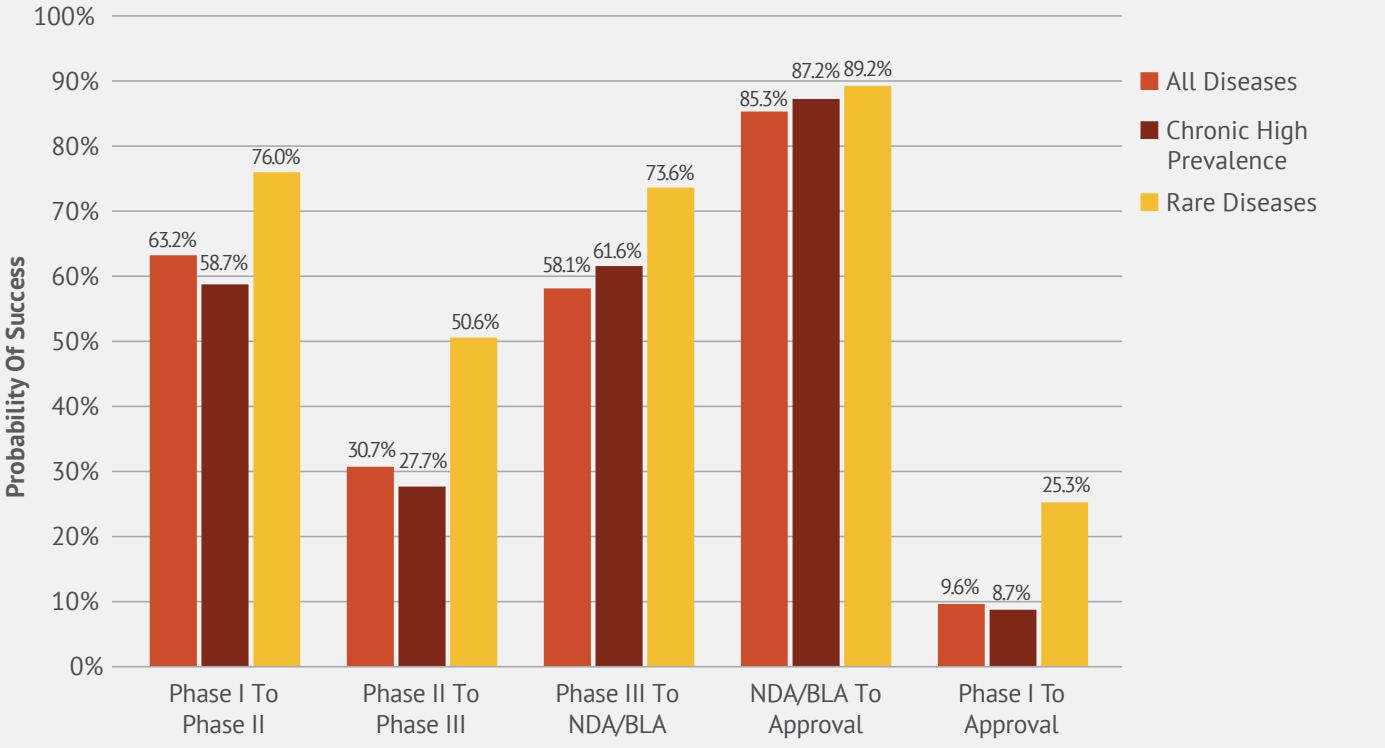
Improving The Odds: Selection Biomarker Candidates 3x More Likely To Get Approved



SOURCE: Biomedtracker | Pharma Intelligence, 2016

Exhibit 4

Rare Disease Candidates Outperform



SOURCE: Biomedtracker | Pharma Intelligence, 2016

8.4%. (*See Exhibit 3.*) The FDA and the pharmaceutical industry have made biomarker use a priority, and in January 2014 guidance was issued that lays out a biomarker qualification process, clinical outcome assessments and animal models. However, to date, the FDA has only officially qualified six biomarkers, with two under review and 18 in the consultation stage. And the transparency of the qualification process has also been under question. (*See "Biomarkers Improve Odds Of Approval, BIO Study Finds"* — "The Pink Sheet," *May 30, 2016.*)

Increased Rare Disease Funding Validated By Clinical Success Rates

Rare diseases present opportunities for biopharma companies to address patients who have few treatment options, and at the same time provide sponsors with potentially lucrative commercial opportunities due to regulatory and intellectual property incentives. According to BIO analysis, since 2010, there has been a steady increase in US venture funding for rare disease-focused firms, most of which are at the preclinical or Phase I stage.

The increased investment and commercial potential for rare disease drugs is even further strengthened by the fact that Phase I non-oncology rare disease programs (mainly for those diseases caused by inborn genetic mutations) are three times as likely to eventually get approved than drugs for chronic, high-prevalence diseases (those that treat more than one million patients in the US, excluding cancer). (*See Exhibit 4.*) The overall LOA from Phase I for non-oncology rare diseases is 25.3%, whereas the comparable figure for chronic, high-prevalence conditions is only 8.7%. Because many rare diseases are identified by specific genetic mutations, it is not surprising that their success rates closely match those observed in clinical trials that used selection biomarkers.

Options For Improving Overall Industry Success Rates

Overall, the updated data say that clinical development success rates are pretty dismal. There are theoretically several ways to make the odds better for getting a drug through the pipeline and approved, according to Dave Thomas, BIO's senior director of industry research and policy analysis. Greater flexibility with alternative and novel surrogate endpoints, the use of adaptive clinical trial design (including adoption of clinical trial master protocols that simultaneously test multiple targeted therapies (*see "Rethinking Oncology Development: Master Protocols May Shorten Time To Approval"* — The RPM Report, *May 2016*)), improved methodologies for assessing patient benefit-risk, and better communication between sponsors and regulators are all options. Simultaneously, improvements in basic science can enable better success rates. For example, more predictive animal models, earlier toxicology evaluation, biomarker identification and new targeted delivery technologies may increase future success in the clinic. The ability to apply these approaches to drug development, and modernize regulatory review processes, combined with healthy capital markets supporting private-sector investment will enable biopharmaceutical companies to develop innovative medicines of the future.

A#2016800108

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Excerpted and adapted from "Clinical Development Success Rates 2006-2015," published in May 2016 and authored by David W. Thomas, Senior Director, Industry Research and Policy Analysis at BIO; John Audette, CEO, Adam Carroll, PhD, CSO and Corey Dow-Hygelund, Data Scientist at Amplion Inc.; Michael Hay, Head of Intelligence and Justin Burns, Analyst at Informa's Pharma Intelligence.

Medtechs Should Not Play Dodgeball With Sales Force Effectiveness

Adoption of sales force effectiveness remains suboptimal across the US medtech industry, which means that companies are missing out on significant annual revenue uplift. But things are changing, and it's no longer an issue to be delegated: SFE has risen all the way to CEO level.

BY ASHLEY YEO

- When medtechs look at their US customer decision-makers, they see the gap between clinical and economic stakeholders narrowing quickly, and in some cases the traditional hierarchy has been turned on its head.
- This change calls for a refined approach to commercial dealings with IDNs, ACOs and hospital purchasers. Bringing sales force effectiveness (SFE) measures into the equation in the reset medtech buying world can lead to consistent annual sales gains for a relatively small investment.
- A new report by ZS Associates lays out where companies can maximize ROI by addressing elements such as territory design and sizing, and sales processes and account planning.
- Sales models are now also extending to a "rep-less" system, and some medtechs are experimenting with telesales and web-based or other technology-based methods. The changes are happening now and the smart companies are already adopting new tactics and reaping the competitive and commercial benefits.

Executive Summary >>52

From a commercial standpoint, medtech has historically been dominated more by sales than by the marketing function. There has also been a strong clinical focus: the clinician stakeholder has traditionally been top of the priority list in all matters regarding the delivery of care – and by a long way.

But that has been changing over time, and the gap between the clinical stakeholder and the economic stakeholder has now shrunk – and in some cases the relationship has "flip-flopped," to the extent that the clinician is often now a customer of the economic stakeholder.

So says Tobi Laczkowski, a principal and a leader in ZS Associates' medtech practice, specializing in marketing, sales and value proposition design. This has prompted a lot of companies to look anew at sales force effectiveness (SFE) and how they define it – for the metrics might have changed since they last had a chance to review them, he says.

ZS Associates recently published the results of a year-long study into companies' use and derived benefits of implementing SFE. Its "Explorer Study" is described by Laczkowski and Eric Scott, co-authors of the resulting report, "Boosting Sales Force Effectiveness in Medtech (How Firms Can Gauge – and Improve Their ROI on Sales Initiatives)," as a rigorous cross-industry analysis of 800 data points from 171 companies, survey respondents and other sources.

The notable top-line result was that a 2% to 8% annual financial return was very consistently achieved by medtech companies that had been strategically investing in SFE. This could be a result of any or all of: revenue uplift, improved profitability or cost savings, Laczkowski tells *In Vivo*. "On the surface, mid-single digits might not look awfully exciting, but take a closer look and you'll see it actually produces a very good ROI," he says.

Laczkowski observes that it takes quite a small investment to get to, say, a 4% to 5% sales improvement. For instance, a $150 million medtech company spending $600,000 on SFE would see a return of 500% or more.

SFE: A RANGE OF INPUT LEVELS

The SFE plan might involve customer segmentation and targeting, or simply making every customer encounter and visit more impactful. "This is as basic as having the right information at your fingertips as you're walking in the door. But it's also about understanding what else has been going on with the account, and ensuring tie-up with colleagues to supplement the contract. Taken further, it can even go as far as changing the design of the sales force," explains Laczkowski.

In fact, the Explorer Study found that medtech companies are more likely than companies in other industries to invest in territory design, targeting, territory sizing and allocation, as well as sales processes and account planning. But they are less likely to invest in training initiatives and data management and analytics.

When they invest in SFE initiatives, medtech companies typically are attempting to:

- Ensure the right customer coverage plan
- Increase the impact of customer interactions
- Create a performance-focused sales team
- Enable efficient and effective sales operations.

But in many instances, it's a case of playing catch-up, as the medtech industry is only just beginning to recognize that information management will be vital as customers and the payer landscape continue to evolve, says Laczkowski. This is perhaps understandable, as mapping out needs is not always a straightforward task for medtech executives.

"The wide mix of products in the industry and the differences in SFE engagements often make it difficult for medtech leaders to define accurate competitor benchmarks and a target return on investment," notes Laczkowski. "Our study helps them by revealing for the first time the true impact of these initiatives and proving that medtech companies can often generate gains significantly greater than the initial investment."

This broad range of products in the medtech industry makes integrating SFE more complicated than, say, for pharma. Certain product categories are relatively commoditized, such as surgical bandages. They are sold primarily on price and may need a different sort of sales force altogether. SFE can still have a positive impact on the remaining sales force, since in those cases, the sales force may be the only differentiator. In other, more differentiated product categories, SFE can supplement the products and drive significant returns.

> The big question for medtech companies is how they modify their sales territory design now that the model is dominated by IDNs."
> - Tobi Laczkowski

Additionally, companies with a higher baseline SFE, and those that have already gotten the easy wins under their belt, will likely see less dynamic results from continued SFE than, say, younger, fast-growing companies that do not have mature sales functions in place.

Nevertheless, the general concept of SFE suits a wide degree of corporate ambition – and can meet either multiple aims or be targeted at individual measures.

TARGETED MEASURES

ZS Associates reports that it has assisted in SFE uptake with many clients who are seeking targeted action. The Explorer Study details several examples. In one initiative, it worked on a project that aimed to present clear information on the hospital and integrated delivery network (IDN). This enabled the medtech company client to see the big picture, target its sales force more accurately and thereby partner with both high- and lower-value customers appropriately and effectively.

In another example, ZS identified where efforts need to be differentiated in different geographies, depending on the maturity of local relationships and the potential to increase the ongoing value of the business. This led to a territory-based plan, a new type of hire identified, new compensation scales and reset business expectations.

In another case, an IVD company was overloaded with data from its distributor network, and was spending too much time on processing the information – leading to suboptimal business decision-making. The solution was to set up a system that filters data for quality and implement a new field force reporting system, which allowed for better sales territory management. The client had time freed up to devote to higher-value, strategic activities.

SIZE MATTERS?

SFE can be beneficial across the board, regardless of company size. The larger the company, the more leverage it can get from incremental improvements. "But even a modest company of $100 to $200 million in revenue can see gains. It also applies to companies in the start-up phase," Laczkowski says.

But it is a concept that also resonates with the majors. Referring to **Abbott Laboratories Inc.**'s recent acquisition of **St. Jude Medical Inc.**, Laczkowski notes that both companies would have had salespeople walking into the same IDNs and working on the same accounts. (*See "Third Cardiovascular Giant Coming With $25 Bil. Abbott-St. Jude Deal"* — "The Gray Sheet," *April 28, 2016.*)

Now they can look at what synergies they want, and how to re-craft roles to get higher impact with low disruption. "SFE has always been part of the lifeblood of these companies, but now it's gaining in importance almost every day – as customers consolidate into fewer and bigger accounts," says Laczkowski. He adds, "To the question: how do I accelerate my growth to get pretty immediate impact? This is one way."

NEW SALES MODELS, EVOLVING SFE

Medtech company sales forces will continue to evolve in many ways. Many clients are keeping watch on the "rep-less" model with great anticipation. The traditional sales force model is ultimately a very expensive resource. There are several other models – including the experimental ones – that tend to "push the thinking." One way is to pitch the sales team as a valuable resource for supporting the aims of the customer. In this case, the importance of the sales force is even greater than ever.

While many companies will be thinking that the very last thing they want to do is cut their sales resources, others are experimenting with greater use of telesales and other non-personal promotions, such as web-based or other technological methods.

Conversely, many hospitals and IDNs do not realize how much they depend on sales

reps already, says Laczkowski. "In some cases, say, where a hospital purchasing department wants to remove some cost and also get price reductions from the manufacturer, it might look to reduce the clinicians' exposure to the sales force. But in doing so, it might ultimately realize that the clinicians depend upon the clinical, technical and logistical knowledge and support of the sales force. Thus the overall quality may drop, and costs may rise, due to the increased burden on the hospital staff."

The rep-less model might not have universal appeal, but the consensus is that there will be different levels of service that emerge. "Some companies will want the 'gold version' and some the 'bronze version.' That's fine: manufacturers should be promoting that segmentation, and saying 'if you want us to be a full-service model – here are the implications,'" says Laczkowski. Where customers and manufacturers get into trouble is when they are not explicit at the start, and a mismatch in expectations suddenly emerges down the line.

"I see a situation where we could have a mutually very happy world: for some manufacturers it would mean a tremendous reduction in SG&A costs. And then again, we understand that it's not universally appealing," he says.

MEETING THE GOALS OF THE CUSTOMER

Case studies (*see above*) show that SFE is being adopted, but there are many more companies that are not yet where they want to be.

"Many companies have a desire to be better, and are investing to that end. They are being bold and are beginning to experiment with their own value propositions," states Laczkowski. Foremost among them are the likes of **Medtronic PLC**, **Philips Healthcare** and **GE Healthcare**, among others, which have scale and can actually go a stage further and take over parts of the hospital P&L account. Their appeal is to be able to, say, run a hospital's radiology lab and take the risk.

This equates to the idea of a "service wrapper" around technologies. "Those concepts are the 'best of breed' at this stage. Many other companies that do not have the scale will need to either continue in their current model or partner up with the Philipses or GEs, etc., of the world." Laczkowski says it will be interesting to see how the value chain will shift, and that some of the traditional manufacturers might also develop into distributors or "gate keepers" for these new responsibilities.

A SHAKE-UP IN WHO ADDRESSES THE MARKET?

In many cases, these traditional companies have not met their own growth forecasts, and they are being pushed hard. Doing more of what they're already doing will not work. However, the last thing they want is to upset their current customer base. "The transition will take time, but as we see more mega mergers and more examples of success, we will see more companies get on board with SFE concepts of all kinds," says Laczkowski.

As to the IDNs, there's a group of a couple of hundred very influential IDNs in the US, and some 80 to 100 are driving the majority of patient volumes. There will also be fewer and fewer successful individual hospitals, and they will need to become part of an IDN or an accountable care organization (ACO).

As they differ in style, reach and purpose – some are for-profit, some urban, some very strategic and consultative in their approach, whereas others are more transactional – manufacturers will have to figure out: "Where will I win?" and "Where do I fit in?" Medtech companies need to make choices and think about their own value proposition – and this of course makes SFE more important than ever.

The big question that is emerging for medtech companies is how they modify their sales territory design based on the fact that the model is now dominated by IDNs. The manufacturer's traditional North-South, etc., geographic model no longer fully applies and will have to be changed. Now it's more about how to best use resources to cover the different IDNs. Companies also need to be mindful that IDNs also compete with each other, and might not necessarily want the same reps.

THE CULTURE OF SFE GOES ALL THE WAY TO THE TOP

The benefit of SFE is that it provides a sustainable advantage that builds on itself, says ZS. It requires ongoing maintenance. Having said that, Laczkowski reiterates that the culture of SFE might be difficult for some companies to embrace.

But he adds that it's an issue that is here to stay and cannot or should not be delegated. "The culture of the future value proposition and the importance of the sales force has risen all the way to the CEO level now in forward-thinking companies. It is no longer delegated to a VP or director of sales," he states.

Indeed, the wider C-suite and board of directors are often involved in these conversations. "This is an indication that SFE is more important than it's ever been. It has bigger leverage points than it's ever had and there is probably also more risk than there has ever been," says Laczkowski. He adds that the difference now is that the CEO and board care.

DON'T DELAY: THE FUTURE IS ALREADY HERE

Laczkowski feels that every medtech senior leader should be well versed on this theme and be thinking critically about its high return on investment. The Explorer Study found that medtech companies are planning to increase their investment in SFE initiatives as a percentage of their overall budgets from 11% to 13% over the next two years. In a comment aimed at the foot-draggers, he says, "You should be active in this right now – not pondering about broaching it at some future date."

SFE is a broad topic area that is becoming pervasive across the whole company. "It also drives how we think about R&D, because what we are building here is not limited to sales." Laczkowski continues, "The best practice is a team initiative with a senior sponsor. Integrating effective SFE requires a cross-functional approach to sales operations, including the less customer-facing elements and the senior leadership. It cannot be done in isolation."

Although a "project manager" is key, ultimately, the SFE change agent needs to be fairly senior in the organization and must be able to hold together this cross-functional team, Laczkowski says. This is because, if it is done properly, SFE permeates the whole culture of the organization.

A#2016800112 IV

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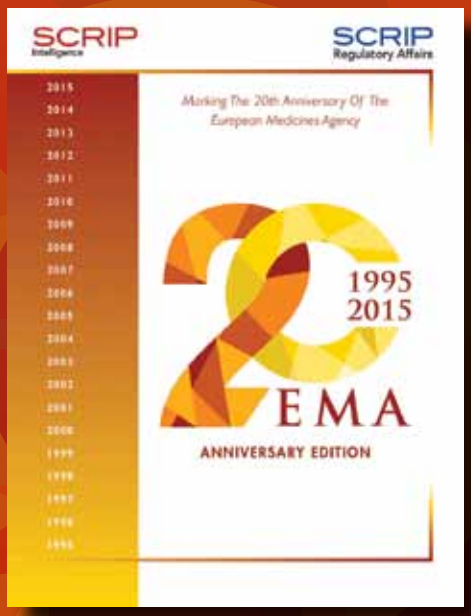

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This issue's Dealmaking covers deals made:

May 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

Luminex pays $77mm for **Nanosphere**

Financings

Oncimmune goes public through £11mm IPO on London's AIM

OpGen gets $10.4mm via PIPE

TearLab nets $13mm via follow-on offering of Class A units

MEDICAL DEVICES

Mergers & Acquisitions

BTG buys **Galil Medical** for $84.5mm plus earn-outs

Smith & Nephew divests gynecology business to **Medtronic** for $350mm

RoundTable Healthcare Partners buys **Symmetry Surgical**

Alliances

Cordis gets marketing rights to **Biosensors International**'s stents

Otsuka gets Asian rights to **ReCor**'s *Paradise* denervation system for hypertension

Financings

Organ implant company **Biostage Inc.** raises $4.5mm in registered direct at-the-market offering

Ligand pays $17.5mm for synthetic royalties from **CorMatrix**'s products

Teleflex nets $395mm in public senior notes offering

Device company **Wright Medical Group** nets $286.5mm in convertible debt

PHARMACEUTICALS

Mergers & Acquisitions

Arbor to acquire **XenoPort** for $467mm

Biogen spins off hemophilia business

Ergomed buys **Haemostatix** for £28mm

Incyte pays $140mm up front to buy European operations of **Ariad Pharmaceuticals**

Renaissance sells non-sterile topicals and generics businesses to **Mylan** for $950mm

Pfizer pays $5.2bn in cash for **Anacor**

Alliances

SciClone licenses new cancer project from **Ability Pharmaceuticals**

Achaogen, **Crystal Bioscience** pen antibody discovery deal

Celgene and **Agios** enter new deal focused on metabolic immuno-oncology

Alcyone, **Nanologica** collaborate on targeted delivery system for CNS disorders

Alder licenses clazakizumab to **Vitaeris**

Cardiome gets exclusive rights to **Allergan**'s *Xydalba*

Arbutus gets RNaseH inhibitors from **St. Louis Univ.**

Incyte gets European rights to **Ariad**'s *Iclusig*

Bayer licenses rights to **Progenics**' targeted prostate cancer antibody

BioDelivery licenses **Collegium** US rights to *Onsolis*

Horizon Pharma acquires worldwide rights to **BI**'s interferon gamma-1b

BI and **LDC** sign agreement for exclusive rights to schizophrenia compound

Daiichi Sankyo gets Japanese rights to **Cell Therapy**'s *Heartcel*

ChemoCentryx licenses complement 5aR inhibitor to **Vifor Pharma**

Chiesi acquires three cardiovascular assets from **The Medicines Co.**

EnBiotix, investment firm create JV

Kastle acquires *Kynamro* rights from **Ionis**

MacroGenics, **Janssen Biotech** sign second deal for preclinical cancer candidate

Marina to acquire intranasal ketamine program from **Turing**

Vifor Fresenius gets exclusive rights to **Opko**'s *Rayaldee*

Piramal pays $16.4mm for four of **Pfizer**'s brands

Pfizer, **Wave** sign potential $911mm deal involving metabolic therapies

Prima licenses *CVac* to **Sydys**; takes equity stake

Thera licenses **RXi**'s *sd-rxRNA* platform for CNS drugs

Financings

Aveo closes $17mm private placement

Regenerative medicine company **Asterias Biotherapeutics** nets $18.6mm in follow-on offering

Coherus BioSciences nets $60.4mm in follow-on public offering

DelMar privately sells $5.6mm of its preferred shares

Ergomed raises £8.4mm through private share placement; some proceeds to fund **Haemostatix** buy

GenVec brings in $5mm through RDO

Intellia closes $115.5mm IPO

Knight Therapeutics raises Cdn$200mm in bought deal financing

Loxo Oncology nets $38.9mm through follow-on offering

MannKind nets $47.5mm via registered direct offering

Merus nets $51.2mm in IPO

Neos gets $60mm in debt financing from Deerfield

Neuralstem nets $7.5mm in FOPO

Oncobiologics gets $4.6mm from Sabby Healthcare in post-IPO PIPE

Oncobiologics nets $32.5mm through IPO

Oryzon completes €10.5mm debt financing

PhaseRx closes $17.6mm IPO

Poxel seeks to go public in US

ProMetic raises $Cdn60mm in bought deal financing

Spring Bank files for IPO; postponed; re-filed and nets $10.2mm

Synergy Pharmaceuticals nets $89.7mm via RDO

VistaGen Therapeutics nets $9.1mm in FOPO of common shares and warrants

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

Financings

Bioprocessing company **Repligen** raises $100mm in convertible notes

IN VITRO DIAGNOSTICS

Mergers & Acquisitions
/In Vitro Diagnostics

LUMINEX CORP.
NANOSPHERE INC.

Luminex Corp. is paying $77mm ($1.70 per share; a 63% premium) in cash to acquire molecular diagnostics firm **Nanosphere Inc.** Luminex also agreed to retire $25mm of Nanosphere debt. (May)

Luminex first announced it was planning to pay $1.35 per share but upped the price in response to an unsolicited third party offer of $1.50 per share. Nanosphere sells the *Verigene* platform for syndromic molecular testing of bloodstream infections. The product, which incorporates a microfluidics processor, touch screen reader, and disposable test cartridge, can perform tests within 45-90 minutes. In addition to bloodstream infections, Nanospheres' diagnostics can test for respiratory, gastrointestinal, and cardiovascular diseases. These products, along with the firm's over 240 customers, will complement Luminex's customer base and portfolio, which includes the *ARIES* technology for targeted molecular diagnostic testing. Nanosphere reported revenues of $21.1mm in 2015, and as of the end of March 2016 the company had $13.4mm in cash and equivalents. Investment Banks/Advisors: Perella Weinberg Partners (Luminex Corp.); Jefferies & Co. Inc. (Nanosphere Inc.)

Financings
/In Vitro Diagnostics

ONCIMMUNE LTD.

Cancer diagnostics firm **Oncimmune Ltd.** netted £9.8mm ($14.2mm) through its initial public offering of 8.46mm shares at £1.30 on London's AIM. (May)

Investment Banks/Advisors: Zeus Capital Ltd

OPGEN INC.

In a first tranche, **OpGen Inc.** (infectious disease diagnostics) raised $10.4mm through the private sale of 9mm units at $1.14375 (a 7% discount). Lead investors Merck Global Health Innovation and Sabby Management were joined by OpGen management and certain directors. Each unit consists of one common share and one five-year warrant to purchase 0.75 of a share exercisable at $1.3125 per whole share. The company will use the funds for ongoing commercial activities and development of its rapid diagnostics and *Acuitas Lighthouse* bioinformatics platform. The second closing is expected to occur in mid-June 2016. (May)

Investment Banks/Advisors: Cowen & Co. LLC; Leerink Partners LLC; Maxim Group LLC

TEARLAB CORP.

TearLab Corp. (provides quantitative tests for disease markers in tears) netted $13mm through the follow-on offering of 18.6mm Class A units priced at $0.75. Each unit consists of one common share and a five-year Series A warrant to purchase 0.5 shares exercisable at $1.125 per whole share. (May)

Investment Banks/Advisors: HC Wainwright & Co.; Rodman & Renshaw Capital Group Inc.

MEDICAL DEVICES

Mergers & Acquisitions
/Medical Devices

BTG PLC
GALIL MEDICAL LTD.

BTG PLC agreed to pay $84.5mm in cash up front to acquire privately held cryoablation company **Galil Medical Ltd.** The deal also includes up to $25.5mm in regulatory- and sales-based earn-outs through December 31, 2018. (May)

Galil's products offer a surgery alternative to both surgeons and cancer patients. The company's technology utilizes argon gas to ablate cancerous tissue through sub-zero temperature freezing methods, with an initial focus on prostate and kidney tumors. This platform also has applications in pain management and is being studied for use with bone, liver, and lung cancers. Products include the *Visual-ICE*, *Presice*, and *SeedNet* systems; *Ice FORCE*, *IcePEARL*, and *IceEdge* cryoablation delivery needles; and thermal sensors and procedure templates. The acquisition of Galil helps BTG boost its presence in the interventional oncology market and complements existing products--mainly for kidney tumors--including drug eluting beads, embolization beads, and radiotherapy microspheres. Investment Banks/Advisors: Houlihan Lokey Inc. (Galil Medical Ltd.)

MEDTRONIC PLC
SMITH & NEPHEW PLC

Medtronic PLC is buying **Smith & Nephew PLC**'s gynecology business for $350mm, or over six times the unit's 2015 revenues. S&N plans to return $300mm of this amount back to shareholders in a share buy-back program. (May)

S&N's gynecology business is part of its "other" surgical businesses franchise (within its advanced surgical devices operating segment) along with the ENT unit. The "other" businesses had $205mm in aggregate 2015 revenues (5% of the company's total), with gynecology accounting for $56mm of this amount, or 1% of S&N's overall sales for the year. The gynecology group is headed up by the *Truclear* noninvasive hysteroscope and tissue resection/removal system

for use in the diagnosis and removal of multiple intrauterine pathologies, including endometrium, myomas, polyps, fibroids, and adhesions. This product line also offers a hysteroscopic fluid management system that enables both uterine cavity visualization and intrauterine pressure management during diagnostic imaging procedures. S&N will continue to manufacture these products during the transition to Medtronic. The divestiture allows S&N to focus on its orthopedic businesses (knee and hip implants, sports medicine, and arthroscopic surgery), which made up over half its 2015 sales. S&N has been building up its assets in orthopedics, completing multiple M&A and strategic transactions within this space over the past five years, most recently last year's $275mm buy of robotics surgical device maker **Blue Belt Technologies** and US license to **Zimmer Biomet**'s *ZUK* knee system, as well as the acquisition of sports medicine company **ArthroCare** in 2014. Although Medtronic does not have a specifically designated gynecology unit, the S&N business will operate as part of Medtronic's surgical solutions division within its **Medtronic Minimally Invasive Therapies** group (formerly Covidien, acquired by Medtronic in 2014), where it will align nicely with the existing minimally invasive devices for gynecological surgeries that this group already offers.

SYMMETRY SURGICAL INC.

Private equity firm RoundTable Healthcare Partners is paying $140.6mm in cash ($13.10 per share, a 29% premium) to acquire public device company **Symmetry Surgical Inc.** (May)

Post-transaction, Symmetry's CEO will continue to lead the firm and a representative from RoundTable joins the board. Symmetry is a global provider of reusable stainless steel and titanium surgical instruments, single-use and disposable instruments, electrosurgery instruments, retractor systems, containers and sterilization devices, and ligation clips. Its products are used in general and specialty surgeries in disciplines including neurosurgery, spine, obstetrics and gynecology, ophthalmology, otolaryngology, orthopedics, pediatrics, cardiovascular, thoracic, and urology. At the end of 2015, the company reported $84.5mm in revenues with a profit of $39.5mm, and it had $8.1mm in cash. Investment Banks/Advisors: Stifel Nicolaus & Co. Inc.

Alliances
/Medical Devices

BIOSENSORS INTERNATIONAL GROUP LTD.
CARDINAL HEALTH INC.
Cordis Corp.

In a long-term agreement, **Biosensors International Group Ltd.** licensed **Cardinal Health Inc.**'s **Cordis Corp.** rights to distribute its coronary stents in Europe, the Middle East, Africa, Australia, and New Zealand. (May)

Included in the agreement are the *BioFreedom* polymer-free drug-coated stent for patients at high risk for bleeding, *BioMatrix NeoFlex* and *BioMatrix Alpha* drug-eluting stents with an abluminal bioabsorbable coating and *Biolimus A9* (*BA9*) drug, and *Chroma* cobalt chromium bare metal stent. Eventually Cordis will start selling the products under the *Lumeno* private label in select countries, and both companies will continue leveraging their distribution capabilities in additional European countries, the Middle East, Africa and other areas of the world. Cordis' cardiology portfolio includes catheters, guide wires, and sheath introducers. The deal represents the company's return to the drug-eluting stent market and allows the firm to offer an expanded portfolio of products for percutaneous coronary intervention procedures. This is Cordis' first licensing agreement since Cardinal Health acquired it from **J&J** in March 2015 for $1.9bn.

OTSUKA HOLDINGS CO. LTD.
RECOR MEDICAL INC.

Otsuka Holdings Co. Ltd. licensed exclusive rights to sell **ReCor Medical Inc.**'s *Paradise* renal denervation system for hypertension in Japan, China, Korea, and other Asian countries. (May)

Otsuka made an undisclosed equity investment in ReCor under terms of the deal. (Otsuka was also the lead investor in ReCor's $15mm Series D round last year.) Otsuka's rights allow the company to conduct trials, carry out regulatory activities, and commercialize the system, with an initial focus on patients with treatment-resistant hypertension. *Paradise* uses ultrasound energy to ablate nerve endings in the lining of renal arteries. The technology deadens the sympathetic nerves in the kidneys, which results in signals being sent to the brain to loosen pressure in blood vessels and subsequently lower blood pressure. ReCor will use the proceeds from Otsuka's investment to fund the IDE-approved RADIANCE-HTN *Paradise* study (currently enrolling patients in the US, Netherlands, and UK).

Financings
/Medical Devices

BIOSTAGE INC.

Biostage Inc. (bioengineered organ implants for cancer and other conditions of the esophagus, bronchus and trachea) netted $4.5mm in a common stock registered direct offering of 2.8mm shares at $1.7625 (20% discount). For each common share purchased, investors will receive an unregistered five-year warrant to purchase one-half of a common share at an exercise price of $1.7625. Rodman & Renshaw was the placement agent. The company will use proceeds for R&D, to advance its *Cellframe* technology toward 2016 IND filing, and for clinical trials of the *Cellspan* esophageal implants. (May)

Investment Banks/Advisors: Rodman & Renshaw Capital Group Inc.

CORMATRIX CARDIOVASCULAR INC.
LIGAND PHARMACEUTICALS INC.

Ligand Pharmaceuticals Inc. is paying $17.5mm to acquire the economic rights to various products in **CorMatrix Cardiovascular Inc.**'s portfolio. (May)

Investment Banks/Advisors: Greenhill & Co. Inc. (CorMatrix Cardiovascular Inc.)

TELEFLEX INC.

Critical care and surgical devices firm **Teleflex Inc.** (offers products for vascular access, respiratory and cardiac, anesthesia, general surgical, and urology procedures) netted $395mm through the public sale of $400mm of its 4.875% senior notes due 2026 at an issue price of 100%. The company will use about $393mm of the proceeds to repay a portion of outstanding debt under its revolving credit facility. (May)

Investment Banks/Advisors: Bank of America Merrill Lynch; Barclays Bank PLC; Credit Suisse Group; Goldman Sachs & Co.; HSBC; JP Morgan & Co.; US Bancorp Piper Jaffray; Wells Fargo Securities LLC

WRIGHT MEDICAL GROUP NV

Wright Medical Group NV (biologics and medical devices for extremities) netted $286.5mm through the sale of $395mm gross amount of convertible senior notes due 2021. The notes convert to cash at the holder's option and bear an interest rate of 2.25% payable semiannually in arrears on each May 15 and November 15 and mature on November 15, 2021. The initial conversion rate is 46.8165 ordinary shares per $1,000 principal notes (represents $21.36 conversion price; 20% conversion premium). Concurrently, selected investors agreed to exchange their 2017 and 2020 notes, however the company will not receive any funds. The company will use a portion of the proceeds to pay for cash convertible note hedge transactions. (May)

PHARMACEUTICALS

Mergers & Acquisitions
/Pharmaceuticals

ARBOR PHARMACEUTICALS INC.
XENOPORT INC.

Private specialty pharmaco **Arbor Pharmaceuticals LLC** plans to acquire public drug delivery biotech **XenoPort Inc.** (mostly focused on neurological disorders) with a tender offer of $7.03 per share (a 65% premium), or about $467mm. The XenoPort board has unanimously agreed to the deal. In a concurrent financing, Arbor raised debt funding from Deutsche Bank to support the transaction. (May)

XenoPort is known for its drug delivery platform that uses transporter proteins in the GI tract to move a prodrug into the bloodstream, where it's converted to the parent drug and released. Prodrugs are created by adding a chemical structure to a known active drug to form a new molecule that is designed for better absorption into the body. Lead product *Horizant* is a transported prodrug of gabapentin enacarbil (formerly known as XP13512), a calcium channel antagonist FDA approved in 2011 for restless leg syndrome and in 2012 for postherpetic neuralgia. Phase II trials for moderate to severe alcohol use disorder (AUD) were initiated in mid-2015. **Astellas Pharma** has rights to the compound in Asia, where it's marketed as *Regnite* for RLS, under a 2005 deal. GSK obtained a license in all other territories in 2007, but terminated the deal in late 2012, returning rights to XenoPort. The company is also developing arbaclofen placarbil (a prodrug of the R-isomer of baclofen) for AUD with **Indivior PLC** (a spin-off of **Reckitt Benckiser**) under a 2014 deal and Phase III-ready monomethyl fumarate prodrug XP23829 for multiple sclerosis and psoriasis (through a collaboration with **Dr. Reddy's** started earlier this year). To focus efforts on *Horizant*, XenoPort discontinued development of XP21279, a prodrug of L-dopa, for

Parkinson's disease (Phase I), but they had been seeking a partner. *Horizant* will join Arbor's neuro portfolio that includes *Zenzedi* (dextroamphetamine sulfate) and *Evekeo* (amphetamine sulfate), both of which Arbor has been marketing for narcolepsy and ADHD since 2013 and 2014, respectively. Investment Banks/Advisors: Centerview Partners LLC (XenoPort Inc.)

BIOGEN HEMOPHILIA SPIN-OFF
BIOGEN INC.

Biogen Inc. is spinning off its hemophilia business as an independent publicly traded company. The new company hasn't been named yet, but Biogen expects the transaction to be completed by the end of the year or early 2017. (May)

Following the divestiture, Biogen plans to focus on developing its neurology pipeline. Because the hemophilia market is dominated by few players--namely **Bayer**, **Novo Nordisk**, and **Baxalta**--there were virtually no buyers for the business since these companies currently have competing marketed products or candidates in late-stage development. The new firm will have its headquarters in Boston, will be headed up by CEO John G. Cox, who was Biogen's EVP of pharmaceutical operations & technology. It will focus on developing new hemophilia therapies but will also take on the currently marketed infusion therapies *Eloctate* for hemophilia A and *Alprolix* for hemophilia B, which combined for $640mm in revenues during the twelve-months ending March 31, 2016. The drugs are partnered under a 2006 collaboration between Biogen and **Swedish Orphan Biovitrum**. Biogen will continue to manufacture both for the next three to five years. (Studies will be conducted to demonstrate that *Eloctate* can rapidly induce immune tolerance in hemophilia patients who develop inhibitors.) The spin-out will use the *XTEN* technology to develop longer-acting therapies; candidates could reach clinical trials in 1H 2017. It will also develop bispecific antibodies and hemophilia-related gene therapies.

ERGOMED PLC
HAEMOSTATIX LTD.

Ergomed PLC agreed to acquire **Haemostatix Ltd.**, a privately held firm developing peptide-based hemostats for bleeding control. Ergomed will pay £8mm ($11.6mm) up front (of which £6.2mm will be paid with consideration shares), and £20mm in sales-based earn-outs. (May)

Haemostatix was spun out of the **University of Leicester** in 2003 and raised over £5.8mm through four financing rounds from investors including Albion, Catapult, Wellcome Trust, Nesta, Lachesis Fund, and Esperante Ventures. Using its technology based on a peptide sequence that binds to fibrinogen and aids in clotting, the company is developing topical and systemic hemostats. Its lead projects are *PeptroStat*, a liquid applied to surgical wounds that is in Phase II trials, and *ReadyFlow*, a preclinical-phase transparent gel for irregular bleeding. (Earn-outs for the acquisition are partially tied to development: Ergomed pays £4mm at the start of a Phase III trial and then the remaining £16mm for sales achievements.) Ergomed, a clinical research services firm that also does drug development work through a co-development set-up, looks forward to gaining its first wholly owned projects through the Haemostatix acquisition. It plans to use about £1.8mm of a concurrent £9mm private placement to fund the up-front portion of the acquisition. (Remaining proceeds from the placement are earmarked for future acquisitions of complementary service businesses.)

INCYTE CORP.
ARIAD PHARMACEUTICALS INC.
Ariad Pharmaceuticals (Luxembourg) SARL

Incyte Corp. paid $140mm up front to acquire **Ariad Pharmaceuticals (Luxembourg) SARL**, the European operations of cancer drug company **Ariad Pharmaceuticals Inc.** (May)

Incyte gains Ariad's 125-employee-strong pan-European team (including medical, sales, and marketing staff) and the ability to create a European hub. Through a separate but related agreement, Incyte also licensed exclusive rights (in the European Union and 22 other countries, including Switzerland, Norway, Turkey, Israel, and Russia) to develop and sell Ariad's *Iclusig*, an approved BCR-ABL inhibitor marketed for chronic myeloid leukemia and Philadelphia-positive (Ph+) acute lymphoblastic leukemia. For that agreement, Ariad could see up to $135mm in development and regulatory milestones if Incyte develops the drug for additional cancer indications (and other money related to development in non-oncology indications), plus sales royalties between 32-50%. Ariad is divesting the European business and rights in order to further focus resources on US commercialization of *Iclusig*.

MYLAN NV
RENAISSANCE ACQUISITION HOLDINGS LLC

Mylan NV paid $950mm in cash up front to acquire **Renaissance Acquisition Holdings LLC**'s non-sterile, topical specialty and generic dermatology business, which had 2015 revenue of $370mm. Renaissance could get another $50mm in earn-outs. (May)

The transaction includes 25 branded and generic topical drugs; 25 candidates in the pipeline, including complex topical generics and brands; a US dermatology sales and marketing force; an integrated manufacturing and development platform; and contract manufacturing and development capabilities for producing topical creams, ointments, aerosols/foams, gels, suspensions, and liquids, plus suppositories. The deal leaves Renaissance with its remaining segments, in both Canada and the US: contract development and manufacturing through its **DPT** and **Confab** units, plus non-topical branded products sold through its **Prestium Pharma** subsidiary, and a sterile drug portfolio. Mylan recently increased its dermatology presence when it bought specialty and OTC drug player **Meda** in February 2016 for $9.9bn, after two-years' worth of negotiations and hostile bids. Currently, Mylan sells 12 products in the dermatology sector, including various creams, ointments, and dressings. The company would have had an even bigger footprint in dermatology had it succeeded in buying **Perrigo** last year, but Perrigo fought off the offer and the transaction never happened (50% of Perrigo's generics are for dermatological conditions).

PFIZER INC.
ANACOR PHARMACEUTICALS INC.

Pfizer Inc. is paying $5.2bn--$99.25 per share, a 57% premium--in cash to acquire **Anacor Pharmaceuticals Inc.** The purchase price is net of cash and assumes the conversion of Anacor's outstanding convertible debt. (May)

Anacor's top asset is crisaborole, a non-steroidal topical phosphodiesterase-4 ointment for treating mild-to-moderate atopic dermatitis (eczema). Anacor and Pfizer believe there's a significant unmet medical need for the condition, which currently has few safe topical treatment options, namely corticosteroids. Anacor submitted the NDA at the beginning of the year, and the goal date for the completion of the FDA's review is January 7, 2017. If approved, Pfizer believes crisaborole's peak annual sales could potentially exceed $2bn annually. The anti-inflammatory will fit nicely in Pfizer's inflammation and immunology portfolio, which includes the two rheumatoid arthritis drugs *Xeljanz* (tofacitinib) and *Enbrel* (etanercept). Another key asset in Anacor's portfolio is *Kerydin* (tavaborole), a topical treatment for onychomycosis (toenail fungus). This was the first product created using Anacor's boron chemistry platform, which produces compounds containing boron to improve biological target interaction. **Sandoz**'s **PharmaDerm** holds exclusive US rights to the product under a July 2014 deal. For FYE 2015, Anacor reported revenues of $82.4mm (mostly from the *Kerydin* agreement) and a net loss of $61.2mm. As of the end of March 2016 it had $137.9mm in cash and equivalents. Investment Banks/Advisors: Centerview Partners LLC; Guggenheim Partners LLC (Pfizer Inc.); Citigroup Inc. (Anacor Pharmaceuticals Inc.)

Alliances
/Pharmaceuticals

ABILITY PHARMACEUTICALS SL
SCICLONE PHARMACEUTICALS INC.

Ability Pharmaceuticals SL granted **SciClone Pharmaceuticals Inc.** exclusive rights to develop and sell its cancer candidate ABTL0812 in China, Hong Kong, Macau, Taiwan, and Vietnam. (May)

Ability gets money up front, research funding, and milestones for development, regulatory, and sales achievements, the sum of which could hit $20mm. SciClone will also pay royalties. ABTL0812 is a PI3K/Akt/mTOR signaling pathway inhibitor in Phase II trials for non-small cell lung and endometrial cancers, and Phase I for pancreatic, brain, and biliary tumors. SciClone has been building up its oncology presence in China, and already markets products there for a few big-name partners including **Baxter** (*Holoxan* and *Endoxan*), **Pfizer** (methotrexate and *Estracyte*) and **BTG** (*DC Bead*).

ACHAOGEN INC.
CRYSTAL BIOSCIENCE INC.

In a multi-year collaboration, **Achaogen Inc.** and **Crystal Bioscience Inc.** are teaming up to discover monoclonal antibodies against multiple targets of interest to Achaogen. (May)

Achaogen will pay technology access fees, research funding, development milestones, and royalties. In return it receives rights to develop and commercialize any resulting antibody therapies. To the alliance, Crystal is contributing its chicken-based antibody discovery platform, genetically-engineered chicken-producing human antibodies, and high-throughput gel-encapsulated microenvironment (GEM) assay.

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Achaogen's early-stage projects are for infections caused by multidrug-resistant Gram-negative bacteria including antibacterial mAbs. Crystal signed a similar agreement with **Boehringer Ingelheim** in 2014.

AGIOS PHARMACEUTICALS INC.
CELGENE CORP.

Building on a successful relationship that began in 2010, **Celgene Corp.** and **Agios Pharmaceuticals Inc.** entered into a new collaboration, this time focused on metabolic immuno-oncology, which involves altering the metabolic state of immune cells to enhance immune response to cancer. (May)

The partners' ongoing previous deal centers on cancer metabolism and resulted in Celgene exercising options to three development projects--AG120 (outside of the US), AG221, and AG881. In conjunction with the current alliance, Agios regains all rights to AG120, but the rest of that deal remains intact. Terms of the newest partnership call for the companies develop and sell new therapies based on Agios' cellular metabolism research platform for an initial period of four years (renewable for an additional two-year term by Celgene for an undisclosed fee). Celgene pays $200mm up front for rights to co-develop and co-commercialize resulting projects. Agios leads all early research and discovery efforts, with Celgene able to designate certain programs upon initiation of preclinical studies. Celgene has an option to license each candidate through Phase I for at least a $30mm option exercise fee. For optioned programs, the partners will operate on a 50/50 global cost and profit share arrangement, with Agios eligible for $169mm in regulatory and sales milestones per program. (Two cancer metabolism candidates from the 2010 deal, focusing on methylthioadenosine phoshorylase (MTAP) cancers move to the current deal under the same financial terms.) Celgene has a one-time chance to choose one of the metabolic immuno-oncology programs and apply a 65/35 (Celgene/Agios) cost and profit share split, under which circumstances Agios would be eligible for $209mm in development and regulatory milestones. Lastly, if the deal turns out new candidates in the inflammation or autoimmune spaces, Celgene has an option for exclusive global development and commercialization rights in exchange for up to $386mm in total milestones and double-digit royalties. For all 50/50 compounds, the partners will alternate leadership in the US (with Agios making the first selection). Celgene leads all ex-US development and commercialization for the 50/50 programs, and global activities for the 65/35 project.

ALCYONE LIFESCIENCES INC.
NANOLOGICA AB

Alcyone Lifesciences Inc. is collaborating with **Nanologica AB** to develop a human embryonic stem cell (hESC) delivery platform it will call *Abela* for motor neuron disorders, including amyotrophic lateral sclerosis (ALS). (May)

Alcyone will use its own drug delivery technology, while Nanologica adds its *NLAB Silica* nanoporous material, combining them both to create a method that will result in targeted delivery (over a sustained time period) of trophic factors associated with hESCs. Trophic factors (such as nerve growth factors) guide motor neurons during development, rescue degenerating neurons, and help promote the survival of transplanted stem cells in patients with ALS or other neurodegenerative disorders. Alcyone makes a microsystem delivery device (smaller than a needle) that provides direct infusions to the brain, overcoming the blood-brain barrier and other limitations. Nanologica's *NLAB Silica* platform is based on material sciences originally developed at **Stockholm University** and **Uppsala University** and controls the form, porosity, and surface area of nanoparticles of silica, which can store, encapsulate in a stabilized form, and transport an active pharmaceutical ingredient (API) inside the particles' pores, maintaining drug efficacy. The nanopores are loaded with an API and then the particles are compressed into tablets that enable the drug's gradual release into the stomach and/or intestines, where it's then absorbed by the body and the particles are excreted. Nanologica licensed from Uppsala and is developing in collaboration with the university's Elena Kozlova, PhD, an hESC delivery approach for early-stage ALS called *Nano-ALS*, which involves loading *NLAB Silica* particles with hESC-derived trophic factors (instead of APIs). This method demonstrated in animal studies the ability for improved stem cell survival and growth in previously unachievable environments. The nanoparticles are subsequently transplanted into the spinal cord (where the stem cells will be released and operate as motor neurons) using microfabricated needles, which is where Alcyone's technology will come into play. Alcyone will develop, fund, and operate the *Abela* program. Although no financial terms were disclosed, Nanologica's collaboration business model includes Nanologica receiving payment up front for delivered material (loaded nanoparticles) and typically also for the related IP. Should the partner advance the project into clinical studies (tablet form) or it results in a finished product, the compensation to Nanologica generally increases in the form of milestones and royalties on future sales.

ALDER BIOPHARMACEUTICALS INC.
VITAERIS INC.

Alder BioPharmaceuticals Inc. licensed **Vitaeris Inc.** exclusive global rights to develop and sell clazakizumab, an interleukin-6 (IL-6) inhibitor in development for a various inflammation-mediated diseases. (May)

Alder made an undisclosed equity investment in Vitaeris and is eligible for sales royalties and other payments. Alder's CEO Randall Schatzman, PhD, also takes a seat on the new biotech's board. Under a 2009 deal, **BMS** previously held rights to clazakizumab, but terminated the alliance in 2014. The compound is in a number of Phase II trials for conditions including rheumatoid arthritis and psoriatic arthritis. Vitaeris, which was just launched in April 2016, counts clazakizumab as its first project.

ALLERGAN PLC
CARDIOME PHARMA CORP.

Allergan PLC licensed **Cardiome Pharma Corp.** exclusive rights to commercialize *Xydalba* (dalbavancin) in the UK, Malta, France, Germany, Belgium, Denmark, Iceland, Finland, Norway, Sweden, Switzerland, the Netherlands, Luxemburg, Ireland, some Middle Eastern countries, and Canada. (May)

Cardiome will pay $13mm up front plus commercial milestones and sales royalties. *Xydalba* was approved in Europe in February 2015 for treating acute bacterial skin and skin structure infections (ABSSSIs). In the US it is sold as *Dalvance* for ABSSSI caused by susceptible Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus. Cardiome plans to commence commercialization in countries in which the drug is already approved possibly this year. *Xydalba* is not yet approved in Canada or Switzerland. The drug was originated by **Pfizer**'s Vicuron, and in 2009, five venture firms created **Durata** to acquire Vicuron. Durata was bought by Actavis (now Allergan) in 2014.

ARBUTUS BIOPHARMA CORP.
ST. LOUIS UNIVERSITY

Arbutus Biopharma Corp. (formerly Tekmira) received a license from **St. Louis University**'s Liver Center to develop ribunuclease H (RNaseH) inhibitors for hepatitis B. (May)

RNaseH is a component of the viral polymerase and critical to the replication of the hepatitis B virus. The early-stage program will join Arbutus' HBV pipeline, which is led by Phase II ARB1467 in development as a multi-component RNAi therapeutic that simultaneously targets three sites on the HBV genome. The company has several compounds in development, all with different mechanisms. Arbutus hopes to add yet another with the RNaseH inhibitor.

ARIAD PHARMACEUTICALS INC.
INCYTE CORP.

In conjunction with its acquisition of the firm's European operations, **Incyte Corp.** licensed exclusive rights to **Ariad Pharmaceuticals Inc.**'s *Iclusig* (ponatinib). Incyte will develop and sell the leukemia treatment in the European Union and 22 other countries, including Switzerland, Norway, Turkey, Israel, and Russia. (May)

In addition to rights in the approved diseases, Incyte pays $135mm in development and regulatory milestones for work on the drug in new oncology indications (plus potential payments for non-oncology indications), plus tiered royalties between 32-50%. The company will also fund some of the ongoing clinical development with *Iclusig* in two of Ariad's trials through cost-sharing payments of up to $14mm ($7mm in each of 2016 and 2017). The deal includes an option for a future acquirer of Ariad to repurchase the licensed rights from Incyte in exchange for fees equivalent to Incyte's payments (up-fronts, milestones, and development costs) and 20-25% royalties. *Iclusig* is a BCR-ABL inhibitor (with activity against the T315I mutation) approved in Europe and other countries for chronic myeloid leukemia and Philadelphia-positive (Ph+) acute lymphoblastic leukemia. Ariad is divesting rights to it (and to its entire **Ariad Pharmaceuticals (Luxembourg) SARL** division) in order to more effectively focus on commercializing *Iclusig* in the US. The drug was approved in the US in 2012 and last year brought in $112.5mm in global net sales.

BAYER AG
PROGENICS PHARMACEUTICALS INC.

Bayer AG received exclusive global development and commercialization rights to **Progenics Pharmaceuticals Inc.**'s Phase II antibodies that incorporate the latter's prostate cancer-specific membrane antigen (PSMA) technology. (May)

Bayer made a $4mm up-front payment and is responsible for $49mm in clinical development and regulatory milestones, $130mm in sales milestones, plus single-digit royalties. Last year, Progenics li-

censed rights to **Johns Hopkins University**'s PSMA imaging agent 18F-DCFPyL; it's unclear if Progenics will use this, or its other imaging agent 1404, in the current deal. Bayer plans to create PSMA-targeting antibodies conjugated with thorium-227, an alpha-emitting radionuclide. The PSMA component targets the conjugate to the prostate tumor cells (more than 95% of which express PSMA), which are treated with and destroyed by the alpha particles. Progenics developed a first-generation version of an antibody-drug conjugate interacting with PSMA using technology licensed from **Seattle Genetics** (the anticancer medication linked to the antibody was monomethyl-auristatin-E). Bayer already has a prostate cancer drug on the market, *Xofigo* (the radioactive isotope radium-223 dichloride, alpharadin), which also uses alpha radiation to kill cancer cells. Both *Xofigo* and the thorium-227 conjugating technology came from Bayer's 2013 acquisition of Algeta.

BIODELIVERY SCIENCES INTERNATIONAL INC.
COLLEGIUM PHARMACEUTICAL INC.

BioDelivery Sciences International Inc. licensed **Collegium Pharmaceutical Inc.** exclusive US development, manufacturing, and commercialization rights to *Onsolis*, a buccal (inner cheek) soluble film version of fentanyl. (May)

The drug (formerly known as *BEMA-Fentanyl*) was first formulated using BDSI's *Bioerodible Mucoadhesive* (*BEMA*) film--which enables controlled systemic and local drug delivery. BDSI originally gained the *BEMA* technology through its 2004 acquisition of drug delivery firm Arius Pharmaceuticals, which had an exclusive license through a deal signed earlier that year with the technology's developer Atrix Laboratories (later acquired by **QLT**). *Onsolis*, an opioid receptor agonist, received FDA approval in 2009 for breakthrough cancer pain, but was voluntarily taken off the US market in 2011 to address two appearance issues raised by the FDA related to fading color of the drug. In August 2015, the FDA approved the supplemental NDA for a reformulated version. BDSI markets *Onsolis* under different names in various other territories through licensing deals with multiple partners including **TTY Biopharma** in Taiwan (as *Painkyl*); **Valeant** in Canada; **Alvogen** in Korea; and **Meda** in Europe (as *Breakyl*). (Meda previously had a North American license under a modified 2006 deal, but reassigned those rights back to BDSI in January 2015.) Under the current agreement, both parties will collaborate on the manufacturing transfer process, which includes submission to the FDA of a prior approval supplement. Collegium will reimburse BDSI for expenses related to the transfer and will also be responsible for reformulating and manufacturing *Onsolis* once the FDA approves the new regulatory filings; Collegium expects this to be mid-2017. BDSI will get $2.5mm up front; $4mm upon the first US sale of *Onsolis*; up to $17mm in commercialization, intellectual property, and sales milestones; plus royalties in the upper-teens (*Strategic Transactions* estimates 16-19%). The addition of *Onsolis* doubles Collegium's portfolio of opioid pain medicines. Just last month Collegium received FDA approval for its opioid receptor agonist *Xtampza* ER (oxycodone) for the management of severe pain, formulated using its *DETERx* abuse-deterrent platform.

BOEHRINGER INGELHEIM GMBH
HORIZON PHARMA PLC

Horizon Pharma PLC received worldwide rights to **Boehringer Ingelheim GmbH**'s interferon gamma-1b product (trade names *Imuki*, *Imukine*, *Immukin*, *Immukine* and *Actimmune*; Horizon already owns rights to the product as *Actimmune* in US, Canada and Japan). Under the agreement the two parties will also enter into a global supply agreement. (May)

Horizon paid €5mm upfront with an additional €20mm payable upon deal closing (expected by the end of 2016). A per unit price will also be paid for all acquired inventory in cash. The transaction is expected to close by the end of FY2016. Simultaneoulsy in a separate deal, Horizon licensed the US, Canadian and European IP rights for interferon gamma-1b for Friedreich's ataxia (not currently indicated or approved for this indication) from an unknown third party. The product is currently launched for chronic granulomatous disease, osteopetrosis, in Phase III for Friedreich's ataxia, Phase II for pulmonary idopathic fibrosis and in Phase I for solid cancer and Preclinical for renal and bladder cancer.

BOEHRINGER INGELHEIM GMBH
LEAD DISCOVERY CENTER GMBH

Boehringer Ingelheim GMBH received an option to an exclusive license to a new lead compound for schizophrenia from **Lead Discovery Center GMBH**. (May)

The product was developed from the research of Prof. Moritz Rossner at the **Max Planck Institute**. BI will gain a seat on the project development team and pay an undisclosed option fee. Once proof-of-concept has been attained, BI has the option to exclusively license the candidate at pre-defined terms for further development. Any revenue that LDC receives from commercialization of a resulting product will be shared with the academic inventors and collaborating institutions.

CELL THERAPY LTD.
DAIICHI SANKYO CO. LTD.

Cell Therapy Ltd. licensed **Daiichi Sankyo Co. Ltd.** Japanese rights to its cardiac regeneration medicine *Heartcel*. (May)

Daiichi will handle all development, regulatory, and commercial activities in Japan and CTL retains rights in the rest of the world and will manufacture the product. Daiichi pays £12.5mm ($18mm) up front plus milestones and royalties. *Heartcel* is comprised of immuno-modulatory progenitor (iMP) cells and has completed Phase II trials in severe heart failure; Phase III is expected to commence sometime this year. CTL divested *Heartcell* rights in Japan, where there is an accelerated regulatory pathway for regenerative medicines and Daiichi has experience. CTL can now focus on US and European Phase III trials and early-stage pipeline development. The company is also working on *Myocardion* for heart failure, *Tendoncel* for tendon injury, *Skincel* for wrinkles, and *Tcel* for B cell malignancies.

CHEMOCENTRYX INC.
GALENICA GROUP
Vifor Pharma Ltd.

Vifor Pharma Ltd. licensed rights in Europe, Canada, Mexico, Central and South America, and South Korea to sell **ChemoCentryx Inc.**'s complement 5a receptor inhibitor CCX168 for orphan and rare renal diseases. (May)

CCX168 is in Phase II trials for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and has orphan drug status in the US and EU; Phase III studies are expected to commence later this year. (It is also in additional trials for atypical hemolytic uremic syndrome and immunoglobulin A nephropathy (IgA nephropathy).) Vifor will pay $85mm up front ($60mm in cash and $25mm through the purchase of 3.33mm ChemoCentryx shares at $7.50, a 233% premium), regulatory and sales milestones, and tiered double-digit royalties. Vifor also gains an option to license global rights to ChemoCentryx's CCX140, a CCR2 inhibitor in Phase II for diabetic nephropathy.

CHIESI FARMACEUTICI SPA
THE MEDICINES CO.

The Medicines Co. divested three non-core cardiovascular assets--*Cleviprex* (clevidipine), *Kengreal* (cangrelor), and argatroban for injection (50mg/50ml)--to **Chiesi Farmaceutici SPA**. (May)

Chiesi will pay $260mm up front in cash and up to $480mm in sales milestone payments. The company will also assume up to $50mm in milestone payment obligations and about $2mm for product inventory. TMC gained exclusive worldwide rights (excluding Japan) to clevidipine, a calcium channel blocker for hypertension, from **AstraZeneca** in March 2002; four years later it acquired Japanese rights. Also from AZ, TMC got an exclusive global license (excluding Japan, China, Korea, Taiwan, and Thailand) to the antithrombotic agent cangrelor in late 2003. The drug is currently marketed as *Kengreal* in the US and *Kengrexal* in Europe. *Kengreal* received FDA approval in June 2015 as an adjunct to percutaneous coronary intervention to reduce the risk of myocardial infarction, repeat coronary revascularization, and stent thrombosis, but only in patients that hadn't been treated with a P2Y12 platelet inhibitor and who aren't taking a glycoprotein IIb/IIIa inhibitor. TMC had hoped to get approval for a broader population but received the limited patient population label due to potential bleeding risks. Argatroban, a direct thrombin inhibitor for thrombosis and thrombocytopenia, was licensed to TMC by **Eagle Pharmaceuticals** in September 2009; under that deal TMC holds rights in the US and Canada. TMC will use proceeds from the transaction to fund pipeline development, including its Phase II PCSK9 inhibitor for dyslipidemia. R&D is key for the company considering its top-selling cardiovascular drug *Angiomax* (bivalirudin) lost patent protection in July 2015 and is now facing generic competition. (The drug only generated $16.9mm in Q1 2016, a significant blow to the company's balance sheet considering *Angiomax* brought in $100.7mm during Q1 2015.) TMC closed out 2015 selling off three of its hemostasis products to **Mallinckrodt** for $175mm up front and up to $235mm in milestones. Investment Banks/Advisors: Goldman Sachs & Co. (The Medicines Co.)

ENBIOTIX (BRASIL) LTDA.
ENBIOTIX INC.

Antibiotics developer **EnBiotix Inc.** formed a joint venture with Wired Holdings Investment Corp. (WHIC) called **EnBiotix (Brasil) Ltda.** (EBL) to develop and commercialize EnBiotix's products in Latin America. (May)

EnBiotix concurrently raised an undisclosed amount in Series A funding from WHICH (added a member to

the board) and Apeiron. WHIC will provide EnBiotix with strategic, regulatory, and commercial support in creating the JV. EnBiotix keeps rights to its products outside of Latin America. The company's current preclinical compounds that EBL will work on are EBX001 (reformulated tobramycin) for P. aeuriginosa infections in patients with cystic fibrosis, non-CF bronchiectasis, and chronic obstructive pulmonary disease; EBX002 (vancomycin) for Gram-negative catheter-associated urinary tract infections; and EPP001 for prosthetic joint infections. EBL will handle Latin American registration and commercialization of all products developed by EnBiotix. The agreement carries an initial term but may be extended if agreed upon by the parties.

IONIS PHARMACEUTICALS INC.
KASTLE THERAPEUTICS LLC

In its first collaboration, **Kastle Therapeutics LLC** acquired global development and commercial rights to **Ionis Pharmaceuticals Inc.**'s (formerly Isis) cholesterol-lowering medicine *Kynamro* (mipomersen) injection. (May)

Ionis receives $15mm up front, a $10mm milestone payment in May 2019, and up to $70mm in sales milestones. Starting next year, Ionis will get global sales royalties in the low-to-mid teens (*Strategic Transactions* estimates 13-16%). Ionis also receives a 10% common equity position in Kastle's parent company (assumed to be key backer VC firm Flexpoint Ford). Under a January 2008 deal, **Sanofi**'s **Genzyme** had exclusive global rights to the drug but that agreement was terminated earlier this year. Genzyme will earn a 3% royalty on *Kynamro* sales and 3% of the cash payments Ionis receives from Kastle. *Kynamro* has FDA approval for patients with homozygous familial hypercholesterolemia to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol as an adjunct to lipid lowering medications and diet. Kastle was formed in July 2015 to acquire and develop drugs for high unmet needs.

JOHNSON & JOHNSON
Janssen Biotech Inc.
MACROGENICS INC.

MacroGenics Inc. licensed **Johnson & Johnson**'s **Janssen Biotech Inc.** global rights to its preclinical bispecific candidate MGD015 for treating hematological malignancies and solid tumors. (May)

MacroGenics receives $75mm up front and up to $665mm in clinical, regulatory, and commercial milestones. The company has the option to fund a portion of late-stage clinical trials in exchange for a profit share in the US and Canada. Upon commercialization, it would receive double-digit sales royalties and can opt to co-promote in the US. Janssen is responsible for finishing IND-enabling activities and clinical development. MGD015 is a *Dual-Affinity Re-Targeting* (*DART*) molecule, which simultaneously targets CD3 (found on T cells) and an undisclosed tumor target. The two firms teamed up back in December 2014 when MacroGenics licensed Janssen global rights to another preclinical *DART* molecule, MGD011, which is now in Phase I for leukemias and lymphomas including B-cell malignancies. That deal, which is structured similarly to the current alliance, could be worth up to $700mm.

MARINA BIOTECH INC.
TURING PHARMACEUTICALS AG

Per a term sheet, **Marina Biotech Inc.** intends to acquire **Turing Pharmaceuticals AG**'s intranasal ketamine, including all patents and intellectual property and existing product inventories. (May)

Marina will issue about 53mm of its shares (valued at $8mm based on the 10-day pre-announcement average) and could provide up to $95mm in pre-commercialization and sales-based milestones, plus a mid-single digit sales royalty (*Strategic Transactions* assumes 5-6%). The transaction is expected to close by July 1, 2016, following the execution of a definitive agreement and related fulfillment of closing requirements. Turing's TUR002 (intranasal ketamine) is an NMDA receptor antagonist under development for suicidal ideation in post-traumatic stress disorder. In January 2016, Turing initiated a Canadian Phase I trial--expected to be completed the first half of 2016--and anticipates registration trials to begin in North America and Europe in the middle of this year. Turing got its start in October 2014 with the acquisition of the psychomodulator (and some other assets) from **Retrophin**, which had initially licensed IP surrounding nasal ketamine administration from its inventor Stuart Weg, MD, in 2013. Marina plans to develop ketamine in additional neurological and psychiatric disease indications. The company hopes to complete a subsequent financing that will enable funding of Phase III, and anticipates having a product on the market in the US by 2019. Intranasal ketamine could also potentially have applications in rare disorders, in which Marina already has three pipeline programs. With Marina's recently ending negotiations with **Microlin Bio**--which was going to buy the former's nucleic acid therapeutics assets--it hopes the current agreement will give it a compound to bring to market quickly. The divestiture of this program enables Turing to focus on other candidates in its own development pipeline. Turing has been the subject of much media attention lately due to multiple fraud allegations brought against its former CEO Martin Shkreli (also previously CEO of Retrophin), who was indicted in December 2015.

OPKO HEALTH INC.
EirGen Pharma Ltd.
GALENICA GROUP
Vifor Fresenius Medical Care Renal Pharma Ltd.

Vifor Fresenius Medical Care Renal Pharma Ltd. (JV between **Galenica Group** and **Fresenius Medical Care AG**; 55%-owned by Galenica) licensed exclusive global rights to develop and sell **Opko Health Inc.**'s *Rayaldee* (calcifediol), a treatment for secondary hyperparathyroidism (SHPT) in chronic kidney disease patients and also for vitamin D insufficiency. (The license excludes the US, Central and South America (excluding Mexico), Russia, China, Japan, Ukraine, Belorussia, Azerbaijan, Kazakhstan, and Taiwan.) The deal is being conducted through Opko's **EirGen Pharma Ltd.** subsidiary, according to an 8-K filing. (May)

In addition to the primary licensed indications, the companies will work together to develop and sell *Rayaldee* for the treatment of SHPT in dialysis patients; Vifor Fresenius gets an option to license US rights for this indication. EirGen gets $50mm up front, up to $52mm in regulatory and launch milestones, $180mm in sales milestones, and tiered double-digit royalties. It could also receive additional sales milestones and double-digit royalties if the US option is exercised. *Rayaldee* is awaiting FDA approval. Opko submitted an NDA last year, but received a Complete Response Letter earlier this year. The company resubmitted, the application was accepted, and the drug's PDUFA date is now October 22, 2016.

PFIZER INC.
PIRAMAL ENTERPRISES LTD.

Piramal Enterprises Ltd. is paying **Pfizer Inc.** $16.4mm to acquire four popular brands. (May)

Included in the deal are the nutritional supplement *Ferradol*, *Waterbury's Compound* for building cough and cold immunity, *Neko* medicated soap for body odor and minor skin infections, and *Sloan* muscle pain reliever. The products have all been on the Indian market for over 30 years. Motivation for the buy was Piramal's goal of becoming a top-three player in India's $10.4bn OTC market. (The company is currently in the seventh spot.) As part of the agreement, Piramal also gets trademark rights for *Ferradol* and *Waterbury's Compound* in Bangladesh and Sri Lanka.

PFIZER INC.
WAVE LIFE SCIENCES LTD.

Wave Life Sciences Ltd. and **Pfizer Inc.** signed an option agreement surrounding the development of nucleic acid therapies that can silence the underlying causes of debilitating metabolic diseases. (May)

Wave will move up to five programs from discovery through to the selection of clinical candidates, at which time Pfizer can opt to receive exclusive rights to further develop and commercialize them. Two targets, including Wave's apolipoprotein C-3, have already been determined, and the rest will be decided within eighteen months. Pfizer will pay $10mm in cash up front and make a $30mm equity investment in Wave ($16 per share, a 15% premium). It could also pay up to $871mm in research, development, and commercial milestones should all five projects be successfully developed. Wave is also eligible for tiered sales royalties up to low double-digits (*Strategic Transactions* assumes 1-30%). Wave will use its stereopure drug development platform to create nucleic acid candidates such as mRNA-targeted antisense therapeutics and exon-skipping therapies. In addition, Wave gets rights to Pfizer's hepatic targeting technology for use in hepatic programs outside the collaboration. In return, Pfizer is eligible for development and commercial milestones and tiered royalties.

PRIMA BIOMED LTD.
SYDYS CORP.

Prima BioMed Ltd. granted **Sydys Corp. Inc.** exclusive global rights (excluding Israel) to its *CVac* immuno-oncology program and related assets. (May)

Sydys was previously an advertising firm, but is now being repurposed as a publicly traded biotech whose first projects are Prima's *CVac* compounds and technology. Prima gets a 9.9% equity stake in Sydys and could receive over $293mm in development, regulatory, and sales milestones, plus low-single-digit royalties. Included in the deal are the *CVac* patient-specific dendritic cell-based platform, related assets (manufacturing protocols, clinical data, patents, and know-how), equipment, and inventory. Prima's chief technology officer Dr. Sharron Gargosky will

transition to Sysys as a consulting CSO and Prima's CEO Marc Voigt joins Sydys' board of directors. Sydys will now work on the *CVac* technology and three compounds--one in Phase II for ovarian cancer and two preclinical-stage projects for colorectal and triple negative breast cancers. The licensed rights are global, excluding Israel, where **Neopharm** already has rights under a 2014 deal.

RXI PHARMACEUTICALS CORP. SYNAERION THERAPEUTICS INC.
Thera Neuropharma Inc.

Synaerion Therapeutics Inc.'s CNS affiliate **Thera Neuropharma Inc.** licensed **RXi Pharmaceuticals Corp.**'s *sd-rxRNA* self-delivering RNAi therapeutic platform--which has potential synergies with its own small-molecule regenerative therapy (SMRT) technology--with the goal of developing neurodegenerative disease drugs. (May)

RXi's *sd-rxRNA* platform yields RNAi compounds with drug-like properties--such as strong cellular uptake and stability, a decreased possibility for immune stimulation, and long-lasting intracellular activity--directly built into the compound itself. Thera will have exclusive research, development, manufacturing, regulatory, and commercialization rights to resulting *sd-rxRNA* compounds, which are targeted to silence a specific gene through its mRNA pathway. The deal will first focus on *sd-rxRNA* compounds that target superoxide dismutase 1 (SOD1); protein misfolding in this gene is implicated in amyotrophic lateral sclerosis (ALS) progression, so reduction of misfolded or mutant SOD1 using the *sd-rxRNA* method could potentially offer therapeutic benefits. In animal studies, in which these compounds were administered by intrathecal injection, they demonstrated the ability to enter the cells of the spinal cord and brain. Thera's own SMRT technology, licensed from **Southern Research Institute**, uses a dual-target approach that addresses both targeting underlying factors in ALS pathogenesis as well as the delaying the disease's progression. By directly activating the nuclear factor KB p65 (a subunit of a transcription complex that controls cell signaling in inflammatory and immune responses) and increasing expression of manganese superoxide dismutase (MnSOD; an antioxidant enzyme that maintains cellular redox homeostasis), the SMRT platform eliminates oxidative toxicity, cell dysfunction, and insufficient neurotransmission. Through this deal, Thera hopes to add to its existing CNS pipeline, which is led by preclinical candidates SYN1 for ALS and SYN2 for traumatic brain injury (TBI), as well as other molecules identified for TBI, Alzheimer's disease, and other neurologic disorders.

Financings
/Pharmaceuticals

AVEO PHARMACEUTICALS INC.

Aveo Pharmaceuticals Inc. (also known as Aveo Oncology; developing therapies for cancer and cachexia/muscle wasting) grossed $17mm through the private sale of 17.6mm units (each comprised of one common share and a five-year warrant for one share at $1) at $0.97 apiece, an 8% premium. New Enterprise Associates led and was joined by New Leaf Venture Partners, Perceptive Advisors, and other institutional investors. Piper Jaffray was the placement agent. (May)

Investment Banks/Advisors: Piper Jaffray & Co.

BIOTIME INC.
Asterias Biotherapeutics Inc.

Asterias Biotherapeutics Inc. (regenerative medicine cell therapy; subsidiary of **BioTime Inc.**) netted $18.6mm in a follow-on offering of 5.9mm units (each unit consists of one common share and one-half of one five-year warrant at a $4.37 strike price; includes 742k of over-allotment shares) at $3.40 per unit. The company will put the proceeds toward clinical trials and R&D. Asterias is developing three clinical stage candidates for oncology and neurology. (May)

Investment Banks/Advisors: BTIG LLC; FBR & Co.; Lake Street Capital Markets; Raymond James & Associates Inc. (Asterias Biotherapeutics Inc.)

COHERUS BIOSCIENCES INC.

Coherus BioSciences Inc. (biologics platform focused on biosimilars) netted $60.4mm in a follow-on public offering of 3.5mm common shares at $18. The company will use the proceeds for manufacturing costs and to fund late-stage projects. (May)

Investment Banks/Advisors: Barclays Bank PLC

DELMAR PHARMACEUTICALS INC.

DelMar Pharmaceuticals Inc. (small-molecule cancer therapies) grossed $5.6mm through the private sale of 700k Series B preferred shares at $8. (The shares convert to 7mm common at the option of the investors.) Proceeds will fund continued development on lead project VAL083, a chemotherapy in Phase II for glioblastoma multiforme and in earlier studies for lung and ovarian cancers. (It has already been approved in China for chronic myelogenous leukemia and lung cancer.) DelMar also announced that it is restructuring about 2mm warrants; both the financing and restructuring help position the company, which currently lists on the OTCQX, to list on a senior exchange in the near future. (May)

ERGOMED PLC

Ergomed PLC (clinical research services and drug co-development partnerships) netted £8.4mm ($12.2mm) through the private sale of 6.4mm initial placing shares at £1.40 apiece (a 4% discount). The company will use £1.8mm to fund some of the up-front portion of its concurrently announced acquisition of **Haemostatix Ltd.**, and will put the rest of the proceeds aside for future product development and acquisitions of complementary services businesses. (May)

GENVEC INC.

In an at-the-market registered direct offering, **GenVec Inc.** (vectors for gene and vaccine delivery) netted $4.7mm through the sale of 5.5mm shares at $0.91 (an 8% premium) to institutional investors. For each share of common stock purchased, investors will also receive a six-year warrant to purchase three-quarters of a common share for $0.83. Rodman & Renshaw was the placement agent. (May)

Investment Banks/Advisors: Rodman & Renshaw Capital Group Inc.

INTELLIA THERAPEUTICS INC.

Gene editing firm **Intellia Therapeutics Inc.** netted $115.mm through its initial public offering of 6.9mm common shares (including the overallotment) at $18. The company filed last month and had intended to sell 5mm shares at a range of $16-18. (May)

Investment Banks/Advisors: Credit Suisse First Boston; Jefferies & Co. Inc.; Leerink Partners LLC; Wedbush PacGrow Life Sciences

KNIGHT THERAPEUTICS INC.

Specialty pharma company **Knight Therapeutics Inc.** raised Cdn$200mm ($156mm) in a bought deal financing of 25mm common shares at Cdn$8 ($6.24). The deal was done by an underwriting syndicate led by GMP Securities L.P. (May)

Investment Banks/Advisors: GMP Securities

LOXO ONCOLOGY INC.

Loxo Oncology Inc. (selective treatments for genetically defined cancers) netted $38.9mm through the public sale of 1.9mm common shares (including the overallotment) at $21.50. (May)

Investment Banks/Advisors: Citigroup Inc.; Cowen & Co. LLC; Stifel Nicolaus & Co. Inc.

MANNKIND CORP.

MannKind Corp. (lead product is *Afrezza* for diabetes) netted $47.5mm through the registered direct public offering of 48.5mm shares priced at $1.03 (a 29% discount) to select institutional investors. The company also issued warrants to purchase another 48.5mm shares at an exercise price of $1.50--two-year Series A warrants for 0.75 of a common share and 18-month Series B warrants for 0.25 of a share. Rodman & Renshaw was the placement agent. (May)

Investment Banks/Advisors: HC Wainwright & Co.; Rodman & Renshaw Capital Group Inc.

MERUS BV

Bispecific antibody company **Merus BV** netted $51.2mm in its IPO of 5.5mm common shares at $10 (below the range of $14-16; the original valuation at the midpoint of range would have been $64.5mm based on 4.3mm shares filed). (May)

Investment Banks/Advisors: Citigroup Inc.; Guggenheim Partners LLC; Jefferies & Co. Inc.; Wedbush PacGrow Life Sciences

NEOS THERAPEUTICS INC.

Deerfield Management provided **Neos Therapeutics Inc.** (extended-release oral delivery of CNS drugs) with a $60mm six-year term loan. Payments are interest only (at a rate of at 12.95%) through May 2019, and the principal is to be repaid after that in four equal installments of $15mm annually through May 2022. The company will use proceeds to repay prior outstanding debt and to fund commercialization activities for its ADHD drug *Adzenys* XR-ODT (amphetamine)--a bioequivalent to **Shire**'s *Adderall XR*--approved in January 2016 and now launching in the US. (May)

NEURALSTEM INC.

Through a previously filed shelf registration, **Neuralstem Inc.** (developing CNS drugs using neural stem cell technology) netted $7.52mm in a public offering of 20mm units at $0.40. Each unit consists of a common share and a five-year warrant redeemable for

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one common share at $0.40. In January 2016, the company announced it would focus its resources on the NSI189, its small-molecule stem-cell candidate in Phase II for Major depressive disorder and in preclinical studies for other CNS indications including anxiety, PTSD, schizophrenia, Alzheimer's disease, and TBI. Proceeds from this financing will fund NSI189's further development. (May)

Investment Banks/Advisors: Brean Capital LLC; Roth Capital Partners

ONCOBIOLOGICS INC.

Sabby Healthcare Master Fund bought 833k of biosimilars firm **Oncobiologics Inc.**'s newly public common shares. Oncobiologics completed a 5.8mm share IPO and concurrently issued the 833k shares (at the IPO price of $6) to its existing investor Sabby. Similar to the IPO, the stock was issued as part of units, with each unit consisting of one common share, half of a Series A warrant (each whole warrant is good for one share at $6.60 and expires in nine months), and half of a Series B warrant (each whole warrant is worth one share at $8.50 and expires in two years). (May)

ONCOBIOLOGICS INC.

Oncobiologics Inc. (biosimilars for immune conditions and cancer) netted $32.5mm through its initial public offering of 5.8mm units at $6. Each unit held one share, half of a Series A warrant (each whole warrant is good for one share at $6.60 for nine months) and half of a Series B warrant (each whole Series B warrant is good for one share at $8.50 for two years). The company filed in February and last month announced that it intended to sell 5mm shares at a range of $11-13. (May)

Investment Banks/Advisors: Barclays Bank PLC; Cantor Fitzgerald & Co.; Jefferies & Co. Inc.

ORYZON GENOMICS SA

Recently public **Oryzon Genomics SA** (epigenetics-based cancer and neurodegenerative disease drug development) raised €10.5mm ($12.1mm) in debt through several Spanish commercial banks that provided long-term loans. The proceeds will help advance the company's pipeline; just last month Orzyon announced it had dosed the first subject in a Spanish Phase I trial for ORY2001, an oral lysine-specific demethylase-1/monoamine oxidase B (LSD1-MAOB) dual selective inhibitor for Alzheimer's disease. (May)

PHASERX INC.

One month after filing, **PhaseRx Inc.** (developing treatments for enzyme deficiencies in the liver) closed its initial public offering and netted $17.6mm through the sale of 3.7mm shares at $5 (the low end of the intended $5-7 range). (May)

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

POXEL SA

Diabetes-focused **Poxel SA** announced plans to conduct a registered initial public offering in the US. (May)

PROMETIC LIFE SCIENCES INC.

ProMetic Life Sciences Inc. (biopharma company focusing on bioseparations, plasma therapeutics, and small molecules) raised $Cdn60mm ($46.9mm) in an underwritten bought deal of 19.4mm common shares at $Cdn3.10 ($2.42, an 8% discount to market price). (May)

Investment Banks/Advisors: Canaccord Genuity Inc.; RBC Capital Markets

SPRING BANK PHARMACEUTICALS INC.

Spring Bank Pharmaceuticals Inc. (infectious diseases) netted $10.2mm in its initial public offering of 920k shares at $12. The company originally filed to go public in January 2016, and two months later it announced plans to offer 2.86mm common shares between $13-15 each. In April it postponed the offering but later that month re-filed stating plans to sell 1.15mm common shares priced between $12-14. (May)

Investment Banks/Advisors: Dawson James Securities Inc.

SYNERGY PHARMACEUTICALS INC.

Gastrointestinal therapeutics developer **Synergy Pharmaceuticals Inc.** netted $89.7mm through the registered direct offering of 29.9mm common shares priced at $3 (a 12% discount) to certain institutional investors. The company will use the funds to commercialize plecanatide for chronic idiopathic constipation, and develop plecanatide for irritable bowel syndrome (Phase III) and dolcanatide for opioid-induced constipation (Phase II) and ulcerative colitis (Phase I). (May)

VISTAGEN THERAPEUTICS INC.

VistaGen Therapeutics (CNS focused biopharma) netted $9.1mm in a follow-on of 2.4mm common shares and five year warrants (strike price of $5.30) to purchase 2.4mm common shares at a combined price of $4.25. VistaGen previously traded on the OTC market and began trading on the Nasdaq on May 11 under symbol VTGN. The company will use the proceeds for R&D including Phase II development of oral prodrug AV101 for major depressive disorder. (May)

Investment Banks/Advisors: Chardan Capital Markets

EQUIPMENT & SUPPLIES

Financings
/Research, Analytical Equipment & Supplies

REPLIGEN CORP.

Repligen Corp (bioprocessing for biologic drugs) raised $100mm in 2.125% redeemable (prior to June 5, 2019) convertible senior notes due 2021. Interest is payable semi-annually in arrears (each June 1 and December 1) beginning on December 1, 2016. The conversion rate is 31.1813 shares per $1,000 principal of the notes representing a conversion price of $32.07 per share. Jefferies served as book-runner with Janney Montgomery Scott and Craig-Hallum as co-managers. (May)

Investment Banks/Advisors: Craig-Hallum Inc.; J. Wood Capital Advisors; Janney Montgomery Scott Inc.; Jefferies & Co. Inc.; Perella Weinberg Partners

EXECUTIVESUMMARY

SUMMARY OF ARTICLE FROM PAGE 8

In Silico Drug Design: Finally Ready For Prime Time?

BY MICHAEL GOODMAN

After decades of disappointment, improvements in computing power are allowing researchers to generate virtual compound libraries and apply the insights of quantum mechanics to the modeling of ligand/receptor interactions. The benefits include novel chemical matter, higher affinity hits, and lower-cost drug design than was possible using high-throughput screening. Observers see the new physics-based computational chemistry as potentially the most powerful of several new technologies in the discovery toolbox. Several companies have entered the field, including Nimbus Therapeutics and Verseon. Each has a portfolio of early-stage compounds, but different approaches to how they access their platform.

SUMMARY OF ARTICLE FROM PAGE 14

Guided Therapy Systems Keeps Options Open On Tissue Regen Device

BY ASHLEY YEO

Disruptive technologies do not come along very often but Guided Therapy Systems' handheld ITU-based imaging and tissue repair device is one that appears to fit the bill. The first groups of US clinical trials are well underway ahead of regulatory filing later this year, but the US will not be the global launch market. GTS' CEO Michael Slayton, PhD, has a firm idea of who would be the ideal partner to go to the market with, and has the simple target of making this happen. The company has selected two prevalent musculoskeletal conditions to start with, but there are many that could follow, including drug delivery, for a product that is so far without a direct competitor.

SUMMARY OF ARTICLE FROM PAGE 18

To Outperform In Pharma, Go Deep – Not Broad

BY NILS BEHNKE, MICHAEL RETTERATH AND TIM VAN BIESEN

The world's most successful pharma companies aren't winning on the basis of absolute scale; they succeed instead thanks to their leadership in a few clearly defined product categories. Category leaders employ a common set of capabilities to develop products that serve a defined set of end-users and often exist within a common competitive class. The products are bought using a common purchasing process managed by common stakeholders. The key to understanding category leadership is to view categories through the eyes of the customer – patients, prescribing physicians and payers. Current industry trends play to the strengths of category leaders. Payers and providers are demanding evidence of efficacy, creating new hurdles for drug approval, and category leaders are the best positioned to deliver compelling evidence. The rise of drugs prescribed by specialists instead of primary care physicians also favors pharma companies with deep networks and strong relationships within the specialty.

SUMMARY OF ARTICLE FROM PAGE 24

Medtech Uptake Drive Shows France's European Leadership Aims

BY CORINNE LEBOURGEOIS

France is a major medical device market globally, and in Europe is beaten only by Germany in terms of size, but medtech manufacturers often find it hard to fully exploit the potential opportunity. To tackle the root causes of this, a high-level group of ministers has agreed to put in place a series of new laws in a bid to create the conditions that encourage device manufacturers to look favorably on France as an innovation launch market. Once the simplified market access processes are in place, companies in the market will need to respond by adapting and providing the right data for registration purposes.

SUMMARY OF ARTICLE FROM PAGE 34

Medtechs Should Not Play Dodgeball With Sales Force Effectiveness

BY ASHLEY YEO

The gap between clinical and economic stakeholders is narrowing quickly, and in some cases the traditional hierarchy has been turned on its head. So when medtechs look at their US customer decision-makers, they now see the need to refine their approach to commercial dealings with IDNs, ACOs and hospital purchasers. Bringing sales force effectiveness (SFE) measures into the equation at the same time can lead to consistent annual sales gains for a relatively small investment. A new report by ZS Associates lays out where companies can maximize ROI by addressing elements such as territory design and sizing, and sales processes and account planning. Sales models are now also extending to a "rep-less" system, and some medtechs are experimenting with telesales and web-based or other technology-based methods. The changes are happening now and the smart companies are already adopting new tactics.