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THE BUSINESS & MEDICINE REPORT

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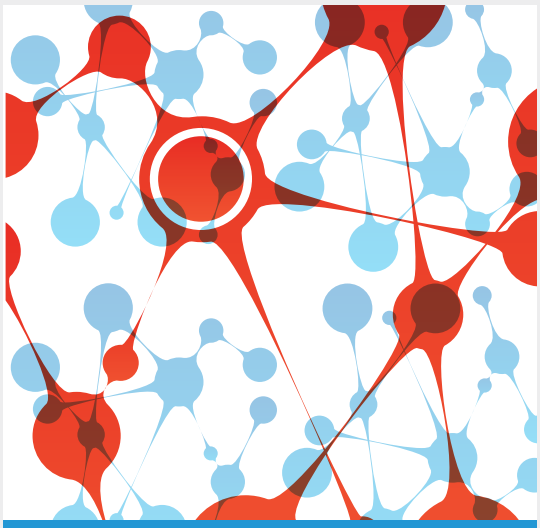

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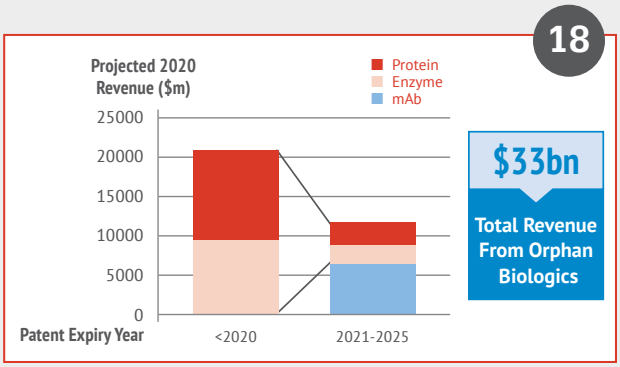

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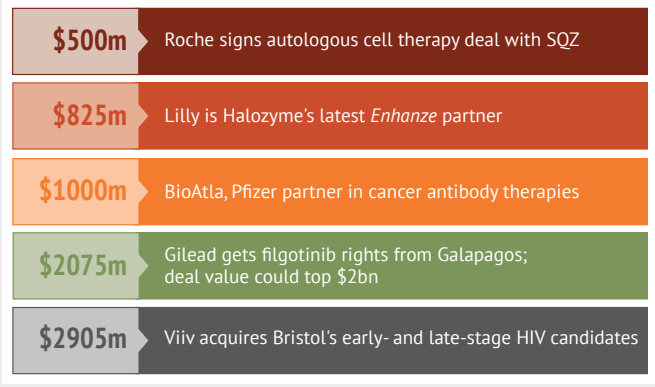

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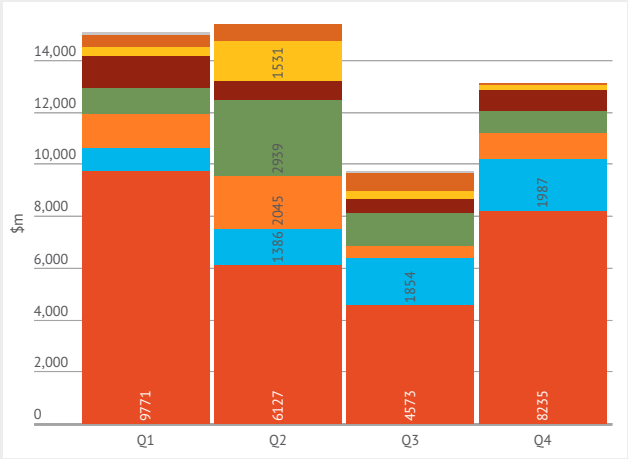
Top Alliances In December 2015



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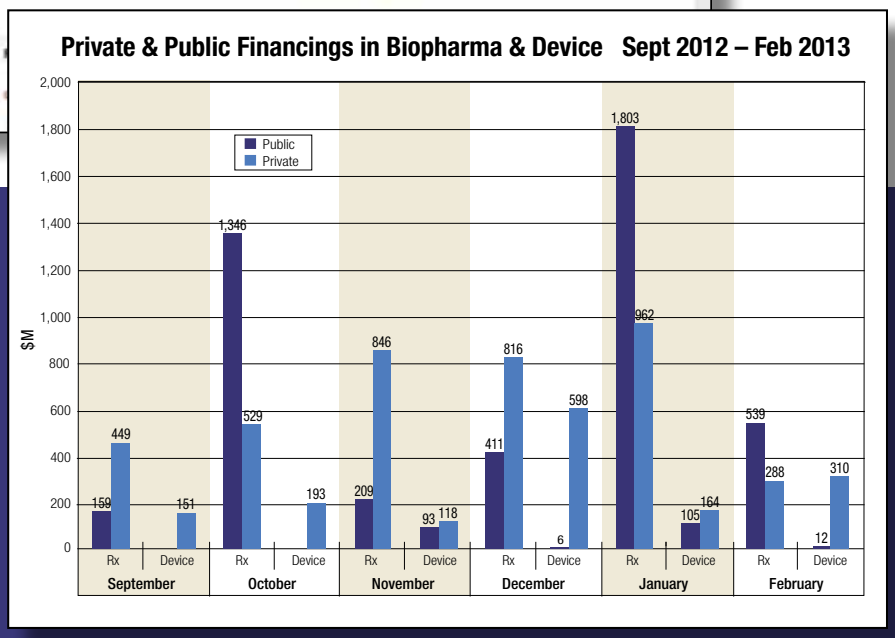

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Digital Health

BOSTON SCIENTIFIC THINKS BIG IN HF PROVIDER RISK-SHARE PLAN

Boston Scientific Corp. is not one of the large caps that risks being left behind as the health care sector transitions increasingly to a value-based model. That much is clear from the recent expansion of its involvement in health care delivery solutions engagement.

In late January, the Marlborough, MA, group announced a new joint project with **Accenture PLC** in the care pathway management of post-discharge heart failure (HF) patients. The project, which has global potential, targets the total cost-of-care management of a patient group that accounts for an average of 2% of health care spending and currently requires an 11-day inpatient stay (European average figures).

Boston and long-term collaborator Accenture jointly designed the plan which started in a pilot phase at Sweden's **Karolinska University Hospital** (one of two customers to develop the program) some 18 months ago. The two companies describe it as cloud-based, data-driven digital health solution for hospitals that will both improve patient outcomes and reduce the costs of caring for chronic cardiovascular (CV) disease patients. Heart failure, the biggest CV burden for most health care systems, was chosen as the natural place to start, but other CV diseases could be added later.

The system combines Boston's custom-tailored *ADVANTICS* solutions brand and Accenture's analytics-based *Intelligent Patient Platform* together in the *Care Pathway Transformation* solution. This service will flag up patient population health patterns and identify opportunities to improve the treatment of HF patients from hospital stay through post-discharge care and in-home support. In a statement announcing the deal, Boston Scientific president and CEO Michael Mahoney said that the resulting digital health platform will help providers standardize care, reduce overall length of stay and lower readmission rates.

Mark Toland, Boston Scientific's senior vice-president for corporate sales (the business unit responsible for the ADVANTICS brand), says, "People may wonder why we're broadening our reach beyond the four walls of the hospital. It's because as the world moves from volume- to value-based models, the value equation is defined by longer-term outcomes other than just by acute care procedural events."

Bundled payments are already a fact in US orthopedics, and the likelihood is that bundling of CV procedures will become a reality in the coming two to five years. That means that companies will be taking some responsibility – sharing the risk – for the patients after the patient leaves the hospital. Toland says, "That's the direction we are heading in – going beyond just the event in the hospital. At Boston, we think we can play a role in ensuring that the outcomes are maximized and optimized in that value-based world."

The Care Pathway Transformation solution will first involve pathway analytics on how efficiently HF patients move through the hospital system. It will also cover elements of their care management, and their engagement, education and monitoring, both during hospitalization and after discharge.

For Toland, the educational aspects in the discharge program are the biggest contributor to successful system change. "Boston is building in a really strong educational element – for both patients and health care providers. Ensuring that the education transfers to the patient in the 30-60-90 day window after they leave the hospital is the crux of making things work well," he says. Post-care follow-up is another vital element.

The process all starts with the data filtering and data mining done by Accenture's analytics. This input, accessing patient data from multiple sources such as payer information, patient records, behavioral information, and clinical research information, allows the data to be standardized and for pattern identification. This then leads to an output on the relevant patient populations and insight on how to apply health care management efforts better. Toland observes, "We've found that health care systems are simply swamped with data and don't know what to do with it."

Another important element is the differing national health care data regulations and laws on patient confidentiality. For instance, many European countries do not let the data leave the country. "That's the benefit of a having a worldwide partner like Accenture, which has the ability to keep the data in-country," says Toland. He feels that some companies in this space or aspiring to be in it may have underestimated issues surrounding the local laws and regulations in this respect.

The Care Pathway Transformation solution is not predicated on any particular Boston Scientific technology, but is rather is a move toward developing service-based solutions surrounding disease states and segments. Boston explains that its devices go into a relatively small percentage of HF patients, who it says actually may not be that sick but are likely costing the health care system a lot of money. "For us, having Accenture as a partner would allow us to capture the entire HF population," says Toland.

Accenture Life Sciences senior managing director Anne O'Riordan sees the new project as combining Boston's "great capabilities that reach into the hospital networks" with Accenture's "pivot to the patient" concept that seeks to drive forward patient outcomes.

She says, "We talked to Boston about how we could make this count, and then set up the pilot studies to see how we could really add value to patients." The two Scandinavian pilots, done in late 2014-early 2015 at the Tampere Heart Hospital in Finland as well as at Karolinska, used analytics to assess HF patients who had been treated and had left the hospital network. They then looked at readmission rates over a period of time and identified quite a number of people coming back in at a very high cost to the system.

The analytics help identify those people at the highest risk of re-admittance, while the outreach program is designed to help patients to help themselves and ensure they are following their care routine. The system, which also allows for predictive modelling, involves a series of inventions – both human and technology-based – is supported by call centers, home compliance monitoring, coaching centres, and apps.

Boston, which put the whole package together, sources the hospitals, works with

them and also provides additional support for the patients, while Accenture provides the technology and is the "nuts and bold behind the scenes". The discharged patients who may be in need of additional help are identified and are provided with care management outreach, which is not a new idea in itself, however being paid on outcomes *is* new.

The revenue model is a per-patient model – the more patients on the system, the more revenue is generated. The project partners are rewarded on patient outcomes and re-admittance rates.

Being paid by outcomes has become a key talking point in the last 18-24 months. In the pharma sector, Novartis has somewhat set the tone with outcomes and performance-based arrangements, and the general consensus among health care CEOs seems to be that this is the way the market is moving.

The Boston/Accenture HF service will be launched first in Sweden, Finland and the UK. The US and rest of Europe will follow. The Scandinavian hospitals were keen to participate. "We want to prove it out and gather more data, but we anticipate that it will take off very fast," says O'Riordan. As to the UK, its health system can be quite advanced in its thinking and it has a very good network of support in the home environment, she adds.

Toland says the service should be ready for first commercialization in H2 of 2016. The US will follow at the end of 2016. The US has both population-based systems and many fee-for-service models still. "We want to test it in both system types with two types of pilot," says Toland, adding that Boston is close to signing up on pilots in the US.

For Boston, the project could evolve relatively quickly from HF into atrial fibrillation, ischemia, vascular diseases and even be used as an approach in cancer care. Having Accenture as a partner means being able to scale-up quickly, and potentially move into countries like China, Japan and Brazil. So far, Boston has deal-exclusivity in CV diseases only.

The partners see it both as an exciting venture and the right thing to do. It fits well with the direction Boston has taken in the solutions space. The project with Accenture is one of five that the company is involved in. Toland says that Boston has solutions engagement teams on the ground in almost every country in Europe at present, and is in negotiations on multiple projects such as cath lab management and improving turn-around-time in CV clinics.

Boston describes the competitors in this space as regional and typically without the breadth or the size to have global reach. Toland considers that "there are not too many competitors that would have the globalization element that Boston and Accenture have."

Boston's network, knowledge and ability to go deep into health care systems make it an attractive partner for Accenture to work with, in Toland's view. "This is one of the biggest challenges for the Googles and others – they just don't have the knowledge base and the footprint to deploy elements in health care systems rapidly." On the other hand, connectivity with a medical device manufacturer makes logical sense, especial one with a track record of solutions and investments that include, most recently, the August 2015 deal to become the exclusive worldwide sales and marketing representative for **Preventice Inc.** for cardiology-related diagnostic and monitoring offerings.

Toland's view is that we are reaching the point of no return. He says, "We are now at a critical juncture as to how we improve outcomes and our ability to treat patients in in a cost structure that is significantly less than what we have today – and we've got to be able to do it with higher volumes."

"It's a problem that requires the cooperation of payers, providers, physicians, medical device companies and patients, and organizations like Accenture, to all come together to fix this problem," he adds. "If not, we'll be operating in silos and not actually fixing the problem. We are being challenged to do better and at a lower cost, and we need to look at the total cost of the care of the patient – not just the device cost in a practical setting. The transformation from a volume-to-a-value-world is happening right in front of our eyes."

A#2016800036

By Ashley Yeo

Diagnostics

EUROPEAN IVD COMPANIES SEE WORRYING TREND IN MARKET ACCESS BARRIERS

The European Union Trilogue meetings – designed to resolve differences of approach between the main EU institutions on the proposed Medical Device Regulations (MDR) and In Vitro Diagnostics Regulations (IVDR) – are now running into a second (originally unscheduled) series. But the medtech industry is still concerned that inappropriately rigid and potentially damaging rules will somehow emerge.

In January, *IN VIVO* voiced the views of Eucomed (the medical devices branch of Medtech Europe), whose chief executive fears for the European medical devices sector ahead of final adoption and implementation of the forthcoming twin Regulations. (*See "Uncertain Reg Climate Could Turn Medtech Investors Off Europe"* — IN VIVO, *January 2016*.) Although the EU IVD industry has a different focus of interests as the debate progresses on and around this new set of five Trilogues (*see "IVD Companies Brace For EU Regulatory Changes"* — IN VIVO, *October 2015*), EDMA, the IVDs branch of MedTech Europe, shares the headline concerns of its medtech counterpart.

Interviewed during the 2015 *European MedTech Forum*, held in Brussels, Belgium in December, EDMA representative Christian Parry (senior vice-president of public affairs at private French hemostasis products company **Diagnostica Stago**) said that the new EU In Vitro Diagnostics Regulation (IVDR) represents a big change for the industry and will bring many constraints and additional expenses with it.

EDMA is at odds with the Council of the European Union's position on the IVDR, and believes the proposal as it stands would endanger SMEs in particular.

ACCESS PROBLEMS ALL ROUND

But it is not the only market where access is a cause of concern for IVD companies. Regulatory system changes and new policy rules in the EU's large easterly neighbor, Russia, are in fact more immediately pressing, especially for companies based outside Russia and other members of the new Eurasian Economic Union that want to take part in Russian government tenders.

Parry voiced the industry's particular concerns over Russia's Resolution 102, of February 5 2015, "Establishing Market Entry Restrictions for Individual Types of Medical Devices Originating from Foreign Countries in the Context of Procurement for State and Municipal Needs." The document, signed by Russian Prime Minister Dmitry Medvedev, lists the individual types of medical devices originating from foreign countries that are subject to import restrictions in Russia. Over 60 categories of medtech products were immediately affected.

It also states that non-Russian/EAEU companies are excluded from public tenders if two local suppliers apply under a call for procurement tenders. The basis for the procurement restrictions in the Resolution is a CIS instrument (Rules for Determining the Country of Origin of Goods in the Commonwealth of Independent States, of November 20, 2009).

There is a sense that Resolution 102 is not just a reaction to the current sanctions being imposed on Russia. In fact, the Russian authorities say they have been pressing to strengthen the local industrial base for many years. However, the import medtech restrictions have actually been stepped up since the introduction of the (with another 100 or so products listed in mid-2015), with the result that there is no longer a single set of criteria applying across the local medtech industry. Many see the "Medvedev law" as harmful to foreign companies and as dissuading potential investment. (A sister resolution on pharma procurement was signed in early December.)

But if Resolution 102 itself is a major cause for concern among non-Russian IVDs companies, then the lack of detail on its scope is equally frustrating. "We don't know what they want," said Parry. "Companies that want to compete in public tenders need to manufacture in Russia, but what level are they talking about – secondary packaging, or full manufacturing?"

Given the lack of clarity, many companies are now going to the market via distributors. IMEDA, the Moscow-based International Medical Device Manufacturers Association (*see "Russia's Medtech Revolution"* — IN VIVO, *April 2014*), says that the text of the Resolution is changing constantly, and still there remain many unanswered questions. But on the surface, it means that foreign companies can be "out of the game," said Parry.

The question that IVD companies are now increasingly asking is: are emerging markets – even those the size of Russia – big enough for the complexity of small-scale products that IVD manufacturers often manufacture? Parry observed that countries that used to be "open", because their markets were quite small or had no local production, have now begun to erect more barriers to foreign companies, be it in the form of special taxes or special systems for public tenders.

For example, Brazil has put in place a system of points which will favor local companies in tender applications. South Korean regulators are pressing to sit in on companies' R&D meetings as part of the regulatory process. Parry's view is that these kinds of restrictions do not sit well with free trade concepts and are often seen as a way for regulators to ask more and more of companies about strategic technical information, manufacturing processes and R&D plans.

"It's a balancing act. Some regulators may demand to retain certain confidential information, refusal to supply which would see the product fail to gain registration." Others might change the rules at will, so that "what is true today is not true tomorrow." Elsewhere, companies may be asked to re-apply and submit even more information, including documents on areas considered by the companies themselves as proprietary.

"It's a dilemma and a major and increasing problem. It makes us as an industry consider how far we are prepared to go."

In hindsight, it was fairly common some 20 year ago to cast Japan as a highly protectionist market, where applicants were requested to do a lot of additional admin work before being admitted to the medtech market. Today, Japan is viewed more or less in the same bracket as the EU or US, but most IVD innovators will see two decades as too long to wait.

Changes that will affect broader numbers of global IVD players companies – and more deeply – are currently being debated by the EU institutions, whose current aim is to have an agreed IVDR text adopted in H2 of 2016. If that happens, it should be implemented by 2021, ie, within a five-year transition period. The length of the transition has not yet been decided – that is still up for debate at Trilogue level – but it is the hope of the collective EU IVDs industry that it will be accorded more than the three years being allowed for medical devices under the MDR.

"We are pressing for a five-year transition. There has been no revision of the EU IVD Directive, 98/79 EC, for quite some time. That is not the case with the medical devices industry, which has undergone more updates," said Parry. This – basic – point has not yet been decided, but the fact that the decision makers understand that notified bodies, as well as the companies, will be under time pressures, prompts EDMA to hope that the longer transition option will be favored.

But compliance with the IVDR, in whatever form it finally emerges, will require much work and heavy costs for all IVD companies. Parry said industry disagrees fundamentally with the Council text proposals that tend to prioritize clinical studies, and rely less on published data and literature. "The cost for industry would be very high, and we hope that the authorities will reasonably understand that this does not bring any extra safety to the patient."

On the contrary, it would merely jeopardize investment by companies, force them to abandon projects, and even put some SMEs at risk. Any new products that are developed will take longer to reach patients.

According to Parry, the cost in France alone – Europe's second leading IVD market – would be an additional cost €900 million ($977 million) over five years, on top of the €160 million that the European Commission originally estimated. "The cost will be tremendous – and be borne by just 25 French companies," he said. "It is out of proportion compared to the benefit it would bring in terms of extra security."

A study by Germany's IVDs industry association, the VDGH, puts the additional cost in Germany at up to €1.19 billion over five years. "For a small industry like ours, it does not make sense, and you have to wonder if the decision makers have thought of the consequences," said Parry.

INNOVATION IS MORE THAN JUST PRODUCT R&D

If the worst scenario came to pass, capacity for both investment in R&D and production would be decreased in the EU, he added. It is often forgotten that "innovation" is not just in product R&D, but also in production. Companies need to ensure that factories are not becoming outdated and must ensure that they maintain high-quality production, which calls for permanent investment programs.

National regulators have consistently asked more of companies over the past 20 years, but industry has reacted well, often adapting ahead of new demands to ensure that they are bringing the best products to the market and to patients. "All this comes with a cost, and the money we have to put into regulation reduces our capacity to innovate in R&D and in production. That's very clear for me," said the EDMA executive.

While companies understand the goals and the risks involved, Parry has been surprised – shocked even – that some of the MEPs who will eventually vote on the text of such huge significance to the economy and to the future companies have but a scant idea of what the industry is or what IVD products are for. Worse still, some have not even shown interest. "We saw this out at meetings. It's not far short of a nightmare," said Parry.

"We are under the impression that the main goal of some of them is to rule out the risk of health scandals," he said. "They think that the more they load onto industry, the safer it will be," he added, clearly vexed at the notion. "They are wrong!"

For Parry, it is a major disappointment that an industry that potentially brings so much benefit is not accorded the status it merits. "We are all patients at one time or another in our lives, and it is often quoted that 70% medical clinical decisions are based on the results of at least one clinical bioassay."

Having said that, the clinical biology costs are relatively small, while the benefits – early diagnosis and good treatment follow-up – are potentially immense for patients and national economies alike. "It's a classic win-win situation," said Parry, borrowing an expression much loved of politicians, but evidently little understood by some of their number, especially in matters of national and regional IVD regulation and market access.

A#2016800026

By Ashley Yeo

DEALS OF THE MONTH

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

TOP ALLIANCE:
MANNKIND LICENSES TECHNOSPHERE TO RECEPTOR

Stealthy start-up **Receptor Life Sciences Inc.** has licensed **MannKind Corp.**'s *Technosphere* dry powder delivery platform to develop inhaled formulations of undisclosed Receptor candidates. The companies will work together on clinical development, with MannKind in charge of initial formulation studies and Receptor handling development costs as well as manufacturing and commercialization. MannKind, which is strapped for cash following the demise of its **Sanofi** *Afrezza* marketing deal, could receive up to $102.25 million in development and commercialization milestones, plus royalties.

TOP M&A:
ROCHE BUYS TENSHA THERAPEUTICS

Roche is spending $115 million up-front and $420 million in potential milestones for **Tensha Therapeutics Inc.**, a Cambridge-based biotech backed by HealthCare Ventures and founded by Dana Farber scientist James Bradner, MD, now the president of the **Novartis Institutes for BioMedical Research Inc.** The appeal for Roche is Tensha's lead drug candidate, TEN-010, currently in a Phase Ib trial, as well as its technology platform, which disrupts epigenetic target bromodomain and extra terminal domain proteins to create cancer treatments. **Eli Lilly & Co.** had an option to acquire the start-up via its partnership with HCV, but decided not to pursue it.

TOP FINANCING:
GRAIL SPINS OUT OF ILLUMINA WITH $100 MILLION

Grail Bio raised a $100 million-plus Series A round from Arch Venture Partners, Bill Gates, Bezos Expeditions, Sutter Hill Ventures and **Illumina Inc.**, which is the majority owner of its spin-out. Grail will develop technology to screen asymptomatic patients for cancer through the detection of circulating tumor DNA. Utilizing Illumina technology, Grail's tests may enable physicians to detect cancer at its earliest stages. Commercialization of its first tests, for lung and breast cancers, could come as early as 2019.

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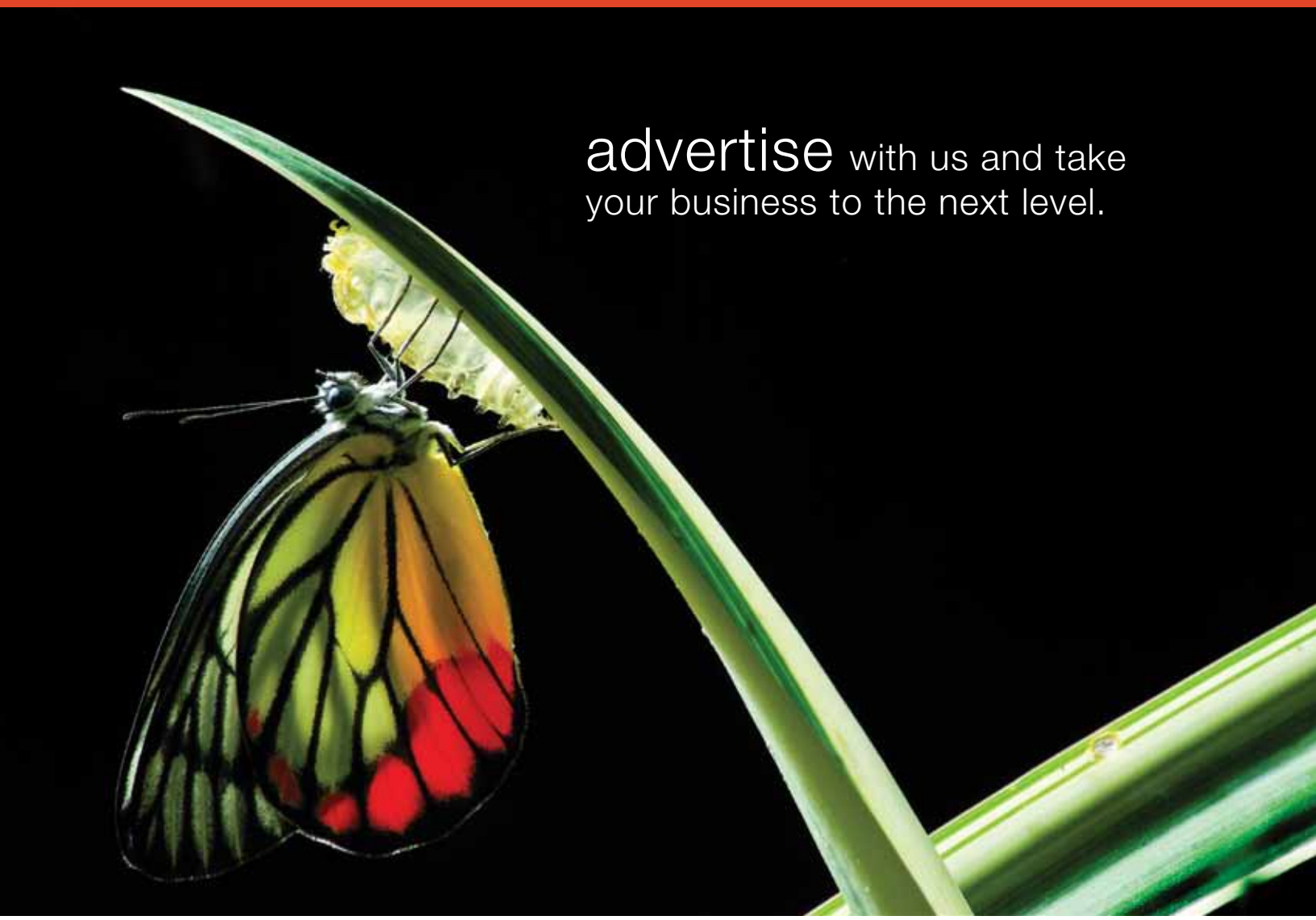

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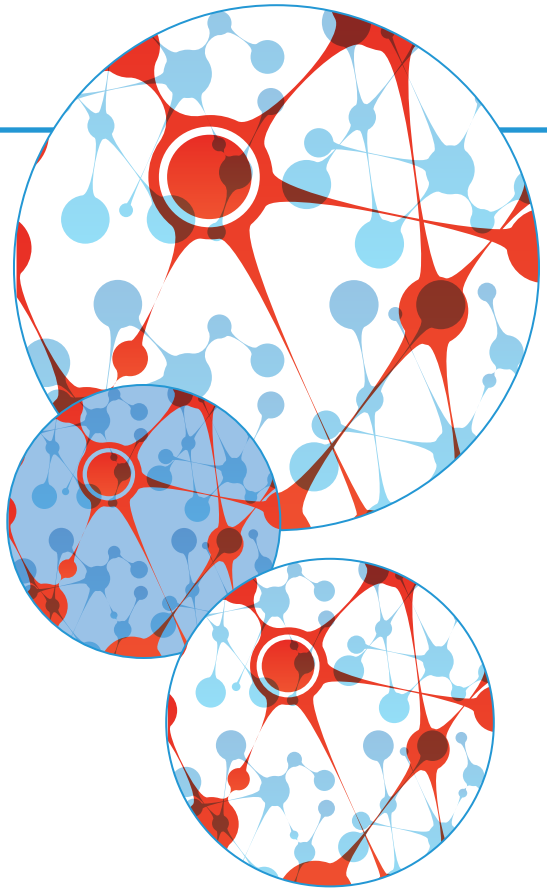

Orphans Should Live Alone

For larger organizations with interests in rare diseases, we believe it is necessary to maintain a separation from the rest of the company in order to keep the culture needed for successful product commercialization. Easier said than done.

BY ALAIN J. GILBERT, ANNE-SOPHIE DEMANGE AND MARK RATNER

- The organization and culture of a rare disease specialist company or program is distinct from that of a traditional pharma or biotech. Commercial success is driven by a patient-centric model focused on access and interactions with KOLs and less on selling features and benefits.
- An ability to connect with rare disease patient communities and physicians at the level of senior management is paramount, giving an advantage to companies of small size: it is the kind of representation a large company cannot afford for a relatively small product line.
- With size and diversity of markets often comes more rigidity and standardization of practices. Many more processes are in place at large firms and decision-making is often dominated by a committee structure. That makes alignment with a successful rare disease model difficult.
- It may be easier for larger firms to acquire ultra-rare disease firms after they have become successful, as Sanofi did with Genzyme – initially leaving it alone to preserve the benefit of the asset.
- We therefore believe orphan drug franchises should live alone – at least until they reach a level of maturity to withstand structural organizational pressures.

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Two recent events have brought into relief important considerations around the business models for developing and selling drugs for rare (ultra-orphan) diseases. **Shire PLC**'s latest acquisition, of **Baxalta Inc.**, will create a specialist rare disease firm of unprecedented size, raising the question of whether the effectiveness of individual programs that by definition are targeted to very small patient populations can maintain their identity and integrity within the organizational structure. **Sanofi**'s decision to more fully integrate its **Genzyme Corp.** into the larger organization as the **Sanofi Genzyme** specialty care business unit similarly calls into question whether the move will remove some of the independence that is widely acknowledged as being critical to the successful development of rare disease drugs. Sanofi completed its acquisition of Genzyme in February 2011.

CULTURE CLASHES TO CONSIDER

Large, established pharmaceutical firms have shown interest in drugs for ultra-orphan diseases, either through R&D or licensing/acquisition. Shire and Sanofi can argue a degree of success. Much of the Shire organization has been centered on ultra-orphan markets since its takeover of **Transkaryotic Therapies Inc.** (TKT) in 2005, which brought it into the lysosomal storage disease therapy area, where it still competes with Sanofi Genzyme. Among big pharmas, **Pfizer Inc.** and **GlaxoSmithKline PLC** have initiated rare disease programs but do not have much to show for them today. Pure-play rare disease specialists including **Biomarin Pharmaceutical Inc.**, **Alexion Pharmaceuticals Inc.** and **Ultragenyx Pharmaceutical Inc.** have emerged, using a combination of internal R&D and in-licensing/M&A to build a portfolio. We believe the distinct culture and development structure needed for a successful rare disease business, especially when weighed against the ability of such assets to drive topline growth in a large firm, argues against conglomerating them inside a traditionally structured pharmaceutical business.

There are general differences between small biotechs and traditional established pharmaceutical firms. In a small company, management is usually dedicated to the disease space it is serving – a therapy area often represents most of or the entire business, which means having to worry less about maximizing ROI across a variety of opportunities in a portfolio. Smaller companies are often bolder, acting with greater flexibility and risk tolerance.

The contrast between large and small is sharpest in the rare disease space, where com-

mercial success is driven by a business model focused on patient access, building relationships with key opinion leaders (KOLs) and establishing new clinical development, regulatory and market access pathways – and less on selling features and benefits of a drug.

Having a patient-focused process is the only way to sell drugs for rare diseases effectively: the nature of these diseases and the unknowns around diagnosing and treating them mandate finding the patient population that needs treatment, educating them to what a drug does, getting them on therapy quickly and helping with country to country reimbursement – a very different model, for example, than having developed an interesting blood pressure medication and selling it into a huge space with millions of patients using a large sales force where the key factors are marketing and competition. Success in a small disease space is also oriented around a physician to physician relationship – making sure KOLs know you, that clinical investigators and physicians trust the company and providing a high level of education. The interaction is more collegial, rather than having a sales and marketing group target physicians.

It is a white glove approach to the patients that includes working with advocacy groups, understanding the natural history of a disease, making sure the organization works closely with the advocacy community to educate it about the product, helping to identify patients and recruit them for trials, and making sure that they understand the purpose of a trial. Physician-sponsored studies to learn about a drug in the post-approval setting are similarly more important than in other areas. The entire process builds a company's credibility as an entity trying to advance the science and not just sell a drug. So physicians become more interested: they participate actively in the clinical development plan, best represent patients' needs and are more loyal to the drug developer.

The approach is also more integrated than what you see in a large company. A big pharma will have thousands of researchers, so from the company perspective, there is often a different level of need to seek out academics for their expertise. In a small company, however, such outreach is needed for expertise and access to patients. "The exchange helps a company get a better sense of what patients are looking for," says John Maraganore, PhD, CEO of **Alnylam Pharmaceuticals Inc.**, whose lead program is in the rare genetic disorder transthyretin-mediated amyloidosis (ATTR). "It is a high impact part of developing drugs in this space."

The patient voice is a more important part of the regulatory process than ever, making the model even more partnership driven. With FDASIA, the FDA safety and drug development program introduced in 2012, a company has to be even more certain it has strong advocates that can help discuss the need for a rare disease drug to FDA. Most small rare disease companies could not do this alone: they need the support of patient advocacy groups and to have physicians and researchers in the field working with them to be able to bring new technologies to market. The interaction is driven more by relationships than by common commercial practices. (*See sidebar, "DMD In The Spotlight."*)

Building those relationships can be a badge of distinction: a large part of being patient centric is having direct interaction with patient communities, particularly at meetings. "It's one example of how impactful small size and senior representation can be on how well the company can do," Maraganore says. A large pharma is not likely to send such a senior contingent.

"We invite patients to come in and talk about their experience and make that available to all employees, who come with great interest to see how what they are working on can make a difference in people's lives," Maraganore says. "In our scale and size it is something very distinct and part of our culture, which is harder to achieve in a larger company."

Unlike some others in the rare disease space, Alnylam also has programs targeting broader indications in metabolic and infectious diseases. "The risk for us is as we get bigger and expand our portfolio beyond the rare disease space, as we grow in size, maintaining a patient-centric culture will become harder," Maraganore says. "As you grow, you have to introduce processes to scale. But there are good examples of companies that have done it well." For this reason, Alnylam was comfortable partnering with Sanofi Genzyme on its ATTR program, a deal later expanded to include other genetic diseases.

Several issues can stand in the way of a larger organization's ability to execute with the flexibility and creativity that mark successful rare disease franchises. With size come more rigid and standardized practices and a decision-making process often dominated by a committee structure. In a small company, nobody is there to bless decisions: executives have to be comfortable making decisions very quickly based on the information at hand and enjoy the larger responsible role they have to take on. In many ways, a rare disease company is doing things no one has done before, especially getting a first-in-class drug approved in a new indication. There is no pathway, no roadmap.

Legal corporate compliance policies at big pharma instituted across the board, often as a result of issues raised by off-label marketing, may not allow for direct interaction with patients at meetings and other settings. It is hard to imagine a company that feels that as a matter of corporate risk they cannot closely interact with patients or patient groups as part of how they do drug development aligning with a patient-centric mentality.

When orphan drugs and broader specialty drugs have been combined, "at some point, the way of working was totally transformed," says Anny Bedard, former vice president, Asia Pacific for Shire and now an advisor to early-stage companies developing drugs for orphan diseases. The metrics are simpler and more direct in a rare disease business: the focus is squarely on what is needed to make sure patients get the drug they need when they need it. "It's a different conversation that occurs," she says. "My experience has been that it works better when this culture is kept isolated and not diluted into another bigger, broader culture."

When creating a rare disease business unit within a large established pharmaceutical company, the functions that would be supporting that business unit need to have a biotechnology mind-set. "I spent 25 years in big pharma and when I moved to the rare disease space I had to relearn everything I knew, especially when it comes to clinical development, market characterization and access and the interaction with patients," says Francois Nader, MD, former CEO of

DMD IN THE SPOTLIGHT

The FDA draft guidance for Duchenne's muscular dystrophy drug development, which advocacy groups tried to push through to make sure the agency understood the complications of getting some of these drugs approved, is a good example of stakeholder interaction in the rare disease space. FDA asked Parent Project Muscular Dystrophy to start putting a draft together. A number of people, not only patient advocates but experts in dystrophin, imaging, clinical outcome measures and natural history, and then a variety of companies, including **Sarepta Therapeutics Inc.**, Prosensa Therapeutics (now part of **BioMarin Pharmaceutical Inc.**), **Shire PLC** and **PTC Therapeutics Inc.**, were involved. Having academics and multiple companies working in a precompetitive space full of development unknowns is something that is not typical for a large company to do.

As part of the process, Sarepta allowed **Summit Therapeutics PLC**, a company working on utrophin regulation, to use its protocol for collecting muscle samples. So much is unknown in the rare disease space that companies will work together to try to come up with a new way of looking at a disease and potentially new endpoints, to help ensure that their drugs will be reviewed and approved quickly. They are trying to standardize the way they do things and in some ways standardize the way they do the same tests. The DMD patient community pointed out that companies will even conduct the six-minute walk test slightly differently.

Despite the guidance, FDA rejected Biomarin's application, canceled Sarepta's advisory committee meeting and delayed completion of its review of Sarepta's drug until May 2016. (*See "BioMarin's Drisapersen 'Compete Response' Shows FDA Flexibility Still Limited"* — "The Pink Sheet" DAILY, *January 14, 2016 and "Sarepta's Duchenne Treatment Likely Making Progress At FDA"* — "The Pink Sheet" DAILY, *February 8, 2016*.) Both companies are forging ahead, but in light of these developments, it will be interesting to see how motivated **Pfizer Inc.** and **GlaxoSmithKline PLC** will be to continue their DMD drug development plans.

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NPS Pharmaceuticals Inc., which Shire acquired in 2015. "It is not how big pharma is usually structured." This may be especially true in R&D and regulatory, which are charged with designing and implementing the clinical trials. "Probably the key factor could be as simple or as complex as determining a clinically meaningful endpoint," Nader says.

"Some of the companies spend too much time on the bench without knowing how it will change someone's life," adds Rogerio Vivaldi, MD, chief commercial officer of retinal gene therapy developer **Spark Therapeutics Inc.** and former head of the rare disease business at Genzyme. "I think there is still a big separation in terms of transferring the research [into commercial]," he says. **Aegerion Pharmaceuticals Inc.**'s *Myalept* (metreleptin) is a good example. Originally thought of as a potential blockbuster diabetes drug, it passed through several hands, eventually finding its niche as a treatment for the complications of leptin deficiency in patients with generalized lipodystrophy. (*See "Repurposing Leptin (Part 2): It Really Is A One-In-A-Million Drug"* — The RPM Report, *December 2013*.) Aegerion acquired it from **AstraZeneca PLC** in 2014.

To be successful, a big pharma should carve out a niche for a rare disease business that is in many ways protected from the rest of the company. Because the development requirements are so unlike the organizational and tactical elements of commercializing drugs for large indications, it should be isolated. And that requires a commitment from senior management. GSK, for example, has not shown that commitment at the senior level to support its rare disease efforts. Pfizer launched an orphan and genetic diseases research unit in 2010, bolstering it with the acquisition of **FoldRx Pharmaceuticals Inc.** But it failed to secure US approval for FoldRx's tafamadis for transthyretin familial amyloid polyneuropathy, and internal support now appears problematic.

The best model has been one in which a rare disease company is acquired and more or less left alone to interact with the customer. "Where it has gone poorly is where they have tried to build it from scratch," Vivaldi says.

The **Children's Hospital of Philadelphia** was a founding partner and the sole initial investor in Spark. This could be a model for hospitals and other academic institutions to look at in rare diseases, says Spark CEO Jeffrey Marrazzo, especially as funding from the **National Institutes of Health** is tighter now.

The very fact of a disease being rare often allows for trials that are highly concentrated and focused, and in many cases less costly than for more common diseases. "Because of that, you have and will see hospitals carry the ball farther down the road," Marrazzo says – especially for technologies that are five to 10 years away from commercialization, where the interest of the investment community or corporate partners may be less. Spark does have an agreement with Pfizer for development of its hemophilia B gene therapy, SPK-FIX. Pfizer has been marketing the recombinant Factor IX *BeneFix* for hemophilia B since the mid-1990s. But competition has increased in that indication. "They were looking at how to maintain their leadership position and leapfrog some new recombinant proteins," Marrazzo says. Indeed, investing for the long term may be one strategy that makes sense for big pharma in rare diseases.

Exhibit 1

Acquisitions By Selected Rare Disease Specialists

COMPANY/ COMPANY ACQUIRED (DATE ANNOUNCED)	POTENTIAL ACQUISITION VALUE ($)	MAJOR ASSET(S) ACQUIRED
SHIRE (EXCLUDES PROGRAMS IN OPTHTHALMOLOGY AND RENAL DISEASES)		
Baxalta (Jan. 2016)	32bn	Recently approved antihemophilia factors Adynovate and Obizur, also Vonvendi for Gaucher's disease, along with a portfolio of other protein drugs in hematology, immunology and oncology. Over 50 programs that address rare diseases.
Dyax (Nov. 2015)	5.5bn	DX-2930, a long-acting plasma kallikrein inhibitor in Phase III testing, which would compete with Shire's Cinryze, its second-biggest drug, in hereditary angioedema. Also Kalbitor for treating acute attacks of HAE.
NPS Pharma (Jan. 2015)	4.9bn	Gattex for short bowel syndrome and Natpara for hypoparathyroidism.
ViroPharma (Nov. 2013)	3.3bn	Cinryze.
BIOMARIN		
Prosensa (Nov. 2014)	851m	Drisapersen for Duchenne's muscular dystrophy.
Zacharon (Jan. 2013)	144m	Small molecules for lysosomal storage disorders.
ZyStor (Aug. 2010)	115m	Reveglucosidase for Pompe disease.
Huxley (Oct. 2009)	58.5m	Firdapse for Lambert-Eaton myasthenic syndrome.
ALEXION		
Synageva BioPharma (May 2015)	8.56bn	Kanuma for lysosomal acid lipase deficiency.
Enobia (Dec. 2011)	1.08bn	Strensiq for hypophosphatasia.

SOURCE: *Strategic Transactions*

WHERE IS THE LEVERAGE?

A key consideration of acquisitions generally is the degree of leverage and efficiencies of scale gained in combining organizations. In the rare disease space an acquirer offers few advantages in this regard, assuming the acquired firm has established domain expertise in its core therapeutic area. That is, unless an acquirer already is immersed in rare diseases. "As you build capabilities you begin to see connections to adjacent therapeutic areas," says Mark Enyedy, head of corporate development at Shire. This is particularly the cases in medical affairs, where experience with natural history – especially bringing the first therapeutic to an area – is key, as well as with registries, diagnostics, patient management and market access. "Once you have a basic understanding of managing small populations, that experience can be extrapolated from one rare disease area to another," he says.

That said, execution still requires focus and a dedicated force. When it first launched *Firazyr* (icatibant), its first product for hereditary angioedema (HAE), Shire tried in some markets to leverage the sales force by selling it with the existing lysosomal storage disease portfolio, adding the HAE product to the bag. It didn't work.

Since its 2005 acquisition of TKT, Shire has been an aggressive acquirer. It recently bolstered its franchise in HAE (which originated with its takeover of **Jerini AG** in 2008) with the additions of **Dyax Corp.** and **ViroPharma Inc.** and with Baxalta, added a core franchise in hemophilia along with assets in immunology and oncology. (*See Exhibit 1.*) With the acquisition of Viropharma, Shire created a fully-dedicated HAE team supporting both Firazyr and Viropharma's C1 esterase inhibitor, *Cinryze*. The model was different with NPS, however. There, Shire added the NPS portfolio to its existing GI business and integrated its centralized patient management capabilities to support NPS's products *Gattex* (teduglutide) for short bowel syndrome and *Natpara* (parathyroid hormone) for hypoparathyroidism.

"As you continue to optimize the rare disease business model to enhance the level of service and care for patients, it creates the opportunity to maintain that level of focus, notwithstanding the increase in size," Enyedy says.

The creativity applied to designing a development pathway can transfer across rare disease areas. There was a significant cross-fertilization between the different therapeutic areas – GI and endocrinology – within NPS, for example. "On the surface,

Exhibit 2

Competitive Areas In Rare Diseases (Commercial Competition)

DISEASE AREA	MAJOR COMMERCIAL DRUGS (NON-EXHAUSTIVE LIST)				ADVANCED PIPELINE DRUGS (NON-EXHAUSTIVE LIST)	
	COMPOUND 1	COMPOUND 2	COMPOUND 3	COMPOUND 4	COMPOUND 1	COMPOUND 2
Fabry disease Genetic disorder	Fabrazyme (Genzyme) agalsidase beta **Marketed**	Replagal (Shire) agalsidase alfa **Marketed**			Galafold (Amicus) migalastat **Pre-reg**	
Gaucher's disease Genetic disorder	Cerezyme (Genzyme) imiglucerase **Marketed**	Cerdelga (Genzyme) eliglustat **Marketed**	Vpriv (Shire) velaglucerase alfa **Marketed**	Zavesca (Actelion) miglustat **Marketed**	Oral glucocerebrosidase (Protalix BioTherapeutics) **Phase II**	
Pulmonary arterial hypertension (PAH) Cardiovascular	Revatio (Pfizer) sildenafil **Marketed**	Tracleer (Actelion) bosentan **Marketed**	Remodulin (United Therapeutics) treprostinil **Marketed**	Volibris (GSK/ Gilead) ambrisentan **Marketed**	Uptravi (Actelion) selexipag **Pre-reg**	Tadalafil (Eli Lilly) **Phase III**
Hereditary angioedema (HAE) Immunology	Cinryze and Firazyr (Shire) C1 esterase inhibitor and icatibant **Marketed**	Ruconest (Pharming Group) C1 esterase inhibitor **Marketed**	Berinert (CSL Behring) C1 esterase inhibitor **Marketed**	Danatrol (generic) (Sanofi) danazol **Marketed**	DX-2930 (Dyax now Shire) **Entering Phase III**	Avoralstat (BioCryst Pharmaceuticals) **Phase III**

SOURCES: *Biomedtracker;* Company reports

there were limited common denominators but the same team did both. In retrospect, if it would not have been the same team, the challenges would have been magnified," says Nader. It's not the "what," but the "how," which lends itself to commonalities in a big way, he says. How a team approaches the regulatory path, how to address the importance of an end of Phase II meeting with FDA or the structure of an NDA are uniquely important within the context a rare disease application.

Despite the novelty involved in establishing a commercialization pathway for an ultra-orphan product, competencies may be applied to multiple programs. The infrastructure cost of building a commercial organization is much the same across one product or three, says Nader, with further leverage gained if a company is in multiple geographic regions. "One general manager, one head of market access, one head of medical in a given geography can certainly absorb more than one product," he says.

Although a common development perspective exists across ultra-orphan disease indications, it differs from that within companies focusing on large indications. For the latter, precedents exist that can be referred to and lessons extracted that provide benchmarks for new development plans. "You have something to rely on," Nader says. That's not the case in the rare disease space. "You have to be innovative but at the same time creative in a way that would be accepted by the regulators and eventually lead to a product approval," he says.

We do have a word of caution in this regard, however. Sometimes a small company's boldness can backfire. It might make sense to power a clinical trial for a rare disease drug based on the small number of patients' prevalence. However, the data generated has to be sufficient for approval and also to demonstrate the value the drug brings to the health care system. Having the input of an experienced rare diseases strategic advisor can be very helpful, especially when planning for a global launch.

THE EFFECT OF COMPETITION

Increasingly, competition has become an added consideration in the rare disease space. "I think we are just at the beginning of a market situation where competition for indication and competition for products will be a meaningful segment of the market," Nader says. "I would certainly spend quite a bit of time studying the market dynamics

Exhibit 3

Competitive Areas In Rare Diseases (Competition Anticipated)

DISEASE AREA	COMMERCIAL DRUGS	PIPELINE DRUGS (NON-EXHAUSTIVE LIST)		
		COMPOUND 1	COMPOUND 2	COMPOUND 3
Paroxysmal nocturnal hemoglobinuria (PNH) Hematologic disorder	Soliris (Alexion) eculizumab **Marketed**	ALN-CC5 (Alnylam) **Phase II**	ALXN-1210 (Alexion) **Phase II**	Tesidolumab (Novartis) **Phase II**
Mucopolysaccharidosis II (MPS II or Hunter syndrome) Metabolic disorder	Elaprase (Shire/Genzyme) idursulfase **Marketed**	Odiparcil (Inventiva) **Phase II**	FT-1050 (Fate Therapeutics) **Phase I**	
Pompe disease Metabolic disorder	Myozyme (Genzyme) alglucosidase alfa **Marketed**	Reveglucosidase alfa (Biomarin) **Phase III**	GZ-402666 (Genzyme) **Phase III**	Alglucosidase alfa + duvoglustat (Amicus) **Phase II**
Phenyketonuria (PKU) Metabolic disorder	Kuvan (Merck/Biomarin) sapropterin **Marketed**	Pegvaliase (Biomarin) **Phase III**		
Familial lipoprotein lipase deficiency/ familial chylomicronemia syndrome Genetic disorders	Glybera (Chiesi/UniQure) alipogene tiparvovec **Marketed**	Volanesorsen (Ionis Pharma) **Phase III**	CAT-2003 (Catabasis) **Phase II**	
Familial amyloid cardiomyopathy Metabolic disorder	**N/A**	Revusiran (Genzyme/Alnylam) **Phase III**	Tolcapone (SOM Innovation) **Phase II**	
Duchenne's muscular dystrophy Genetic disorder	Translarna (PTC Therapeutics) ataluren **EMA Conditional Approval**	Kyndrisa (Biomarin) drisapersen **US: Rejected by FDA** **EU: Pre-reg**	Eteplirsen (Sarepta) **Pre-reg**	Domagrozumab (Pfizer) **Phase II**

SOURCES: *Biomedtracker;* Company reports

given how quickly competition is evolving nowadays, as there will be more and more pressure on pricing."

A lack of competition makes access and pricing more straightforward. And while a dedicated infrastructure to get access to the patients is needed, it does not have to be large and the overall NPV may be significantly more interesting, with products commanding value for longer than in other areas. We do not favor maintaining rare disease and large indication programs under the same roof; even if getting into the more competitive markets like Gaucher's or Fabry or HAE requires a little bit more of those skill sets of big pharma. "You need to shift the thinking of the solo blank space," says Bedard. "You need that and to make sure you have those competitive skill sets you typically find in big pharma."

New entrants needing to establish their credentials as companies recognized and committed to the rare disease space can more easily do so when the competition is limited or non-existent. Coming for the first time with the fourth product in the disease makes it hard to stand out and to establish relationships with the rare disease communities and organizations. Yet despite tremendous unmet need – with 7,000 rare diseases, only a few hundred have treatments – competition is attracted to some of the more established markets. (*See Exhibits 2 and 3.*)

Competitors may struggle because patients have an allegiance to the product that has allowed them to get control of their disease. So switching happens slowly – a factor bound to be magnified with the introduction of biosimilars for rare diseases. (*See "The Birth Of An Orphan Biosimilar Market" — this issue.*) "I think many of the new entrants see it as financially a way of perhaps getting a quick return, but there is nothing quick about the rare disease business," says

David Meeker, MD, executive vice president and head of Sanofi Genzyme. "You have to commit, do the hard work of working with communities, patient by patient, trying to improve outcomes. That's not something competitors are often willing to do." Plus, some of the largest areas of growth are in developing markets – early heath care systems where there is little infrastructure.

"The work that is required to support it is laborious," Meeker says. Operating margins are not what people think, and when that reality hits, they are "more sensible" about getting into a price war, he says, because giving a 5% to 10% discount to get a few more patients is not that significant. "The market force dynamics that drive significant pricing shifts in other areas are not in play here," he says.

THIS IS NOT FOR EVERYONE

Companies that fail in rare diseases – and they can be large or small – often miss the highly personal nature of the area. "Your proximity to the communities and your ability to connect with that aspect is infinitely greater and the expectations of the community as a result of that are different," says Meeker. "We are 20 years later in the area of Gaucher's disease and the level of disease awareness is still low," he says. Sanofi Genzyme is still diagnosing as many Gaucher's patients now as Genzyme did in the beginning.

Although Genzyme's presence in the disease has transformed the community, giving a patient a better chance of being diagnosed and getting an appropriate treatment, the company is still a long way from getting it right. "There are parts of the disease we don't treat well, parts of the world that can't access therapy in the same way that others can access it, and even in the best most sophisticated health care systems these patients are still missed," he says. The question for us is: does that prolonged time frame jibe with a big pharma's expectations for growth?

The R&D elements of the former Genzyme may now be more closely integrated with the global elements of Sanofi. That could be good: according to one partner, there previously may have been more uncertainty or ambiguity regarding who the key stakeholders were on the R&D side in the model that existed, when Genzyme had its own R&D autonomy from the rest of the organization. Instead of having to navigate through many people within the old organization to get key decisions made on trial design or budget, now the process may be more streamlined.

We agree that because Sanofi Genzyme had already been successful at the commercial level, it was easier for Sanofi to initially leave it alone and then integrate it, de-risking losing the benefit of the asset. It may be that the new set-up will not cause distractions because Sanofi has long viewed the rare disease space as one of the growth drivers for the company. On the other hand, it adds unrelated infrastructure that takes away from the pure-play nature of the rare disease business and could dilute the commitment-driven culture through absorption or departure – as has happened, for example, with **Roche**'s **Genentech Inc.** unit over time. (Note that while Meeker remains at the helm of Sanofi Genzyme, several executives including Vivaldi, Enyedy and Edward Kaye, MD, chief medical officer and interim CEO at **Sarepta Therapeutics Inc.**, which is applying an RNAi technology platform to the development of treatments for various forms of Duchenne's muscular dystrophy, were key members of the Genzyme team who departed post acquisition.)

In the 1990s, the big culture issue was around how to incorporate large-molecule drug development programs into an organization focused on developing small molecules, because of the differences in clinical development and manufacturing. That affected some parts of the organization. In the rare disease space, it's not only a few pieces of the organization, but from R&D all the way down to distribution, getting the drug into the hands of patients and sustaining them in terms of the service that they need. Rare disease drug development may be transformational in nature, but it does not have the range of opportunity biological drugs offered, which forced the pharmaceutical culture to embrace them.

Rightly, rare disease franchises are too valuable to ignore. Their development is important to patients and they represent a potential opportunity for innovation. But we also believe they are not for everyone, given the distinctive processes and practices needed to be successful. Certainly, a broad-based traditional pharmaceutical firm should leave these orphans alone – at least until they reach a level of maturity to be able to withstand structural organizational pressures. IV

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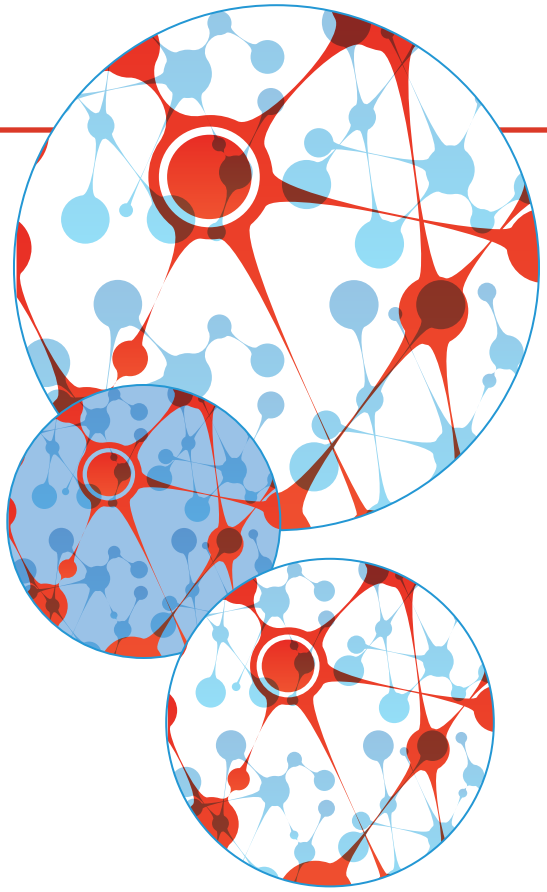

The Birth Of An Orphan Biosimilar Market

Hard-won experience from the first wave of broad-market biosimilars will inform development of "orphan biosimilars," but biopharmas entering this orphan market will face a unique set of challenges.

BY PAUL ZHANG, TRIONA BOLGER, VARUN RENJEN, BRIAN SATTIN, ANNY LIN AND ADITYA VENUGOPAL

- Biosimilar pathways have been paved, patent expirations are sweeping across the product landscape and the first batch of biosimilars are establishing safety and credibility with physicians and patients.
- Investments made by major biologics companies and start-ups alike will unmistakably accelerate and intensify biosimilar market growth.
- Biosimilar versions of biologics for orphan diseases present a unique set of unknowns, including availability of clinical study subjects, KOL loyalty and payer activism.
- Pricing strategy and payer effectiveness will be the most critical considerations for orphan biosimilars' commercial success, while a less strenuous clinical development program could make the path to market that much more favorable.

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Biosimilars have attracted great interest from traditional biologics powerhouses and start-ups alike as a large estate of patents is expiring and clear regulatory pathways are emerging across major markets. Unsurprisingly, the first salvo of the modern era "biosimilar" is aimed at blockbusters, such as **Abbvie Inc.**'s *Humira* (adalimumab) and **Genentech Inc.**'s *Rituxan* (rituximab), based upon their aging patent lives and lucrative commercial potential; many more oncology and autoimmune biologics will soon face a similar fate.

Biosimilar versions of orphan biologics, on the other hand, have not been earnestly pursued yet, even though biologics comprised 67.5% of the global orphan drug market in 2015 and this is expected to continue to grow, according to BCC Research. Is it due to difficulty of clinical trial patient recruitment, high-touch customer service, or lack of key stakeholder interest? Armed with an understanding of the commercial challenges and opportunities of "broad-market" biosimilars (e.g., adalimumab, rituximab, etc.), we examine how the underlying nuances of orphan drug development will impact the commercial viability of "orphan" biosimilars.

$33 BILLION OF ORPHAN BIOLOGICS GOING OFF PATENT

Orphan diseases, those with prevalence of less than 650 per million population (roughly 200,000 in the US), became an area of high interest to the pharmaceutical industry starting in the late 1990s as targets for more prevalent diseases became less productive. Scientific advances enabled by government-supported financial incentives led to significant investment, development and ultimately commercialization of a wide range of orphan drugs. Both specialty pharmaceutical companies as well as some of the major industry players saw strong opportunity for return on investment in the orphan drug space and invested earnestly. (*See also "Orphans Should Live Alone"* — IN VIVO, *February 2016*.) Fast-forward 15 years, and we are now facing a significant trove of orphan biologics with impending loss of exclusivity (LOE). According to some estimates, five products with annual revenue over

a billion dollars face LOE by 2025, as do an additional 14 products with revenues in excess of $500 million. (*See Exhibit 1.*)

In aggregate, more than $33 billion in annual sales of orphan drugs are at risk for biosimilar entry between now and 2025. (*See Exhibit 2.*) Many enzyme and protein-based orphan disease biologics have already lost exclusivity. Over the next 10 years, several monoclonal antibodies (mAbs) will also lose patent protection. Despite the number of orphan products that have already reached LOE, there are no true biosimilar versions on the market. This has been largely due to a) the lack of a regulatory pathway for biosimilars prior to 2010, b) manufacturing hurdles – for example, a coagulation factor VIII is nearly as complicated to produce as a monoclonal antibody, and c) the competitive dynamic, such as multiple competitors in the hemophilia space.

Omnitrope (somatropin), developed by **Sandoz Inc.** for pituitary and adult growth hormone deficiency and launched in 2007, is an example of an earlier generation "orphan biosimilar" that is commercially available. However, because it was submitted prior to the development of the 351(k) pathway, Omnitrope went through the 505(b)2 pathway for regulatory approval. At the time, the FDA found that growth hormone was not a complex molecule, and Omnitrope was considered a follow-on product. Although Sandoz delivered three registrational clinical studies comparing Omnitrope with originator molecules, the drug was approved as a small-molecule chemical rather than a biologic and was not assessed for "biosimilarity" in the same manner as a product approved via the current 351(k) could expect. Omnitrope is priced at a 40% discount to the originator molecule (**Pfizer Inc.**'s *Genotropin*), and achieved a peak market share of 15%, which is quite significant in a growth hormone market with nine brands.

Now with more clearly defined regulatory pathways for biosimilar approval, there are still many critical questions facing originators and biosimilar makers regarding orphan biologics:

- Will patient identification and clinical trial recruitment pose an insurmountable hurdle for orphan biosimilars?
- Will regulators entertain relaxing evidence requirements to enable biosimilar development?

Exhibit 1

Top 25 Orphan Biologics

Ranked by Projected 2020 Sales

PRODUCT NAME	MANUFACTURER	2020 PROJECTED SALES ($m)	PATENT EXPIRY DATE
Soliris	Alexion	5,600	2021
Advate	Baxalta	1,907	2019
NovoSeven/ NovoSeven RT	Novo Nordisk	1,679	2010
Kogenate	Bayer	1,130	2014
Cerezyme	Sanofi	1,076	2013
Myozyme	Sanofi	927	2023
Fabrazyme	Sanofi	910	2015
Cinryze	Shire	832	2015
Eloctate	Biogen	815	2025
BeneFIX	Pfizer	780	2011
Pulmozyme	Roche	728	Prior to 2015
Strensiq	Alexion	649	2025
Elaprase	Shire	645	2019
Prolastin-C	Grifols	641	Prior to 2015
Nplate	Amgen	597	2022
Natpara	Shire	591	2022
ReFacto AF/Xyntha	Pfizer	530	2014
Replagal	Shire	509	2017
Genotropin	Pfizer	507	2008
Ilaris	Novartis	420	2024
Vprive	Shire	386	2022
Adcetris	Seattle Genetics	382	2023
Alphanate	Grifols	367	Prior to 2015
Alprolix	Biogen	345	2025
Aldurazyme	Sanofi	307	2019

SOURCE: Navigant

- Are physician and patient services a highly proprietary and costly barrier to biosimilars?
- Are, or will there be, particular incentives for reimbursement of orphan biosimilars?
- Is there a market size threshold for biosimilars to achieve positive commercial returns?

MANY STAKEHOLDERS SHAPE THE MARKET

Four primary stakeholders will shape the contours of the orphan biosimilar landscape, and we must pay close attention to their interests for a glimpse of the future. (*See Exhibit 3.*)

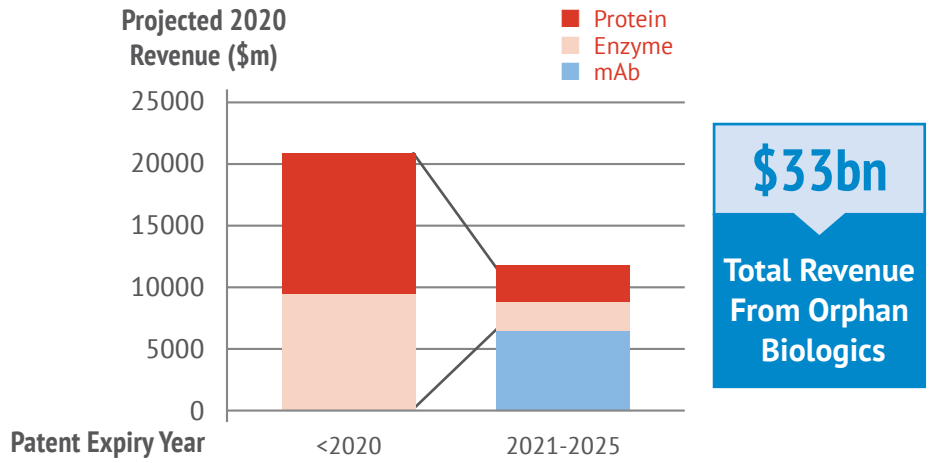
1. Regulators. First and foremost, regulators seek to ensure that approved products are safe and efficacious and they will not compromise on those goals. Presently, orphan biosimilars must follow the same development path as broad-market biosimilars. Under the Biologics Price Competition and Innovation Act (BPCIA), an application for approval of a biosimilar must include animal studies and a head-to-head clinical study or studies sufficient to demonstrate safety, purity and potency (effectiveness) in an appropriate condition of use. BPCIA also permits FDA to determine, at its discretion, what data will ultimately be required for any given submission to achieve approval. "It remains to be seen how, or whether, FDA exercises its authority to waive the requirements for information supporting biosimilar products. In general, FDA tends to exercise flexibility when there is a medical or scientific, rather than financial, reason to do so. A very small patient population might be a factor FDA would consider in determining the data requirements for a biosimilar product," comments Suzanne O'Shea, who served as regulatory counsel at FDA headquarters and is now a director in Navigant's Life Sciences D&I practice.

The possibility that some data might not be required could increase the commercial viability of an orphan biosimilar. Otherwise, development costs and time lines could hamper product profitability. However, to date, no biosimilar has been approved in either the US or EU without a pivotal head-to-head trial versus the originator. Early engagement with regulators will be important to build understanding of the rationale and viability of an abbreviated pathway to market.

Exhibit 2

Orphan Biologics Market Size

Sales Potential By Patent Expiry Date



SOURCE: Navigant

2. Payers. Payers are highly vested in enabling the availability of safe and effective products that can lower the cost of health care. Payers' attitude toward managing orphan disease pharmacy budgets is nuanced and varies by country. On one hand, the total budget impact of a single orphan drug is relatively small due to low disease prevalence. As a result, payers do not necessarily consider orphan drugs high priority targets for cost management efforts. On the other hand, given the high single-patient price tag and typically single-source status of a drug, payers are also interested in a safe and effective alternative to create price competition. Furthermore, some payers keep tight control over orphan drugs budgets and access to therapies. In the UK, for example, the centralized National Health Service (NHS) England, rather than regional Clinical Commissioning Group (CCG), regulates orphan drug costs. This means that policies favoring orphan biosimilars can be driven across country effectively. Many other European countries follow the same approach, resulting in greater regulation of patient access to therapy including individual "named patient" approval. As such, payers can implement policies to favor a biosimilar over the originator (e.g., step edits, formulary restrictions).

"Orphan drugs face less scrutiny from AMNOG today [compared with broad-market drugs], and there is little we can do to cap their price. But the German health care system is under reform and the prescription management focus will shift from capping total costs to shifting the structure of prescribing, mandating more prescription of generics and biosimilars. Under this structure we can expect that high-price biologics such as orphan drugs will produce significant savings by switching to biosimilars," says Mathias Flume, PhD, who is the head of drug department at Physicians Association of Statutory Health Insurance (Kassenärztliche Vereinigung) in Germany.

Payers have demonstrated an early willingness to extract high-price discounts in exchange for broad adoption. In July 2015, AGEPS, which is the purchaser for the public hospital system in Paris covering 40 hospitals, awarded an exclusive contract to **Celltrion Inc.**, the maker of *Inflectra* (a biosimilar of **Janssen Biotech Inc.**'s TNF-inhibitor *Remicade* [infliximab]), after negotiating a 45% price discount.

3. Physicians. Physician awareness and acceptance of biosimilars vary widely. However, higher levels of understanding and sophistication can be expected among the clinicians treating orphan diseases. They are often clinical experts and researchers who have a deep understanding of disease etiology, mechanisms and clinical development.

Exhibit 3

Key Stakeholders' Influence On Orphan Biosimilars

DRIVERS		CHALLENGES
▪ Desire to increase the availability of safe and efficacious treatment options	Regulator Attitude 	▪ High bar of preclinical and clinical evidence required to ensure product safety and efficacy
▪ Increasingly constrained budgets ▪ Having biosimilar creates tools to pressure orphan biologics	Payer Incentives 	▪ Most ophan diseases have a relatively low total budget impact ▪ Safety and efficacy are important considerations
▪ Discontent with the lack of full accessibility to orphan biologics due to price and payer limitations ▪ Accustomed to drugs with limited clinical data for orphan disease	Physician Acceptance 	▪ Established/exclusive experience with originator manufacturers ▪ Close relationship with patients ▪ Varying levels of biosimilar understanding and acceptance
▪ Lower co-pay provides financial relief and access for those previously unable to afford	Patient Interest 	▪ Fear of the perceived risks (poor efficacy/safety issues) ▪ Branded manufacturer service and support provides high value

SOURCE: Navigant

These clinicians can have an appreciation of the biosimilar development process, which will likely increase their willingness to adopt. In addition, physicians who manage orphan diseases are accustomed to working with limited clinical data – using products off label and/or those approved with only single-arm trials.

Additionally, these physicians frequently complain that their patients do not have full access to the orphan drugs that are highly effective and can make a huge difference in patients' lives, because of the high costs of the drugs. They are willing to use the drugs earlier, and more frequently in broader segments of patients if costs are not a constraint. The yearning for more affordable orphan medication is clear and present, creating space for lower-priced biosimilars to enter.

On the other hand, orphan diseases are usually treated by a small community of clinicians for whom manufacturers of orphan drugs have built strong services. Manufacturers provide clinicians with a high degree of engagement and support – for example, involving them in clinical trials, and providing reimbursement support services. Therefore, in addition to product and biosimilar education, orphan biosimilar manufacturers will have to match the high levels of service and engagement of the originator companies.

4. Patients. Orphan disease patients also face a series of nuanced trade-offs with respect to drug access, cost and medical/behavioral needs. On one hand, payer actions geared toward shifting cost burden to patients, especially in the US, have saddled many with insurmountable financial challenges, or "fiscal toxicity." Financial sensitivities are particularly notable for those patients with chronic diseases requiring ongoing treatment with advanced specialty therapeutics (i.e., biologics).

On the other hand, orphan disease patients and their caregivers are often very involved with their treatment decisions and seek value above and beyond cost. Like their physicians, many patients are highly engaged in the services and support that a specialty drug company provides. Patients are also inherently risk averse and the perceived possibility of poor efficacy and/or safety/tolerability issues will drive many patients toward the more proven, "tried and true" option, even if it is more expensive. The fear of losing both the physiological benefits and the service and support that come with use of a branded orphan drug will weigh heavily against the economic benefits of a biosimilar.

Looking across the landscape, Navigant's perception is that payers are going to be the single most influential stakeholder that will be motivated to drive for orphan biosimilar

adoption. Physicians are critical stakeholders and are uniquely tied to the branded biologics, but they are also quite challenged by the high costs of orphan biologics and sympathetic to the use of lower-cost alternatives.

ADDITIONAL CHALLENGES OF ORPHAN BIOSIMILAR DEVELOPMENT

A biosimilar for an orphan product will face higher hurdles in recruiting for clinical trials. Orphan disease patients tend to be treated by a small number of physicians who have historically worked exclusively with the originator company. To develop a biosimilar, a new entrant will need access to these patients and therefore the support of the specialists who manage them. Shifting on-treatment patients to a biosimilar that is not aiming to prove superiority will be a difficult sell. As a result, the more likely approach will be to recruit previously untreated patients – either newly diagnosed patients or patients who could not afford the biologic before. This leaves a narrow pool of patients and makes enrollment potentially prohibitively challenging. Hemophilia A, for example, has an incidence rate of 1 in 5,000 births in the US and there are only 800 new patients each year. Moreover, more than half of prevalent hemophilia patients are perceived as mild cases not requiring treatment, and hence are not attractive candidates for clinical trial recruitment. Ultra-orphan diseases – those that occur in less than 20 per million population, present an even higher hurdle. For example, cryopyrin-associated periodic syndromes (CAPS) are a group of auto-inflammatory diseases with a prevalence of one to two cases per million population. Given the ultra-rare nature of CAPS, recruiting patients for a biosimilar clinical study would be nearly impossible.

Biosimilars can be approved in all indications afforded the originator product, based on one or more pivotal studies. Remicade, for example, was approved in six rheumatological and gastroenterological disorders: moderate to severe rheumatoid arthritis, active ankylosing spondylitis, psoriatic arthritis, chronic moderate to severe plaque psoriasis, Crohn's disease and ulcerative colitis. For Celltrion's biosimilar product *Remsima* (infliximab), Health Canada accepted "indication extrapolation" from rheumatoid arthritis to psoriatic arthritis and plaque psoriasis, but not Crohn's disease or ulcerative colitis. The European Medicines Agency (EMA) approved it for use in all the originator indications in line with the 2014 guidance that ruled, "If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification." Such indication extrapolation vastly accelerates the commercial adoption of a biosimilar. However, orphan disease drugs are typically "one trick ponies" and may not be able to take advantage of such expedited indication approval, further dampening the cost/value trade-off of an orphan biosimilar.

THE FINANCIAL THRESHOLD FOR ORPHAN BIOSIMILARS

Clearly, orphan biosimilars have their "quirks" compared with broad-market biosimilars. We constructed two case studies to evaluate the commercial viability of potential orphan biosimilars.

- Product One is a billion-dollar mAb with no competitors on the market for its ultra-rare indication. With only 5,000 patients in the world, 60% of patients are diagnosed and treated, all in specialized centers of excellence.
- Product Two is a protein with an annual revenue of $270 million that does not have any competitors either. With 10 times the patient pool size as Product One and a less life-threatening condition, the drug price is set at $9,000 per

Exhibit 4

Scenarios And Select Assumptions For Financial Modeling

	On Treatment Patient Pool (US + EU5)	Annual Originator Drug Price	Scenario	Biosimilar Price	Approval Requirement	Sales Rep # (US + EU5)	Biosimilar Market Share
Product One	3,000	$350,000	A	$280,000	PIII head to head	80	20%
			B	$175,000	Bioequivalence	30	50%
Product Two	30,000	$9,000	A	$7,200	PIII head to head	150	20%
			B	$4,500	Bioequivalence	50	50%

SOURCE: Navigant

year. Patients are managed by specialists in the community, and thus the sales and marketing resource requirement is higher than for Product One.

For both products, we have considered several key dimensions in their valuation assessment:

- Regulatory approval path – whether an orphan biosimilar product can be approved with only bioequivalence data or a full-fledged head-to-head pivotal trial versus the originator product is mandated; in the latter case, the launch time will be two years later.
- Pricing – an industry consensus 20% discount to originator, or a more significant 50% discount as we have seen in some early cases of biosimilar contracting.
- Sales and marketing focus – whether the company will market to both clinicians and payers, or largely focus on payer messaging/contracting with targeted KOL support.

We consolidate the considerations for these dimensions into two scenarios. (*See Exhibit 4.*) In Scenario A, the biosimilar is priced with a modest 20% discount, and payers are not likely to enforce formulary switching. The biosimilar would most likely be adopted in newly diagnosed patients or those who chose non-treatment due to cost sensitivity. This would translate to a peak market share of around 20% (10% representing untreated patients, 10% from on-treatment pool). In Scenario B, with a faster time to market but no head-to-head data against the originator product, it would be wise for the biosimilar maker to offer more significant price discounts and market heavily to payers for switching, with a potential of achieving half of the market share.

Navigant's financial modeling shows that for a billion-dollar orphan biologic, regardless of whether a biosimilar can be approved via an expedited path or standard route, whether it is priced at a modest discount or a drastic one, the financial payoff for a

Exhibit 5

NPV Analysis Of Products One And Two

SOURCE: Navigant

biosimilar company is highly attractive.

The case for a biosimilar with a more modest-selling originator biologic, however, hangs in the balance of several factors. In Scenario A, where the biosimilar maker took the modest price discount approach achieving only 20% of patient share, the sales and marketing costs alone will drain out any financial payoff, leading to a negative NPV for the product. Even an expedited approval path in this case is not sufficient to make a meaningful difference. The revenue-maximizing approach for this product is a heavy price discount approach to allow payers to enforce formulary switching. Attaining 50% market share is a strong market performance that will turn the product NPV into a positive one. This type of strong market penetration is more likely in European markets where payers are less fragmented and historically accustomed to driving formulary shifts, in comparison with the US market where price sensitivity is less acute and payers have more-limited tools at hand. (*See Exhibit 5.*)

CONCLUSION

We are at the precipice of a new biosimilar era. Regulatory pathways have been paved, complex mAbs biosimilars like Remsima have been approved, a wave of patent expiries are sweeping across the product landscape and the first batch of biosimilars are establishing safety and credibility, providing comforting experience to physicians and patients. Investments made by major biologics companies and upstarts alike will unmistakably accelerate and intensify the growth of biosimilar markets. In this context, while orphan disease presents a unique set of unknowns to biosimilar players such as the availability of clinical study subjects, KOL loyalty and payer activism, the law of pharmaceuticals will prevail in the end. If the orphan biologic has revenue over $250 million, it will likely attract imitators. Pricing strategy and payer effectiveness will be the most critical consideration in its commercial success, while a less strenuous clinical development program will make the path to market that much more favorable.

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Glaukos Holds Lead In Microinvasive Glaucoma Surgery

Glaukos Corp. has emerged as the leader in microinvasive glaucoma surgery, a new treatment for the multibillion-dollar market. CEO Tom Burns lays out his vision for his company and for the future of MIGS.

BY TOM SALEMI

- Glaucoma affects tens of millions of people worldwide, causing a buildup in intraocular pressure that can lead to vision damage and blindness.
- Current treatments exist on the fringes. If the condition is caught early patients are given eyedrops, although many forget to use them. More serious cases require invasive eye surgery.
- A field of start-up companies has developed another way to treat glaucoma by creating or reopening drainage passageways in the eye using microinvasive surgery.
- Publicly held Glaukos Corp. is the reigning leader in this emerging field as the only company with an FDA-approved product. But the gap between the iStent and rival technologies may be closing.

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Two decades ago, cardiology underwent a revolution when interventionalists began using smaller tools to repair heart damage that once required an open incision. Interventional cardiology didn't emerge smoothly into mainstream health care as cardiologists fought the push, but the impact on costs and efficacy of treating damaged hearts or vessels can't be refuted.

Ophthalmology has seen a similar change, at least in the normally sleepy field of glaucoma, which is actually a group of eye diseases that can lead to vision loss. The most common form of glaucoma elevates the pressure within the eye. This is brought on by the inability of the aqueous humor – the watery fluid in the front of the eye – to escape the eye due to some blockage. Patients typically are given eyedrops, but compliance is weak. The more serious cases require invasive surgery called trabeculectomy.

A crowd of start-ups is developing a middle way by creating devices that can improve the flow of fluid, which reduces the pressure in the eye that damages vision. These microinvasive glaucoma surgery (MIGS) companies are looking to create a new market for the treatment of glaucoma, which affects roughly 80 million people worldwide, according to Market Scope estimates.

The field of start-ups pushing MIGS technology is crowded, but one company has emerged as a leader in the space – **Glaukos Corp.** The company launched its flagship product, the *iStent,* in 2012 for the treatment of mild to moderate open-angle glaucoma, and it has the market to itself. The next likely competitor is **Transcend Medical Inc.**, which filed the final component of its pre-market approval application late last year (At press time, **Alcon Inc.**, a division of **Novartis AG**, announced that it was acquiring Transcend.)

Transcend could get the FDA nod for its *CyPass Micro-Stent*, an implant designed to reduce intraocular pressure (IOP) in patients with primary open-angle glaucoma, sometime this year. **AqueSys Inc.** represents another fast-mover in the sector. **Allergan PLC** paid $300 million up front for the start-up, which had raised just under $80 million in private financing, for access to its *XEN Gel Stent*. The company's management and investors could be due a larger payout if the FDA issues 510(k) notification for the implant.

But right now the MIGS market belongs to iStent – which Glaukos notes is the smallest device ever approved by the FDA. The stent is implanted during cataract surgery through a 1.5-mm corneal incision. According to Market Scope data cited in Glaukos' S-1, over 4.2 million people in the US suffer from glaucoma. That total could grow to close to five million in three years. Global sales of glaucoma treatments reached nearly $5 billion in 2014. That total should hit $6.6 billion by 2019. By the year 2020, more than 11 million people could be blinded by glaucoma.

With three years of sales behind it, Glaukos estimated its fourth-quarter 2015 net sales to be around $20.1 million. This put the company on pace to record annual sales of more than $71 million, a 57% year-over-year growth. The company went public in 2015. (*See "Ophthalmology Surgeons, Companies Finding Solutions In Medtech"* — START-UP, *September 2015.*) For most of last year, shares bounced between $20 and $30, but they took a dive in January along with the rest of the public markets. With share prices hovering around $15 at press time, Glaukos is pushing forward with a line of microinvasive surgical tools.

Tom Burns
Glaukos Corp.

And Glaukos continues to make a case for its iStent, if not for all of MIGS. Last month, the company shared the results of a clinical study, published in the *Journal of Cataract and Refractive Surgery*, showing that the implant provided a 36% reduction in mean intraocular pressure (IOP) and an 86% reduction in the mean number of glaucoma medications three years following surgery. The open label, non-randomized study was conducted at the Eye Clinic Marienplatz in Munich, Germany, by Medical Director Tobias H. Neuhann, MD.

The long-term data will help Glaukos build a case for reimbursement and payment going forward.

Under the direction of CEO Thomas W. Burns, Glaukos is also building out a broader platform of eye care devices. In January, the company announced that the FDA was allowing it to move forward with an Investigational New Drug (IND) Phase II study of its *iDose* delivery system. Injected through a clear incision in the cornea, the implant is secured in the anterior chamber where it releases *Travoprost*, a prostaglandin analog used to reduce elevated IOP. The titanium implant can be removed once all of the drug is delivered.

Glaukos and other MIGS companies represent a bold move in medtech and ophthalmology. Burns sees Glaukos emerging as a leader, not only in MIGS and glaucoma but more broadly in ophthalmology. He has spent over two decades in the field, most notably serving as president and chief operating officer of Eyetech Pharmaceuticals Inc. Prior to that, he was senior vice president and general manager of Chiron Vision Corp. and vice president, global strategy and general manager, refractive surgery of Bausch & Lomb.

Burns agreed to be interviewed by *IN VIVO* to talk about MIGS and Glaukos. The following is an edited version of that discussion.

IN VIVO: This is an interesting time in ophthalmology. Pfizer's acquisition of Allergan is shining a bright light on the sector. How would you characterize ophthalmology? Is it a "sleeper" specialty?

Tom Burns: Fifteen years ago, I would have said yes. At that time, ophthalmology really resided in the "back waters" of life sciences investing. But in the intervening years, research and innovation have driven new interest in the space. We're also seeing a push for consolidation of the major players within ophthalmology. These players are being absorbed and acquired by pharmaceutical companies that want to build a long-term presence in the space.

What changed? What are the more attractive qualities of ophthalmology?

Ophthalmology has unique components. It's led by a front-line group of innovators who are highly attuned to and are early adopters of new technologies coming into the space. In addition, the entire sector is still in an embryonic stage with respect to unmet clinical needs and is fueled by demographics which portend rapid growth in age-related eye diseases. The dynamics of the aging baby boom population is leading to higher incidence rates in major disease areas such as glaucoma and other chronic, asymptomatic and blinding eye diseases like age-related macular degeneration, or AMD.

Is it simpler to sell directly to the decision-makers than in other specialties? Does the decision-making still fall mostly to the physicians, rather than a technology committee?

In general, ophthalmology is more vertical and efficient in terms of market dynamics than other specialties. You can reach the ophthalmic customer, who overall continues to exercise considerable power in product decision-making, directly through highly targetable channels. As a result, the commercial model in ophthalmology is efficient and requires a relatively low expenditure of manpower to optimize sales.

Ophthalmologists might be quick to adopt new technologies. But how would you characterize innovation in ophthalmology?

Innovation in certain areas such as the treatment of AMD, DME [diabetic macular edema], refractive disorders and cataract-IOL exchange has been rapid and consequential over the last two to three decades.

The pace of developing new techniques and technology in other areas such as surgical glaucoma, however, has arguably been glacial for the last 100 years. The first full-thickness sclerotomy was performed in 1907. We witnessed the introduction of the modern trabeculectomy in 1968. Argon laser procedures and aqueous shunts were introduced in the 1970s. Since that time, there has been very little innovation in surgical glaucoma to address the omnipresent issue of patient non-compliance and non-adherence to medication therapies.

This dearth of innovation has increasingly highlighted the unmet clinical need within the glaucoma surgical community that, until recently, was unable to provide an effective, sustained and highly safe surgical alternative to life-long medication use.

And that brings us to Glaukos and the microinvasive glaucoma surgical space. Where is MIGS in its maturation? And what is the upside? Can this upend ophthalmology like interventional techniques changed cardiology?

The emerging MIGS category, spearheaded by its flagship product, iStent, has the potential to transform glaucoma treatment over the next several years. iStent procedures have demonstrated safe, effective and sustained glaucoma therapy in several long-term prospective clinical studies. Recent published clinical data of a single iStent in combined cataract surgery demonstrated significant reductions in intraocular pressure and medication burden for more than four years.

The iStent's current US indication in combined cataract surgery represents our initial addressable market. This market alone is incipient in terms of initial procedural penetration.

Glaukos founded the MIGS category, launched the first MIGS product, iStent, and intends to lead the next major stage of the category's growth. We have already begun a US IDE trial for phakic/pseudophakic open-angle glaucoma which, if approvable, we believe will allow us to promote iStent therapy to a markedly higher number of patients afflicted with glaucoma.

The pressing need for a highly safe surgical alternative to life-long drug therapy, beset by high rates of non-compliance, we believe will drive the adoption and widespread use of iStent implantation and new-generation iStent injectable therapies.

What is driving the need for MIGS?

I would cite three major drivers: first, the rampant patient non-compliance and local and systemic side effects associated with prescribed life-long medical therapies. Second, you have the current published failure rates of existing laser procedures, and third, the marked sequelae associated with trabeculectomy and aqueous shunt surgical procedures.

How does your iStent solve that problem?

The iStent implant has demonstrated safe and effective therapy and is currently being studied in 17 prospective clinical trials. The implant itself is not subject to patient non-compliance as an impediment to effective therapy.

The procedure's clinical validation of efficacy in combined cataract surgeries is drawn from several published, peer-reviewed clinical studies at three or more years post-operative. The procedure's demonstrated safety profile provides a clinical benefit-to-risk ratio that greatly serves glaucoma patients and provides confidence to comprehensive ophthalmologists who choose to perform iStent procedures.

You received FDA approval for iStent in 2012. Is adoption as strong as you'd hoped it would be? Or has it been a learning curve for your sales force?

The adoption of the product more than exceeded our expectations and the sales team has performed admirably to introduce a new technology that has created a new commercial marketplace. Following our mid-2012 FDA approval, we posted first full-year sales in 2013 of $21 million, which we believe to be the highest revenue, new market, medical device launch in the history of ophthalmology. In our first seven months of commercial introduction, we secured full, national Medicare coverage for the iStent procedure and device. We continue to exhibit strong growth, with annual year-over-year sales up approximately 120% and 57% in 2014 and 2015, respectively.

Looking ahead, our next stages of growth will be fueled by increasing US penetration into the combined cataract-glaucoma co-morbid market, international expansion and the approval of new iStent products and expanded glaucoma indications.

What sort of barriers are you facing from patients and physicians?

New market creation is invariably subject to some minor headwinds. Consumer awareness and comprehensive ophthalmologists' embrace of glaucoma surgery requires capital, the consistent application of multiple resources and effective promotion.

By founding the MIGS category, we embrace the challenge of establishing the long-term safety and efficacy of our iStent pipeline.

And you're doing that by continuing to run clinical trials. So what sort of clinical data have you been releasing recently, and what is it showing?

As surgeons become acclimated to the procedure and implant placement, we have seen efficacy results with a single stent that appear superior to the efficacy results we obtained in our US pivotal trial, which was enrolled by investigators performing their first iStent surgeries and submitted as a PMA in 2008. Moreover, clinical trials with multiple stents have produced promising efficacy results. The iStent's safety results have been consistently and highly positive in all clinical studies.

Recently published peer-reviewed clinical results have also been very positive. Dr. Tobias H. Neuhann's peer-reviewed data show significant reductions in medication burden [86% reduction] and intraocular pressure [36% reduction] to below 15 mm Hg out to three years with the implantation of a single iStent in combination with cataract surgery. An examination of retrospective iStent data presented at a Glaukos symposium during the *AAO 2015* and generated by iStent-certified surgeons is also highly encouraging and further validates improvement in iStent results among trained surgeons.

Further, peer review results from a recently published study evaluating stand-alone iStent implantations in phakic and pseudophakic patients demonstrated that a single iStent reduced intraocular pressures below 15 mm Hg in approximately two-thirds of implanted eyes.

These results are highly compelling, and although no direct comparisons of data can be drawn, appear to be far superior to what we saw in our initial US pivotal trial. I think this reflects the fact that surgeons, once acclimated to the procedure, are placing these stents with a high degree of facility that achieves these positive results. With a single stent, we are highly encouraged with the demonstrated clinical results we are witnessing in combination with cataract surgery. We become even more enthusiastic when we start to think about the

addition of a multiple stent injectable platform. For our *iStent inject*, which is preloaded with two micro-scale stents that a surgeon places through a single corneal entry point, we are conducting two US IDE studies, one in combination with cataract surgery and a second in a stand-alone procedure for phakic and pseudophakic eyes.

So how much of a game changer would that second approval be?

The game changer would come with an expanded indication for phakic/pseudophakic open-angle glaucoma that could allow us to provide clinical benefits to glaucoma patients without the restriction of implanting the device as part of a combined cataract procedure. A stand-alone procedural indication could greatly increase the number of potential glaucoma patients who could benefit from iStent therapy.

You've got the field to yourself right now but competition is coming. AqueSys might have its product available by the end of 2016, Transcend by 2017, Ivantis* [Ivantis Inc.] *a couple years after that. There's a convoy coming, but are you really building the bridges and the roads for everybody else?

I believe that our primary competition continues to be topical glaucoma medications, which comprise the vast majority of the current $5.1 billion global glaucoma market.

By founding the MIGS market category, however, we were able to negotiate and create the initial regulatory path for combined cataract-iStent implantations. This has become the proven regulatory path for potential MIGS competitors pursuing non-refractory glaucoma.

We secured temporary category III current procedural terminology codes for both trabecular bypass and suprachoroidal stents, to which potential competitors will become beneficiaries if approvable.

I believe we have effectively marketed, created rapid commercial adoption and clinically validated in multiple peer review publications the safety and efficacy of iStent therapy. Potential competitors will attempt to use the commercial market and customer base we have created as a base-addressable target market for promotion.

First movers such as Glaukos have enviable commercial advantage in building the marketplace. In so doing, the company may have bridged the entry of potential MIGS competitors by solving issues and retiring several obstacles that potential competitors would normally have to confront in their own development and commercialization process.

Competition can be good and bad. Would it actually help you to have others telling the same story to ophthalmologists about how glaucoma can be treated surgically? This might bring a larger critical mass to this philosophy.

We have a great deal of respect for what potential competitors in the MIGS space are trying to accomplish. And I think that the influx of new products, if approvable, will usher in additional capital, additional focus, and additional promotion that will materially aid growth in what today is a very embryonic space within ophthalmology.

But there has been some jostling. Can you address the settlement of issues with Transcend and what that was about?

We entered into a settlement with Transcend Medical where we agreed to a covenant not to sue Transcend for patent infringement in connection with their current products designed for use in the suprachoroidal space. And Transcend entered into a conditional covenant not to challenge our patents. As part of that settlement, Transcend offered as consideration a limited royalty to Glaukos on sales of its future suprachoroidal stents, if approvable, in global markets.

Was there anything unusual to ophthalmology about that legal entanglement? Or was it just sort of what happens in medtech?

Unfortunately, patent litigation is routine in medtech. Our settlement retires an issue that had become a distraction to our business, and allowed us to refocus our energies on creating what we believe is an enviable and prolific product line that will continue to build corporate value.

OK. What is the significance of the IND application for the Travaprost Intraocular Implant with iDose? This is really a next business line for you, correct?

Correct. We are attempting to build a hybrid medical device company that can provide both outflow and extended drug delivery treatment alternatives that utilize our proprietary injectable microstent platform to treat glaucoma. In so doing, we hope to provide clinicians with customizable, titratable and combination treatment approaches to effectively manage glaucoma. This will allow the clinicians to achieve patient target pressures based upon disease-stage severity at a benefit-to-risk calculus that can best serve each patient.

Our iDose travoprost implant is a key component of this overall strategy to provide customizable treatment approaches to best serve each glaucoma patient.

How will this impact the market?

The iDose travoprost implant may be able to deliver continuous prostaglandin therapy for extended periods of time to effectively manage glaucoma. We believe this product fulfills a clear unmet need in glaucoma treatment and will be widely embraced by the ophthalmic physician community, particularly in light of the longstanding and material clinical issues associated with patient non-compliance and non-adherence to glaucoma medical treatment.

How would this work?

We are attempting to build a customized algorithm and portfolio of micro-injectable technologies that will allow surgeons to customize therapy for each patient based upon disease-stage severity and predesignated patient target pressure.

We believe that we will create a bifurcated market with powerful treatment options. We estimate that a significant cohort of surgeons will prefer injectable extended drug delivery iDose as initial treatment, while a significant cohort of surgeons will prefer our injectable iStent flow devices as initial glaucoma therapy. Most importantly, we believe that surgeons will use these micro-injectable drug and flow technologies in combination as "cocktail therapy" to achieve the highest efficacy result with minimal risk for each patient.

Glaucoma is a multifactorial disease and clinicians have repeatedly recognized the value of using different and combined mechanisms-of-action to reduce intraocular pressure in glaucoma patients. Glaukos has prepared the landscape for various treatment approaches by securing coding and coverage that will enable these new treatment approaches in the future.

How broad a platform could this be? Are you building off of the sort of core technology that started the company? Or are you really moving into completely different technological approaches as well?

We are using the micro-injectable and proprietary core technology that we've worked to develop for more than a decade. We're building upon this with additional new, proprietary drug delivery technologies to create a unique and novel blend of market-leading technologies that could effectively serve the glaucoma community for the next two to three decades. So the answer is we are attempting to do both.

If we are successful in creating this drug delivery platform, we may be able to develop new, extended drug delivery products that can greatly add value to our product pipeline, to the glaucoma community and, we hope, to glaucoma patients worldwide.

We started the conversation talking about the Pfizer Allergan acquisition. We'll see if the new Pfizer will retain a strong interest in ophthalmology, but if it doesn't this could create a vacuum that smaller companies can grow into. Is Glaukos that kind of company? Can you not only develop your own products but become an acquirer of other technologies? Do you see that happening down the road?

I believe so. First and foremost, we will remain a glaucoma-centric company and maximize our core set of technologies and new generations within the discipline. But I also believe that we will be able to identify and acquire additional technologies in the future that can both serve new ophthalmologic indications and create increased corporate value.

Our advantage may lie in our nimbleness and speed, our demonstrated execution and our proven ability to create new markets in ophthalmology that may allow us to attract and commercialize novel, new technologies.

Well, it changes a lot of things. Is there a precedent for you where a company created around a single concept goes public on that idea, and eventually grows into a full-service device medtech company, serving an entire sector? Is there a model?

Innovative companies that launched novel cardiac stents and drug-eluting cardiac stents have created an entirely new interventional market category and have developed fuller medtech capabilities upon this core can be regarded as interesting predicates for us. But I believe what we are ultimately trying to accomplish is somewhat unique in medtech.

A#2016800035

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

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Medtechs Bet On Transcatheter Mitral Valve Repair

The success of transcatheter aortic valve replacement has generated optimism that the much larger pool of mitral regurgitation patients can be similarly served. While big strategics bet on replacement, other companies are betting on repair, developing less invasive devices inspired by an array of established mitral valve surgical repair techniques.

BY JENNY BLAIR

- Big medtechs made a number of mitral valve replacement M&A deals in 2015, while other companies, including start-ups, are betting on mitral valve repair, a market that may be four times larger than TAVR.
- But the road for new mitral interventions may be rockier than it was for TAVR. Among aortic stenosis patients, it is much more obvious who needs TAVR, whereas for MR patients indications often are unclear.
- Due to the complexity of the mitral valve, it's likely that multiple minimally invasive devices will share the space in the future, perhaps in a stepwise or combination fashion.

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The summer of 2015 saw massive strategic acquisitions by **Edwards Lifesciences Corp.**, **Medtronic PLC**, **HeartWare International Inc.** and **Abbott Laboratories Inc.** of transcatheter mitral valve replacement devices; also in 2015 – Abbott's transcatheter mitral valve repair device *MitraClip* saw its 25,000th patient. The success of transcatheter aortic valve replacement (TAVR) has generated optimism in the industry that the much larger pool of mitral regurgitation (MR) patients can be similarly served.

While big strategics bet on replacement, however, other companies are betting on repair, developing less invasive devices inspired by an array of established mitral valve surgical repair techniques. These companies are ambitious. For instance, **Mardil Medical Inc.** projects a $3.2 billion US market for its ventricle-reshaping device to treat MR.

Some estimate that the transcatheter mitral valve replacement/repair (TMVR) market opportunity is four times larger than TAVR's; estimates for replacement alone are as high as $10 billion. New mitral valve options not requiring open-heart surgery could be on the market as soon as 2017.

However, many insiders say the road for new mitral interventions will be rockier than it was for TAVR. Among aortic stenosis patients, it is much more obvious who needs TAVR, whereas for MR patients indications often are unclear. Anatomical and technical problems relating to the mitral valve are also more challenging compared with the aortic valve.

DARING TO REPAIR FMR

There are two main types of MR, a condition in which blood backs up abnormally into the left atrium through a compromised mitral valve as the ventricle squeezes blood out the aortic valve.

Degenerative mitral regurgitation (DMR) distorts the valve itself. Standard of care for advanced cases is surgical repair via a complex array of techniques, and sometimes replacement. Repair techniques include annuloplasty (optimizing size or shape of the ring at the base of the valve), leaflet reshaping or sewing, chord repair or replacement, and the Alfieri approach, which clips together the valve leaflets, creating two apertures instead of one and reducing regurgitation. In open surgery, this approach is usually combined with other repair techniques, including annuloplasty. MitraClip uses the Alfieri approach and is FDA-approved for patients with significant symptomatic DMR at prohibitive risk for mitral valve surgery.

By contrast, functional mitral regurgitation (FMR) is a disease of the ventricle that only secondarily affects the valve. The ventricle becomes abnormally dilated, often after heart attacks, and the valve's leaflets are pulled apart. Few FMR patients are currently considered good surgical candidates, although many are treated with MitraClip.

Many early-stage repair companies are aiming at FMR, adapting an established surgical technique to a minimally invasive approach. Complicating their prospects, however, is a lack of consensus as to the gold standard treatment for FMR. In contrast, those companies aiming at DMR must compete with an accepted surgical gold standard. (*See Exhibit 1.*)

REPRODUCING ANNULOPLASTY

Millipede Inc. believes it may have an FMR repair solution that more faithfully reproduces surgical solid-ring annuloplasty. Backed by Santé Ventures, Millipede has flown under the radar since its 2011 founding by Steven F. Bolling, MD, a mitral valve surgeon at the **University of Michigan**, and veteran device engineer and current CEO Randall Lashinski, who also co-founded the TAVR start-up **Direct Flow Medical Inc.** and the cerebral-protection start-up **Claret Medical Inc.** The company's patented adjustable mitral valve ring compresses to a slender diameter, then expands to anchor in the stretched-out native annulus and contracts to reshape it, reducing the anteroposterior diameter of the annulus. (*See "Millipede's Play In Percutaneous Mitral Valve Repair"* — START-UP, *January 2016*)

According to Santé partner James Eadie, MD, the device allows for future repair or replacement options, including a surgical annuloplasty ring. That means Millipede could target younger, healthier patients who may need further mitral intervention down the road. The company completed early first-in-human studies and is now "well on our way" to developing a 32 French (32F) transfemoral delivery system, according to Eadie. It plans to publicly release data in 2016.

Bolling says Millipede's is the only therapy that brings the dilated mitral valve annulus back to a normal size.

Mitralign Inc.'s *Mitralign System* is an annuloplasty device for FMR delivered transfemorally. Rick Geoffrion, president and CEO, believes the system could make a good frontline therapy option because its small footprint keeps future options open for the relatively young FMR patient population.

The company presented six-month data from its now-complete CE mark trial at the 2015 *Transcatheter Cardiovascular Therapeutics* (TCT) meeting held in San Francisco in October. The 41-patient study found statistically significant postprocedure reductions in the size of the ventricle and mitral annulus, as well as significant improvement in patient symptoms. These were sick patients with an average preprocedure ejection fraction (EF) of 32.7%. Residual MR from grade 1 to 4 remained in all patients; the six-month mortality rate was 12.2% due to five patient deaths within 60 days. That percentage is "lower than that reported by competitive technologies in the FMR population," Geoffrion says.

"We showed statistically significant remodeling of the heart at six months, which we believe is a more accurate portrayal of how the heart is functioning than the measurement of pure MR," Geoffrion says. "You're literally reversing the course of the disease."

As it awaits CE mark approval for its mitral device, Mitralign is enrolling patients in its US IDE SCOUT Study to investigate tricuspid repair using its platform.

This October at TCT, the angel-backed company **MVRx Inc.** presented results of its ongoing CE-mark MAVERIC trial of the *ARTO System (Septal Sinus Shortening)*; at 30 days, every patient was noted to have at least a one-grade reduction in MR. ARTO consists of a 12F transfemoral delivery system that places a polyethylene suture across the mitral valve in FMR patients, reducing its anteroposterior diameter and reducing MR. Co-founder, president and CEO Robert T. Chang estimates the trial will conclude in 12 to 15 months and anticipates CE mark in third-quarter 2017.

Chang says ARTO's cost and simplicity make it competitive "for parts of the world that can't afford MitraClip. We also think it can compete directly with MitraClip and others in this space."

In preliminary discussions with reimbursement authorities in the EU – the company will begin more detailed discussions during the trial's final phase – Chang has found that Abbott has already partially cleared the path. MVRx aims for acquisition or partnership, as it does not plan to build its own sales force.

Cardiac Dimensions Inc. earned CE mark in 2009 for its *CARILLON Mitral Contour System*, a double-anchored annuloplasty device that is placed in the coronary sinus via the jugular vein. Last March, the company announced a $43 million funding round led by Life Sciences Partners and Aperture Venture Partners. CARILLON is currently undergoing a prospective, multicenter, randomized, double-blind trial launched in June 2015 called REDUCE FMR.

HeartWare International Inc. in September purchased **Valtech Cardio Ltd.**, which is developing *Cardioband*, a transfemoral annuloplasty device that allows for real-time reduction in annular diameter and MR in the beating heart. At TCT this October, Valtech presented the results of a single-arm multicenter study of 45 patients in Europe receiving Cardioband, all with moderate to severe FMR and all high-risk surgical candidates. At 12 months, 95% of the patients had MR at or below grade 2. There were two deaths deemed not device-related. Some insiders believe this device may be the repair-side frontrunner. (*See "More Than Just A VAD Maker: HeartWare Broadens Heart Failure Focus With Valtech Buy"* — "The Gray Sheet," *September 2, 2015*.)

In addition to the developed markets, **Phoenix Cardiac** focuses on emerging markets like India and China where cardiac disease is on the rise. *BACE* – Basal Annuloplasty of the Cardia Externally – is a lower-cost approach developed for FMR by cardiac surgeon Jai Raman, MD, PhD, of **Rush University Medical Center**. The procedure requires open chest incision and has so far

Exhibit 1

Selected Minimally Invasive Mitral Valve Repair Companies, By Technique

COMPANY	TECHNOLOGY	COMMENTS
ANNULOPLASTY: RESHAPING OR REDUCING SIZE OF FIBROUS RING, OR ANNULUS, AT BASE OF MITRAL VALVE		
Cardiac Dimensions	CARILLON Mitral Contour System: double-anchor device in coronary sinus	Delivery through jugular vein; peri-procedural recapture possible; CE mark 2009; current multi-site randomized blinded trial, REDUCE FMR
Millipede	Adjustable mitral valve ring	Mimics surgical annuloplasty for FMR; first-in-human study completed; will release data in 2016
Mitralign Inc.	Mitralign System: pledgets across annulus	First-in-human study in FMR found significant reductions in ventricle and annular dimensions with 12% mortality rate and residual MR
MVRx Inc.	ARTO System: suture across valve for FMR	For FMR; lower-cost; CE mark anticipated in Q3 2017; MAVERIC trial underway
Phoenix Cardiac	BACE, or Basal Annuloplasty of the Cardia Externally: annuloplasty without open-heart	For FMR; requires sternotomy; lower-cost; CE mark study underway; goal is CE mark in Q4 2016 or Q1 2017
Valtech (now part of HeartWare International)	Cardioband: flexible annuloplasty band	Allows for real-time adjustment of annular diameter during procedure; single-arm study of 45 patients found substantial reductions in MR at 12 months
ENHANCED COAPTATION		
Cardiosolutions Inc.	Mitra-Spacer: leaflet spacer consisting of balloon tethered at apex	Adjustable, allowing gradual reduction in FMR; lower-cost; CE mark trial in Europe in Q1 2016
coramaze technologies GMBH	mitramaze valve repair system: leaflet spacer consisting of balloon anchored in left atrium	Intended for use in FMR by cardiologists; received €4.5m Series A in Sept. for first-in-human
Guided Delivery Systems	Accucinch: cable across ventricle, pulling leaflets together	Case report of FMR patient: MR reduction from grade 3 to grade 1 at 30 days; completing feasibility trial
SHORTENING, REPAIR, OR REPLACEMENT OF CHORDAE TENDINEAE		
Harpoon	Harpoon device: chord replacement in DMR	Transapical delivery of adjustable neochords; feasibility study found moderate to trace MR at 30 days; CE mark anticipated in Q2 2017
NeoChord	DS1000: chord replacement in degenerative mitral regurgitation (DMR)	CE marked and in clinical trials in Europe; 6 reported reoperations in study of 30 patients; raised $20m Series C in June
Valtech (now part of HeartWare International)	V-Chordal: chord replacement in DMR	First-in-human study complete; trial timing not released
EDGE-TO-EDGE APPROXIMATION OF LEAFLETS (ALFIERI REPAIR)		
Abbott	MitraClip	FDA-approved in DMR; often used in FMR; over 25,000 patients treated; often residual MR
EXTRACARDIAC ANNULOPLASTY		
Mardil	VenTouch: compressive sleeve placed around ventricle	Transapical delivery; adjustable fluid chamber; proof-of-concept study underway; CE mark trial and Series C anticipated in 2016

SOURCE: *Medtech Insight*

been studied both as a stand-alone procedure and also as a concomitant operation with cardiac bypass grafting. But with BACE, the cardiac surgeon does not open the heart itself, instead plastying of the mitral valve annulus near the atrioventricular groove is performed. The annular diameter can later be adjusted in an outpatient setting via subcutaneous saline ports placed in the flank. In addition to post-op adjustability, the BACE device provides sub-annular support.

Fourteen people in India have received the operation alongside CABG. CEO Gopal Muppirala says that the first patient, implanted in 2008, continues to have an MR of grade 1, the lowest grade, and that there have been no major device-related significant adverse events. The company is now halfway through a five-country CE mark study that commenced in January 2013. Its goal is CE mark in fourth-quarter 2016 or first-quarter 2017, and it plans to meet with the FDA early next year to start the IDE process.

Phoenix's founders were originally part of Mardil, but left to start Phoenix Cardiac as a self- and angel-funded concern in 2012 to continue the development of the BACE device. They licensed global IP rights to BACE from Mardil. Muppirala says BACE will be premium-priced at a little higher than annuloplasty rings, a key differentiator he says may aid Phoenix to serve patients who cannot afford percutaneous approaches such as MitraClip, as well as offer US hospitals the chance to keep a larger portion of a Medicare reimbursement for mitral valve repair.

"It's going to be very hard for someone charging $10,000 or $20,000 just for the device itself to get in" to markets such as India, Muppirala says. Similarly, devices requiring hybrid surgeon-cardiologist teams may be at a disadvantage in less wealthy countries, whereas BACE, he says, takes surgeons 20 minutes to learn. Phoenix will soon talk to US strategics in hopes of an exit after CE mark.

"People should be thinking about making the device development more surgical-friendly," Muppirala says. "Percutaneous is not the only way."

ENHANCED COAPTATION TECHNOLOGIES

Rather than mimicking surgical repair approaches, the German medical device start-up company **coramaze technologies GMBH** aims to create a mitral valve repair system for severe FMR patients that pioneers spacer coaptation technology. Delivered via the transfemoral artery through a 12F delivery system, the *mitramaze* valve repair system places a spacer balloon in the mitral valve that is atraumatically anchored in the left atrium. The mitral leaflets close around the spacer balloon, closing the gap in the mitral valve. With a less-demanding delivery system that involves no suturing or clipping, says CEO Laura Figulla, PhD, the process is intuitive for cardiologists. "That is definitely something that will be important for market penetration, because not every hospital has a hybrid room," she says, referring to an operating room designed for both interventional cardiologists and surgeons.

> Beyond a certain degree of heart failure, it's not clear how much recovery the ventricle will undergo even after a successful mitral repair or replacement.

coramaze announced a €4.5 million Series A round on September 1, led by Israeli holding company **Elron Electronic Industries Ltd.** The funding covers a first-in-human study.

Employing a variant on this technique is **Cardiosolutions Inc.** This start-up's device for FMR patients, *Mitra-Spacer*, consists of a transapically delivered (through the tip of the ventricle via the chest wall) balloon placed between the anterior and posterior leaflets of the mitral valve. The partially filled Mitra-Spacer balloon, which is tethered at the ventricular apex, then conforms to each leaflet, enabling them to seal against the balloon. The balloon's size can be adjusted in an outpatient setting via a subcutaneous injection port, allowing for a gradual rather than abrupt reduction of MR.

"You don't change any of the anatomy of the native mitral valve," says John Wilson, senior technical director of clinical operations, who adds that the device could bridge a patient to future repair or replacement. (He should not be confused with Jon Wilson, the company's former COO.)

Wilson says Mitra-Spacer costs about $150 to make, will be "value-priced" and will be attractive in an era of outcome-based reimbursement because it could keep patients from returning repeatedly to the hospital.

Contingent on funding, the company plans a CE mark trial in Europe in first-quarter 2016. Its IP relates to adjustability and tethering, and it shares some licensing with Edwards, which is pursuing a similar balloon strategy with its *Forma* device for the tricuspid valve. (coramaze holds tricuspid-related patents as well.)

VENTRICULAR RESHAPING

Whereas most repair and replacement approaches to FMR focus on the valve itself, Mardil Medical treats the dilated ventricle, which is the primary cause of FMR.

The company's implantable device, *VenTouch*, is a woven sleeve that surgeons place around the beating heart through a small incision between the ribs. The sleeve helps reduce wall stress and "helps the heart to repair itself and result in a smaller size and improved shape," says CEO Jim Buck. VenTouch also includes a prescriptively positioned adjustable fluid chamber, which is inflated to bring the leaflets of the mitral valve back together and further reduce the severity of the MR. (*See "Mardil Medical Inc."* — START-UP, *March 2014*.)

"We think the battle will be fought and won around improving heart health, not just reducing the regurgitation," says Buck, a medtech veteran and the former CEO of SetPoint Medical Corp.

Winning that battle, according to Mardil's estimates, could mean a US market as large as $3.2 billion.

Mardil builds upon the ideas and IP of several previous companies, including **Acorn Cardiovascular Inc.** and **Myocor Inc.**, whose *Coapsys* ventricular-reshaping device demonstrated improved survival in a randomized study of FMR patients published in a 2010 *Journal of the American College of Cardiology* paper. The company currently holds about

100 patents in the US and Europe. The first patients received VenTouch in February 2014 in Malaysia, with what Buck says are "compelling results," and now Mardil is in the midst of a proof-of-concept clinical trial in Canada and the EU that it expects to complete next spring. Buck says the firm will raise a Series C round and anticipates beginning a CE mark trial in mid-2016, as well as applying for an IDE with the FDA. Sales could begin as soon as late 2017, he estimates.

Guided Delivery Systems Inc. is also developing a ventriculoplasty approach in which it cinches the ventricle and reportedly reduces the circumference of both ventricle and mitral valve annulus. The company presented a case report at TCT this October of a patient with heart failure and severe FMR whose severity was reduced from grade 3 preprocedure to grade 1 postprocedure. GDS said at that time that it was completing its feasibility trial.

MitraSpan Inc., a stealth-mode company that has raised a Series B round, is testing a version of suture-based annular and ventricular reshaping via a size 5F to 9 F transapical system. Co-founder and CEO Jonathan Rourke says the system allows surgeons to implant suture spans across the annulus and ventricular cavity, durably anchoring them within the heart in structurally sound locations and reshaping the mitral apparatus and adjacent ventricular structures for greater efficacy. Over 25 years, Rourke has held leadership positions at Viacor Inc., TransMedics Inc., EndoTex Interventional Systems Inc. and Hewlett-Packard Co.

DMR REPAIR: AN UNUSUAL NICHE

Unlike in FMR, for DMR, there are already safe and effective surgical options. Still, there may be advantages to a less invasive approach, and some repair companies are aiming at this type of MR.

Harpoon Medical Inc. is first exploring a beating-heart, transapical repair option for degenerative mitral valves, one intended to replicate the gold standard but highly invasive surgical approach to chordal repair. Its *Harpoon* device allows for the placement and anchoring of neochords made of ePTFE and delivered via a 9F system. The chords contain a pre-tied knot. The device fires them through the mitral leaflet at high speed, then the knot emerges on the atrial side, securing the chord in the leaflet and then to the ventricle. The chords' length can be adjusted under image guidance in real time, allowing for fine-tuning based on the degree of remaining MR. The device is the brainchild of mitral valve surgeon James S. Gammie, MD, chief of cardiac surgery at **University of Maryland School of Medicine**.

The company hopes its approach will allow for earlier referral of patients with severe DMR, including low-risk surgical candidates, and for later replacement or repair if necessary. It estimates a potential $9 billion US market segment. (*See "Harpoon Medical Inc."* — START-UP, *June 2015*.)

At TCT, Harpoon presented the results of a two-site European feasibility study in early 2015 that enrolled 10 patients with severe DMR and an average EF of 61%. Results at 30 days ranged from moderate to trace MR, with no mortality; perioperative complications included two perioperative reoperations for cardiac tamponade and one late reoperation for recurrent MR.

Surgeons can learn the technique quickly, according to Harpoon president and CEO Bill Niland.

Unusually for this space, Harpoon is aiming at low-risk patients as well. "We feel we can repair these same patients with as good as or close to as good a repair as open-heart surgery," Niland says.

The company will conduct a six-site CE mark study, planned to begin in first-quarter 2016; Niland anticipates a CE mark by second-quarter 2017, at which point it will follow patients in a registry.

Harpoon, too, plans to begin a US pivotal trial late next year, according to Niland. "[The FDA has] been very good, pushing us to move toward our pivotal trial sooner rather than later," he says. "They don't want to see the big lag of TAVI in the US compared with TAVI in Europe [with mitral technologies]."

Harpoon's chief competitor is **Neochord Inc.**, which targets early and/or asymptomatic DMR patients in a transapical beating-heart repair; it replaced damaged chordae by attaching leaflets to papillary muscles with a suture. As reported in October at TCT, a safety and feasibility study of 30 patients led to one death from post-cardiotomy syndrome with sepsis and six reoperations for failed repairs. Neochord's *DS1000* is CE marked and in clinical trials in Europe.

In addition to repair device Cardioband and replacement device *Cardiovalve*, Valtech is also developing *V-Chordal*, a chord-replacement device for DMR. In September, Valtech's purchaser Heartware said in a press release that it is evaluating the timing of a trial.

REPAIR, REPLACE, OR BOTH?

Insiders agree that, due to the complexity of the mitral valve, multiple minimally invasive devices will share the space in the future, perhaps in a stepwise or combination fashion. But getting to that point may take a while, as big questions remain. Will repair or replacement dominate? Which route is best? For which MR patients will devices be indicated? (*See Exhibit 2*.)

FMR leads to a vicious circle of ventricular damage and heart failure, with the mitral valve itself not only an effect of that damage but an exacerbator. Beyond a certain degree of heart failure, it's not clear how much recovery the ventricle will undergo even after a successful mitral repair or replacement.

"The question of 'repair/replace/do nothing' has been raging in the surgical community for decades, even before consideration of catheter-based therapies," Rourke says.

"If you take myopaths [patients with weakened, dilated heart muscle] with a lot of MR and just repair the valve, no one's ever been able to show any mortality benefit," says William E. Cohn, MD, a **Texas Heart Institute** cardiothoracic surgeon, device-industry veteran and venture partner with Millipede backer Santé Health Ventures. "Now people are saying, 'Well, we should just replace the mitral valve in these patients instead of repairing them,' … but that's not been shown to have a big mortality benefit either."

"The only technology that I'm aware of that really showed a mortality benefit in these big dilated ventricles with bad MR is the Myocor device," Cohn continues, referring to the now-defunct company whose Coapsys device consisted of a cable threaded through the heart that pulled the ventricle in on itself slightly. (Mardil inherited Myocor's IP.)

Bolling, the mitral-valve surgeon and Millipede founder, also points out that in FMR the ring at the base of the valve, or annulus, gets so stretched that any replacement valve necessarily is much larger than a native valve. By consequence, he says, "the ventricle is then not allowed to come back down to normal size," referring to potential ventricular remodeling. (The degree to which such remodeling occurs in FMR after repair, at least, may

Exhibit 2

Minimally Invasive Mitral Valve Interventions: Repair Versus Replacement

MINIMALLY INVASIVE MITRAL VALVE INTERVENTION	REPAIR (compared with replacement)	REPLACEMENT (compared with repair)	BOTH, versus surgery
PROS	• May allow future interventions • May allow ventricular remodeling • Failure may have lower stakes • Ventricular-repair options may treat root cause of FMR • Some options inexpensive	• Less recurrent MR • May correct MR almost completely	• May carry usual advantages of less invasive procedures, including less pain, greater safety, shorter hospital stay
CONS	• May not completely correct MR • Recurrent MR	• Large valves in FMR make transcatheter packaging technically difficult • Large valves in FMR may limit beneficial ventricular remodeling • Failure may have higher stakes • "Patient for life," requiring anticoagulation	• DMR patients already have effective surgical options • Mortality benefit and indications unclear for FMR intervention, whether surgical or minimally invasive

SOURCE: *Medtech Insight*

become clearer from MitraClip's randomized multicenter US clinical trial, COAPT.)

So, large strategic bets notwithstanding, it's still unclear whether patients with large, dilated ventricles and FMR will benefit by replacing those regurgitant valves.

HEAVY STRESSES

A replacement mitral valve is under heavy stresses, Rourke points out, calling this part of the body a "merciless environment. ... Every time the mitral valve closes, the entire systolic pressure of the heart is trying to pop the mitral valve into the atrium," he says. Some transcatheter mitral valve manufacturers like **Tendyne Holdings Inc.** employ supplemental anchoring devices in the ventricle.

Rourke cites concerns about catastrophic fatigue failure with the commonly employed device material nitinol and the risk of paravalvular leakage and dislodgement of replacement valves that hold themselves in place exclusively by grabbing the anatomy around the annulus (as opposed to being anchored in the ventricle).

"I think it's very, very much in question whether that concept can soon be made to work with sufficient reliability and safety, given the early results," Rourke says. "These valves have to stand up to the absolutely sternest possible performance requirement. I think in all this rush of enthusiasm, a lot of history has been forgotten." In the 1980s, the early-generation Bjork-Shiley replacement valve suffered catastrophic fatigue failures in some patients.

"Three years ago … longtime mitral people looked at catheter-delivered replacement valves as this challenging bridge too far," Rourke adds. "Now there's all this investor-driven enthusiasm. ... [With] repairs, notably so far with MitraClip, you fail back to where you started. With replacements, you fail and you very often face life-threatening complications."

WHICH PATIENTS? HOW TO STUDY THEM?

Determining indications in FMR patients may take longer than overcoming technical hurdles, says Ted E. Feldman, MD, director of the Cardiac Catheterization Laboratory at NorthShore University Health System in Evanston, IL. With FMR patients, there is no consensus on surgical benefits. For TAVR, it was clearer which patients would benefit, he says, but even with a mature technology like MitraClip, "we're still, a decade into it, arguing about who's the right patient." Similarly, Bolling, the mitral valve surgeon, believes that it will be harder to demonstrate a clear mortality benefit for these devices in FMR patients than it was in aortic stenosis patients; the sickest ones may die of other causes despite having their MR corrected. Yet many insiders expect regulators will require studies of FMR interventions to begin with this very sick population.

Raj Denhoy, a managing director and senior research analyst with Jefferies, says early data suggest less sick patients may do better, citing Tendyne's experience so far with its transapically delivered mitral valve: "The general consensus was they were very

good about picking patients that were not super sick."

"With most of these devices, where you can help the most is if you could intervene earlier in the process and stop people from getting to Class IV heart failure," Chang explains.

Some insiders say that the potential efficacy of early intervention argues for repair over replacement, as repair can be undertaken in younger patients and leave more options for future repair or replacement.

Also in favor of repair is a surgical saying: A patient with a replaced valve is a patient for life. Such valves often require anticoagulation and lifelong monitoring, whereas at least in surgical experience, a patient with a mitral valve repair can walk away and do fine indefinitely.

That said, residual MR dogs repairs. Shmuel Banai, MD (a stockholder in replacement-valve company **Neovasc Inc.**) of the Tel Aviv Medical Center told a TCT audience in October that many repair procedures – including MitraClip, Mitralign and Cardioband – leave the patient with substantial residual MR, whereas so far, transcatheter mitral valve replacement does not. He predicted replacement will become standard of care for high-risk severe MR patients.

An article in the *New England Journal of Medicine* in November 2015 reported the Cardiothoracic Surgical Trials Network's outcomes of a study of 251 FMR patients randomized to either surgical repair or surgical replacement. At the two-year mark, there were no significant differences in a measure of left-ventricular recovery or clinical outcomes. But the repair group showed much higher rates of recurrent moderate or severe MR than did the replacement group – 58.8% versus 3.8%.

In July, a multidisciplinary group of experts, the Mitral Valve Academic Research Consortium, or M-VARC, published research guidelines for studies of transcatheter mitral valve therapies. Co-author and **Columbia University** interventional cardiologist Gregg W. Stone, MD, told a TCT 2015 audience that, for instance, DMR and FMR shouldn't be studied in the same pivotal approval trial, and devices for DMR should be compared with surgery while devices for FMR should be compared with medical care or, perhaps in the future, MitraClip. Such standards should help researchers to clarify the many unknowns in this space.

HOW LONG A WAIT?

This multiple-device scenario for mitral valves isn't just around the corner, but it may not be long now, either.

"These things could be on the market in a couple of years. Companies are pushing," says Denhoy. He suggests a product could be approved in late 2017 for the European market.

Rourke believes the field will undergo steady but not exponential progress, with no pivotal studies of replacement valves in the US for at least two to three years. "There won't be a Big Bang in mitral," he says.

Cohn says, "It wouldn't surprise me if there weren't aggressive marketing battles in the mitral space in the next three years – unless of course the data's no good."

In September, Joanne Wuensch of BMO Capital Markets projected a replacement product on the market in Europe in 2017 and in the US in 2020.

In the meantime, repair and replacement companies alike are treading unknown territory, with the lamp of TAVR precedent shining perhaps not as brightly as some investors might believe. As Cohn puts it, "There's tons we don't know. We don't know more than we know."

A#2016800032

IV

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

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ONTHEMOVE

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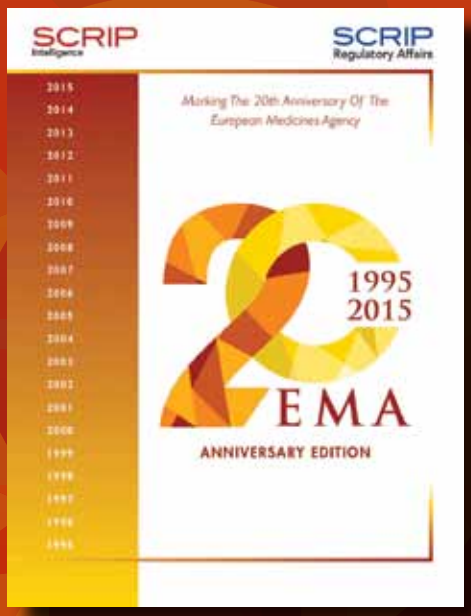

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DEALMAKING

This issue's Dealmaking covers deals made:

January 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

bioTheranostics spins off of **bioMerieux** and regains independence following $32mm venture round

Thermo Fisher Scientific acquires **Affymetrix** for $1.3bn

Alliances

DiamiR, **Janssen** team up in neurodegenerative conditions

KineMed licenses **Pfizer** biomarker technology

MEDICAL DEVICES

Mergers & Acquisitions

Almirall exercises option to acquire remainder of **Thermi** for $80mm

Digirad acquires **DMS Health Technologies**

Katena buys **Sensor Medical Technology**

MiMedx pays cash and stock for **Stability**

NuVasive pays $380mm in cash for **Ellipse**

ResMed buys fellow respiratory device maker **Inova Labs**

Sectra AB acquires Swedish cloud-based IT company **RxEye AB**

SurModics acquires device company **NorMedix** for $14mm

Teleflex acquires catheter tip placement company **Nostix**

Theragenics takes over the US and Canadian brachytherapy seed business of **Eckert & Ziegler Bebig**

Alliances

Nanotherapeutics grants **Amend Surgical** exclusive rights to *NanoFUSE*

Unilife to supply injector devices to **Amgen**

Financings

Digirad secures up to $40mm in credit facility with Wells Fargo Bank

Senseonics files for IPO

PHARMACEUTICALS

Mergers & Acquisitions

Acorda acquires PD-focused **Biotie** for $363mm

Allergan buys **Anterios** for $90mm to expand aesthetics offerings

Anterios divests botulinum assets to form a new company

Juno buys **AbVitro** for $132mm in cash and stock

PPD spins-off **X-Chem**

Roche pays up to $535mm for epigenetics-focused **Tensha Therapeutics**

Alliances

4D Molecular Therapeutics to discover gene therapy vectors for **Pfizer**

Affimed and **Merck** enter trial collaboration for Hodgkin lymphoma

Grunenthal gets rights to **Akashi**'s DMD compound

Centauri acquires **Altermune**'s *Alphamer* technology

Gene therapy company **Angiocrine Bioscience** collaborates with **Terumo** for clinical cell manufacturing

Merck sells corticotropin NDAs to **ANI** for $75mm

Arbor gets US rights to **Debiopharm**'s triptorelin

Boehringer and **Arena** team up in schizophrenia research collaboration

AZ and **Moderna** expand relationship, now in immuno-oncology

AZ and **Incyte** investigate combo therapy for NSCLC

AZ licenses PCOS candidate to **Millendo**

Athersys finds new Japanese *MultiStem* partner in **Healios**

Avalon gets *NexoBrid* rights from **MediWound**

Baxalta options rights to six immuno-oncology projects from **Symphogen**; could pay up to $1.78bn

Biogen enters CNS research collaboration with **Rodin**, secures option to buy company

Merck and **BioLineRx** enter pancreatic cancer trial collaboration

Kedrion gets US *Bivigam* rights from **Biotest**

Dual Therapeutics and **Bristol** sign small-molecule cancer deal

Roche, **C4 Therapeutics** focus on targeted protein degradation

Rhythm to develop new formulation of setmelanotide using **Camurus**' *FluidCrystal* technology

Following **AbVitro** purchase, **Juno** ponders IP transfers to **Celgene**

Complix to develop cancer *Alphabodies* for MSD

Takeda and **enGene** partner

Enterome to help create Crohn's therapies for **Janssen Biotech**

Teva and **Checkpoint Therapeutics** agree to collaborate on CEP8983/CEP9722 for cancer

Sanofi and **Innate** partner in new immuno-oncology deal

Janssen, **ViiV** work on another combination HIV therapy

Zymeworks invests in **Kairos**; gains option to merge

MannKind, **Receptor** ally in *Technosphere* partnership

Merck partners with **Quartet Medicine** in pain; gains option to buy company

Merck KGAA, **Pfizer**, and **Syndax** enter ovarian cancer trial collaboration

Nestle Health Science gets ex-US and Canadian rights to **Seres**' CDI and IBD compounds

Novartis, **Surface Oncology** collaborate on immunotherapies

X-Chem runs discovery engine for **Sanofi** programs

Servier Canada gets rights to four of **Spectrum**'s cancer therapies

Janssen gets ex-Chinese rights to HBV therapies from **Chia Tai**

Proximagen, **Saniona** collaborate on small-molecule CNS therapeutics

Financings

Acadia Pharmaceuticals nets $282mm in public offering

Acceleron Pharma nets $141mm in follow-on offering

Adamas Pharmaceuticals nets $54mm in FOPO

Agile Therapeutics nets $33mm in FOPO

Akebia nets $61mm in FOPO

FOPO nets $81mm for **Ardelyx**

Bavarian Nordic seeks to go public in US

CASI gets $10mm through first PIPE closing

Cempra nets $94mm via FOPO

Clearside Biomedical seeks to go public

Corvus Pharmaceuticals files for IPO

Genome editing company **Editas Medicine** files for IPO

Epizyme closes $130mm public offering

ESSA Pharma closes $15mm private placement

Public offering nets $20mm for **Galena**

Halozyme enters into $150mm debt financing backed by *Enhanze* royalties

Moberg Pharma enters into loan agreement for SEK 300mm

Otonomy nets $94mm in follow-on public offering

Reata Pharmaceuticals files for IPO

SAGE Therapeutics Inc. nets $141mm in public offering

Spring Bank files for IPO

TherapeuticsMD nets $117.5mm through public offering

Visterra seeks to go public

MERGERS & ACQUISITIONS

/In Vitro Diagnostics

INSTITUT MERIEUX
bioMerieux SA
bioTheranostics Inc.

Following a $32mm venture investment from MVM Life Sciences, Canepa Healthcare, and HealthQuest Capital, **bioTheranostics Inc.** (molecular diagnostics for cancer) has spun off of **bioMerieux SA** and will operate as an independent company. (Jan.)

In 1996, bioTheranostics was founded under the name Arcturus Bioscience, and renamed AviaraDx before bioMerieux bought the company in 2008 and gave the firm its current name. Flagship products include *Breast Cancer Index*, a PCR-based tool that helps determine likelihood of success for extended endocrine therapy in patients with ER+ breast cancer, and *CancerTYPE ID*, a gene expression test for metastatic patients that helps determine cancer of origin in cases where the tumor type is otherwise classified as unknown or unspecified.

THERMO FISHER SCIENTIFIC INC.
AFFYMETRIX INC.

Thermo Fisher Scientific Inc. is paying $14 per share in cash (a 43% premium) to acquire public genetic analysis company **Affymetrix Inc.** (DNA-based systems for research instrumentation and clinical diagnostics). The transaction is expected to close by the end of Q2 2016 and is subject to approval from Affymetrix shareholders (Thermo Fisher board has already approved it). The combined company will feature complementary technologies of both Thermo and Affymetrix in the areas of genomic and cellular analysis. (Jan.)

Affymetrix was founded in 1991 as a division of Affymax NV (which was purchased by Glaxo Wellcome in 1995) and completed an $83mm IPO in 1996. It has particular strengths in translational medicine, molecular diagnostics, genotyping, and single-cell biology, with technologies that enable parallel and multiplex analysis of biological systems and assist in the transition of research tools into clinical and applied markets. The $1.3bn price is almost four times Affymetrix's annual revenues of $349mm. Affymetrix has built up its business through the years with major acquisitions of IVD and life sciences research players, including **eBioscience** (oncology antibodies, multiplex RNA, and protein and single-cell assays for flow cytometry and research); **Panomics** (assays for genetic, protein, and cellular analysis); and **USB Corp.** (molecular biology products and biochemical reagents). Thermo will integrate Affymetrix into its life sciences solutions (LSS) business; the companies say Affymetrix is a good fit, particularly in the biosciences (molecular biology, protein/cell analysis, and cellular/synthetic biology) and genetics sciences (PCR, sequencing, agrigenomics) divisions within the LSS group. Through its strong market ties, especially in the Asia Pacific (and particularly China), Thermo will expand the commercial and geographic reach of Affymetrix's products. Investment Banks/Advisors: JP Morgan & Co. (Thermo Fisher Scientific Inc.); Morgan Stanley & Co. (Affymetrix Inc.)

Alliances

/In Vitro Diagnostics

DIAMIR LLC
JOHNSON & JOHNSON
Janssen Pharmaceuticals Inc.

DiamiR LLC is teaming up with **Janssen Pharmaceuticals Inc.** to look into how DiamiR's technology can be used to create clinical candidates aimed at neurodegenerative diseases. (Jan.)

Janssen will provide undisclosed up-front and milestone payments and can opt to license a companion diagnostic for use with its own therapeutics. DiamiR has developed a method for the early detection and monitoring of neurodegenerative diseases using quantitative analysis of brain-enriched microRNA pairs in plasma.

KINEMED INC.
PFIZER INC.

KineMed Inc. licensed **Pfizer Inc.** rights to use its kinetic biomarker platform to discover and develop biomarkers in various therapy areas where there is an unmet medical need. (Jan.)

Both companies will work on biomarker discovery, after which the Big Pharma takes over development and gets rights to commercialize any resulting biomarkers or companion diagnostics for the Pfizer-selected targets. KineMed receives money up front, R&D funding for Pfizer's targets, and development and regulatory milestones. KineMed's technology uses mass spectroscopy and stable isotope labeling to monitor the activity of biochemical pathways, measure molecular fluxes within those pathways, and observe the appearance and disappearance of thousands of individual proteins and biological biomarkers. The company says this approach is better than other techniques in de-risking and advancing drug development.

MEDICAL DEVICES

Mergers & Acquisitions

/Medical Devices

ALMIRALL SA
THERMIAESTHETICS

Almirall SA exercised its option to acquire the remaining 92.3% of **ThermiAesthetics** (formerly ThermiGen LLC, and also known as Thermi; radiofrequency energy-powered aesthetic devices) it doesn't already own for $80mm, almost eight times Thermi's 2014 revenues of $11.4mm. (Jan.)

In September 2015 Almirall paid $7.5mm to acquire a 7.7% stake and a call option to acquire Thermi outright. The company has a portfolio of medical aesthetic devices based on its thermistor-regulated technology, which uses heat generated from radiofrequency (RF). The *ThermiRF* (formerly known as *Symphony RF*, an RF-powered electrosurgical cutting and coagulation tool, was FDA-approved in 2013 for use in dermatological and general surgical procedures for electrocoagulation and hemostasis and to create lesions in nervous tissue; it received additional approval the following year for applications in soft tissue and nerves. (Used in conjunction with *ThermiRF*, the company's *Thermi250* (FDA-approved in December 2015 for temporary reduction of cellulite) is used to deliver regulated heating to the surface of the skin, initiating an inflammatory response that stimulates fibroblasts to produce new collagen over time.) These tools are used in non-surgical procedures: *ThermiRase* for facial frown lines; skin-tightening techniques known as *ThermaSmooth* and *ThermaTight*; and *ThermiVa* to treat vaginal laxity resulting from aging or childbirth. The addition of these Thermi platforms will enable Almirall to expand its offerings to plastic surgeons, cosmetic physicians, and dermatologists. Just two months ago, Almirall also enhanced its dermatology pharmaceuticals offerings in by acquiring **Poli Group** (marketed prescription and consumer skincare products) as well as gaining a license to **Stiefel**'s marketed dermatology antibiotics *Veltin* (clindamycin phosphate/tretinoin) for acne and *Altabax* (retapamulin) for impetigo.

DIGIRAD CORP.
DMS HEALTH TECHNOLOGIES INC.

Digirad Corporation acquired **DMS Health Technologies Inc.** (medical imaging equipment and diagnostic imaging services) for undisclosed cash consideration. Concurrently with the transaction, Digirad closed a senior secured credit facility with Wells Fargo Bank for up to $40mm, which will be used to partially fund the transaction, along with cash on hand. (Jan.)

DMS Health provides medical imaging equipment and diagnostic imaging services to health care systems throughout the U.S. The company is headquartered in Fargo, North Dakota and employs approximately 250 people. The new combined Digirad entity is expected to generate pro forma sales and adjusted EBITDA of over $125mm and $17mm, respectively.

KATENA PRODUCTS INC.
SENSOR MEDICAL TECHNOLOGY LLC

Katena Products Inc. is paying an undisclosed sum for fellow private ophthalmic device maker **Sensor Medical Technology LLC** (SMT). (Jan.)

SMT offers single-use and reusable lenses for use by ophthalmologists and optometrists during procedures. There are several advantages to single-use procedure lenses including convenience, elimination of the need for cleaning and disinfection/sterilization, and reduced concern for disease transmission. SMT's reusable bi-aspheric lenses are scratch resistant with an evaporated diamond hard coating and anti-reflection coating. These products will be a nice fit with Katena's ophthalmic portfolio of instruments and biologics.

MIMEDX GROUP INC.
STABILITY INC.

MiMedx Group Inc. is acquiring **Stability Inc.** (private firm offering human tissue products to the surgical, spine, and orthopedics sectors) for $6mm in cash and $4mm in stock, plus assumed debt. MiMedx will also pay an earn-out--60% cash and 40% stock--based on performance in 2016 and 2017. (Jan.)

Post transaction, Stability becomes a wholly owned MiMedx subsidiary and its executives will join MiMedx's management team. Founded in 2010, Stability first began operations with a focus on allografts, but has since moved into developing human tissue and bone products. The company offers the *Physio* line of 100% bone tissue for maximized bone-forming potential. Because of a unique manufacturing process, *Physio*'s microstructure retains endogenous growth factors, osteogenic proteins, and biologic calcium phosphate minerals, and offers superior handling, injection, moldability, stability, and graft retention. The firm also sells demineralized bone matrix products, structural allografts, and skin products for burns and traumatic wound care. MiMedx will capitalize on Stability's 100-strong sales team who specialize in specific surgical areas.

NUVASIVE INC.
ELLIPSE TECHNOLOGIES INC.

NuVasive Inc. is buying private musculoskeletal device firm **Ellipse Technologies Inc.** for $380mm in cash up front plus a potential $30mm revenue-related milestone payable in 2017. (Jan.)

NuVasive will fund the transaction with its cash on hand. Ellipse will become a wholly owned NuVasive subsidiary and its president and CEO will join the leadership team. Ten-year-old Ellipse develops devices for complex skeletal deformity. The company has used its *MAGEC* (*MAGnetic External Control*) technology to create magnetically adjustable implant systems. Its *MAGEC* spinal bracing and distraction line is intended for skeletally immature patients younger than age ten with severe progressive spinal deformities and treatment of early onset scoliosis. Ellipse's *PRECICE* brand is an intramedullary nail designed for limb lengthening of the femur and tibia and for limb length discrepancy. The system incorporates an external remote controller to non-invasively lengthen the implant. NuVasive itself offers the *iGA* (*Integrated Global Alignment*) platform and will continue its push into the adult deformity market but also now expand into the early onset and idiopathic scoliosis space. The acquisition enables NuVasive to move from a spine implant-focused firm to one that provides complete spine solutions, in addition to expanding its footprint into new niche orthopedic markets. Ellipse filed to go public just three months ago. Investment Banks/Advisors: Goldman Sachs & Co. (NuVasive Inc.); Piper Jaffray & Co. (Ellipse Technologies Inc.)

RESMED INC.
INOVA LABS INC.

ResMed Inc. is acquiring closely held **Inova Labs Inc.**, which develops oxygen therapy systems for respiratory conditions including chronic obstructive pulmonary disease. (Jan.)

Terms were not disclosed. Inova's key products include *LifeChoice Activox* portable oxygen concentrators, which have extended battery life (an industry-leading feature) and therefore provide freedom and mobility. The company also sells *Activox DUO2*, the first available fully-integrated stationary and portable oxygen concentrator system. Just last month the device received a new product award. ResMed will add Inova's offerings to its respiratory portfolio containing the *AirCurve* and *Stellar* non-invasive ventilators and *Astral* non-invasive life support platform.

SECTRA AB
RXEYE AB

Sectra AB acquired Swedish cloud-based IT company **RxEye AB** for an undisclosed cash payment along with additional contingent consideration. RxEye will be incorporated into Sectra's Imaging IT Solutions business area. (Jan.)

RxEye is developing a secure communications network and web-based collaborative platform for diagnostic imaging. The company has a network for remote viewing of radiology, nuclear medicine and pathology images and has over 2k users in Europe. Founded in 2010 by Magnus Hok and Olf Hertin, RxEye was started to address the supply/demand imbalance of expert diagnostic services. The company reported sales of SEK7mm ($800k) in FY2015.

SURMODICS INC.
NORMEDIX LLC

SurModics Inc. acquired minimally invasive catheter company **NorMedix Inc** for $14mm--$7mm up front and $7mm in revenue-based milestone payments. (Jan.)

NorMedix has developed a hemostasis sealing device along with advanced braiding technologies for catheters for complex interventional procedures. This technology complements SurModics' new hydrophilic coating innovations and future drug-coated balloon platforms. The acquisition strengthens SurModics' position with medical device customers along with recently acquired **Creagh Medical** (percutaneous transluminal angioplasty balloon platform).

TELEFLEX INC.
NOSTIX LLC

Teleflex Inc. acquired catheter tip placement company **Nostix LLC** for undisclosed consideration. (Jan.)

Nostix offers a differentiated PICC (peripherally inserted central catheter) tip placement system used to increase the accuracy of vascular access device placement. The company's ECG-only system offers an alternative to X-rays for adults and is currently sold in the US. The system will complement Teleflex's *ARROW VPS G4* system and allow for future expansion into tip confirmation for central venous catheters, chronic hemodialysis catheters, and ports. Investment Banks/Advisors: JMP Securities LLC (Nostix LLC)

THERAGENICS CORP.
ECKERT & ZIEGLER STRAHLEN UND MEDIZINTECHNIK AG
Eckert & Ziegler Bebig SA

Theragenics Corp. acquired the US and Canadian brachytherapy seed business of **Eckert & Ziegler Bebig SA**, a division of **Eckert & Ziegler Strahlen und Medizintechnik AG**. (Jan.)

The deal includes access to all current customers in the regions; Theragenics also takes over manufacturing, which will be carried out at its Buford, Georgia facilities. Included in the transaction are the prostate cancer treatments *AnchorSeed*, a loose low dose rate brachytherapy encapsulated in a synthetic biopolymer and designed to improve seed fixity and reduce misalignment and migration; *VariStrand*, a customizable biopolymer strand that allows for varied loading patterns; and the *SeedLock* needle, a carrier for seeds during placement procedures. Theragenics enhances its own existing brachytherapy business through the acquisition; the company already sells its *TheraSeed* Palladium (Pd-103)-based seed with a biocompatible

titanium casing, and *Agx100*, an iodine-based device with a 60-day half-life (in contrast to the 17-day half-life of *TheraSeed*).

Alliances
/Medical Devices

AMEND SURGICAL INC.
NANOTHERAPEUTICS INC.

Amend Surgical Inc. received worldwide exclusive rights to **Nanotherapeutics Inc.**'s FDA-approved *NanoFUSE* demineralized bone matrix. (Jan.)

Though specific terms were not disclosed, Nanotherapeutics takes a minority stake in Amend Surgical. *NanoFUSE* is a putty-like bone void filler indicated for use in orthopedic procedures. The allograft is placed into bony voids or gaps of the skeletal system that are not intrinsic to the stability of the bony structure and provides a bone graft substitute that remodels into the recipient's skeletal system.

AMGEN INC.
UNILIFE CORP.

In a nonexclusive deal, **Unilife Corp.** will provide **Amgen Inc.** with wearable injector devices for use with certain of the Big Biotech's large volume drug products. (Jan.)

In addition, Unilife will exclusively provide Amgen with its 1ml wearable injector for use with certain small volume drug products of Amgen. All the wearable injector devices will be developed, manufactured, and supplied by Unilife, and Amgen will pay the company for each device, based on annual volumes and device features. In return, Unilife receives a $15mm up-front payment. Amgen can opt to source and/or sublicense manufacturing of up to 20% of its total annual volume needs for the devices. Should this occur, Unilife will receive the difference between the per unit price of the device as if sold by Unilife and Amgen's manufacturing and procurement costs for the device. If Unilife is unable or unwilling to manufacture the devices or doesn't meet required quality and/or supply obligations, Amgen can source/sublicense the manufacture of all volume needs in exchange for a nominal royalty fee per unit to Unilife (not to exceed 10% of the cost of goods sold). The parties will also exclusively negotiate a grand alliance until at least January 31, 2016. It would result in Amgen making an additional cash payment in return for purchasing up to 19.9% of Unilife's common stock, gaining the preferred right of access to new delivery platforms and entering into a manufacturing arrangement. The partnership comes at an opportune time for struggling Unilife, which fired 50 employees in September and reduced operating expenses in an effort to focus on commercializing its *Imperium* insulin patch pumps.

Financings
/Medical Devices

DIGIRAD CORP.

Digirad (medical imaging equipment and diagnostic imaging services) entered into a new senior secured credit facility with Wells Fargo Bank for up to $40mm. At a fully funded level, the current weighted average interest rate of the facility is approximately 3.24%. Part of the proceeds were used to fund the company's acquisition of **DMS Health Technologies**. (Jan.)

SENSEONICS HOLDINGS INC.

Senseonics Holdings Inc. (glucose monitoring devices) filed for its initial public offering. (Jan.)

Investment Banks/Advisors: BTIG LLC; Canaccord Genuity Inc.; Leerink Partners LLC

PHARMACEUTICALS

Mergers & Acquisitions
/Pharmaceuticals

ACORDA THERAPEUTICS INC.
BIOTIE THERAPIES CORP.

Acorda Therapeutics Inc. acquired all outstanding Nasdaq Helsinki-listed shares and Nasdaq (US)-listed American Depositary Shares (ADSs) of Finnish biotech **Biotie Therapies Corp.** (neurodegenerative and psychiatric disease therapeutics) for $363mm, over 20 times Biotie's 2014 revenues of $18mm. (Jan.)

The price includes $118mm in ADSs at €23.5680 ($25.68) per ADS; $196mm in shares at €0.29 ($0.32)/share (an 88% premium); plus $49mm in option rights and warrants. Biotie, public in Finland since 2002, completed a US IPO on Nasdaq in June 2015. Acorda will fund the transaction through concurrent financings: a $75mm private placement and a $60mm loan facility from JPMorgan Chase. The acquisition will establish Acorda as a prominent player in the Parkinson's disease (PD) therapeutics market. The deal adds to its pipeline Biotie's PD candidates tozadenant (formerly known as SYN115), an oral adenosine 2A receptor antagonist in Phase III, and the Phase II SYN120, an oral 5-HT6 and 5HT2a dual receptor antagonist for Parkinson's-related dementia (both gained through Biotie's 2011 buy of Synosia Therapeutics). Acorda's own PD pipeline includes the Phase II CVT301 (inhaled dry powder formulation of levodopa) gained through its 2014 buy of **Civitas**; an NDA is planned for 2017. Originally licensed from Elan (now **Perrigo**) in 2003, Acorda currently sells *Ampyra* (dalfampridine) for multiple sclerosis and completed a Phase I/II trial for gait impairment in PD patients in July 2014, but hasn't reported any more recent development in that indication. Outside of PD, Biotie has the Phase II BTT1023--an anti-VAP-1 mAb for primary sclerosing cholangitis--and through a licensing deal with **H. Lundbeck** signed in 2006 and amended several times since, gets double-digit royalties from Lundbeck's sales of *Selincro* (nalmefene; to reduce alcohol consumption in adults with alcohol dependence). Biotie also has several additional clinical-stage candidates; it's expected to file NDAs for three of these programs by the end of 2018. Investment Banks/Advisors: JP Morgan & Co.; Lazard LLC; MTS Health Partners (Acorda Therapeutics Inc.); Guggenheim Partners LLC (Biotie Therapies Corp.)

ALLERGAN PLC
ANTERIOS INC.

Allergan PLC acquired private biotech **Anterios Inc.** (delivery technologies and botulinum toxin Type A formulations for aesthetic, cosmetic, and dermatology indications). (Jan.)

Allergan will pay $90mm initially, plus development and commercialization earn-outs related to Anterios' *NDS* platform, a technology that allows for the site-specific delivery of macromolecule neurotoxins through the skin without an injection and also enables the formulation of large-molecule liquid injectables. Allergan also gains ANT1207 (botulinum toxin type A)--Anterios' lead compound in Phase IIb for hyperhidrosis (excessive sweating) and Phase II for acne and crow's feet. Just prior the acquisition announcement, Anterios spun out a new company called **Eirion Therapeutics**, which will retain rights to its preclinical botulinum candidate AI09 (a ready-to-use injectable for the reduction of glabellar lines) and will also hold certain non-exclusive rights to ANT1207. Anterios exclusively licensed the cell line that produces its botulinum toxins from the **University of Massachusetts** through agreements in 2006 and 2007 and also licensed IP from **Louisiana State University** in 2008. Anterios filed for an IPO in March 2015 and had even set a price range of 3.9mm shares at $12-14, but postponed the offering in May 2015; the current deal gives it much more cash up front as well as the opportunity for downstream monies if milestones involving *NDS* are achieved. The addition of Anterios' delivery platform and botulinum pipeline give Allergan's dermatology and aesthetic neurotoxin offerings a boost. It currently sells the blockbuster *Botox* (onabotulinum toxin A) for nine FDA-approved medical and cosmetic uses including migraines and crow's feet (with more indications in clinical trials). In November, **Pfizer** announced it would acquire Allergan for $160bn.

ANTERIOS INC.
EIRION THERAPEUTICS INC.

Concurrent with its acquisition by **Allergan**, **Anterios Inc.** is spinning out a couple of its botulinum toxin assets into a new company, which will be called **Eirion Therapeutics Inc.** (Jan.)

Eirion will retain rights to Anterios' injectable botulinum toxin type A candidate AI09 (in preclinical development for the reduction of glabellar lines) and will also hold certain nonexclusive rights to ANT1207 (botulinum toxin type A), Anterios' lead compound for indications including hyperhidrosis, acne, and crow's feet, which Astellas will gain global rights to under the acquisition. AI09, which doesn't contain human albumin (which poses a risk for transmittable diseases), is intended for uses in which deeper delivery of the botulinum toxin is required. The compound uses Anterios' *NDS* formulation technology, and because it isn't lyophilized (a freeze-dried powdered form), it doesn't require reconstitution prior to injection. AI09, with its ready-to-use liquid formulation, showed therapeutic equivalence as well as long-term stability to current albumin-containing, reconstituted commercialized products; the company expects to soon file an IND application to initiate clinical trials.

JUNO THERAPEUTICS INC.
ABVITRO INC.

Juno Therapeutics Inc. acquired privately held **AbVitro Inc.** (next-generation single cell sequencing) for $78mm in cash and 1.3mm Juno shares (valued at about $54mm based on the pre-announcement market average). (Jan.)

Spun out of **Harvard University** in 2010, AbVitro's high-throughput single-cell sequencing technology allows for the identification of fully human natively paired T-cell receptors (TCRs) and chimeric antigen receptor (CAR) T binders from cancer patients. Binders that recognize known targets, as well as new cancer antigen targets, will be used by Juno to create

cancer therapies (including monoclonal antibodies, antibody-drug conjugates, and TCR/CAR-T immunotherapies) and expand upon Juno's own CAR and TCR offerings. Juno also plans to use AbVitro's technology for translational assays in the study of the immune response to cancer and for monitoring of the immune system in cancer patients undergoing treatment. AbVitro's IP could also be worked into a new collaboration with Juno's existing partner **Celgene**; the companies agreed in principle to enter into a deal in which Juno may license Celgene a subset of the acquired assets and options to potential related products. The acquisition provides a hefty return for AbVitro investors, who only put $3mm into the firm through a Series A in 2012. AbVitro's staff will relocate from Boston to Juno's Seattle location and the firm's co-founder (George Church, PhD) and CEO (Jeffrey Ostrove, PhD) will become consultants for Juno.

PHARMACEUTICAL PRODUCT DEVELOPMENT INC.
X-CHEM INC.

Pharmaceutical Product Development LLC (PPD) is divesting small-molecule biotech division **X-Chem Inc.**, which will now operate as an independent, private company. PPD acquired X-Chem back in 2014 after making an initial investment in the company in 2010. (Jan.)

X-Chem is a leader in DNA-encoded library technology and its current DEX library has over 100 billion small molecule compounds for a range of high value targets. The library is generated by iterative combinatorial synthesis of small molecules tethered to DNA tags that record the synthetic history of the small molecule. The company has partnered with nine major pharma and biotech companies including **Alexion**, **AstraZeneca**, **Bayer**, **Janssen Biotech**, **Pfizer**, **Roche**, and **Sanofi**. Furthermore, X-Chem has licensed 16 programs to partners and established collaborations on over 70 therapeutic programs.

ROCHE
TENSHA THERAPEUTICS INC.

Roche acquired private epigenetics-focused **Tensha Therapeutics Inc.** for $115mm up front and up to $420mm tied to clinical and regulatory milestones. (Jan.)

Tensha was founded in 2011 around research led by James Bradner, MD, out of the **Dana-Farber Cancer Institute** and **Harvard Medical School**, and is developing small-molecule bromodomain inhibitors for cancer and other diseases. Bromodomains are epigenetic targets found within proteins that bind to chromatin and affect gene expression, potentially promoting cancer growth. The company's lead candidate TEN010 is in Phase Ib for solid tumors including NUT midline carcinoma, a rare epithelial cancer caused by chromosomal rearrangement in the nuclear protein in testis (NUT) gene. In 2011 Tensha raised $15mm Series A financing from HealthCare Ventures, which partnered with **Eli Lilly** as part of the Big Pharma's venture funding program for single-asset companies. Lilly worked with Tensha to develop their bromodomain inhibitors; as part of the arrangement with HealthCare Ventures, Lilly had an option to buy Tensha, but said it didn't fit the company's strategy. Lilly currently focuses on endocrine, metabolic, and CNS areas. Oncology, on the other hand, is Roche's top therapeutic area in pharma sales, accounting for over 62% of revenue in 2014.

Alliances
/Pharmaceuticals

4D MOLECULAR THERAPEUTICS LLC
PFIZER INC.

4D Molecular Therapeutics LLC (4DMT) will use its *Therapeutic Vector Evolution* adeno-associated virus (AAV) vector discovery platform to identify and develop next-generation gene delivery vectors targeting cardiac disease indications (with high unmet need) for **Pfizer Inc.** (Jan.)

Pfizer will make an equity investment in 4DMT and pay undisclosed money up front, development and commercial milestones, and tiered sales royalties. The Big Pharma also gets a seat on the start-up's board and has agreed to purchase additional equity in a future 4DMT financing. 4DMT's *Therapeutic Vector Evolution* platform, which uses about 100mm unique AAV variants with unmatched diversity, can discover leads that are highly optimized for a specific target cell or organ and route of therapeutic administration and are also able to evade antibodies. This is the biotech's second tie-up with a Big Pharma; in April 2015 it signed a gene therapy deal with **Roche**.

AFFIMED NV
MERCK & CO. INC.

Affimed NV and **Merck & Co. Inc.** entered into a trial collaboration to investigate the combination of Merck's *Keytruda* (pembrolizumab) with Affimed's AFM13; a Phase Ib trial conducted and funded by Affimed will look at safety, efficacy, and dosing for patients with Hodgkin lymphoma that has relapsed or is refractory to chemo treatments including the antibody-drug conjugate *Adcetris* (brentuximab vendotin). (Jan.)

Keytruda, a PD-1 antagonist, is marketed by Merck for non-small lung cancer and melanoma, and is in a wide range of trials for blood and solid tumors including renal, bladder, head and neck, breast, and colorectal cancers, as well as lymphomas and myeloma. AFM13 is a bispecific antibody targeting the CD30 and CD16 antigens that is in Phase II studies for Hodgkin lymphoma and solid tumors, and is also being investigated for cutaneous T-cell lymphoma. Preclinical studies conducted at **Stanford** looked at the utility of AFM13 paired with a PD-1 antibody, and found highly synergistic results. The collaboration between Merck and Affimed includes an option to continue into Phase III trials.

AKASHI THERAPEUTICS INC.
GRUNENTHAL GMBH

Akashi Therapeutics Inc. licensed **Grunenthal GMBH** rights to its HT100, which is currently in Phase Ib/IIa for promoting healthy muscle fiber regeneration in Duchenne muscular dystrophy (DMD). (Jan.)

The deal could be worth $100mm to Akashi, although the specific breakdown was not disclosed. Grunenthal pays money up front, milestones, and sales royalties. The firm is responsible for all post-Phase II global development costs through commercialization of an approved product and will get commercial rights in Europe and Latin America. Akashi retains rights in the US and other markets. Grnenthal receives royalties on US sales in exchange for funding the development of Akashi's US commercial infrastructure. HT100 is an oral small molecule therapy with orphan drug status in the US and EU. In addition to being developed for DMD, the compound also has potential for reducing fibrosis and inflammation in diseases including scleroderma and idiopathic pulmonary fibrosis.

ALTERMUNE TECHNOLOGIES LLC
CENTAURI THERAPEUTICS LTD.

Centauri Therapeutics Ltd. acquired **Altermune Technologies LLC**'s *Alphamer* drug discovery technology. (Jan.)

Under the agreement, Altermune handed over full rights to patents, compounds, know-how, and collaborations related to *Alphamer* in exchange for an undisclosed payment from Centauri. The technology creates chemically synthesized molecules that redirect the body's own immune system to more effectively fight infection. One end of the molecule uses an aptamer to bind a cell-surface target on the pathogen and the other presents specific epitopes that attach to the circulating antibodies. Prelinical studies showed that *Alphamers* can redirect pre-existing antibodies to bacteria and trigger an immediate antibacterial immune response. Centauri concurrently raised £3mm ($4.7mm) to develop its first candidate and also appointed industry expert Dr. Clive Dix as its chairman.

ANGIOCRINE BIOSCIENCE INC.
TERUMO CORP.
Terumo BCT Inc.

Angiocrine Bioscience Inc. entered into a three-year collaboration with **Terumo BCT Inc.** to use Terumo's *Quantum Cell Expansion System* as a manufacturing platform for Angiocrine's *E-CEL* technology. (Jan.)

Quantum is a functionally closed hollow-fiber bioreactor technology that streamlines the cell culture process and enhances process scalability and reproducibility. The system offers protocol flexibility and process control through automation. Angiocrine's *E-CEL* core technology was licensed from **Weill Cornell Medical College** where it was invented and developed by Professor Shahin Rafii, MD.

ANI PHARMACEUTICALS INC.
MERCK & CO. INC.

Merck & Co. Inc. sold two corticotropin NDAs to **ANI Pharmaceuticals Inc.** for $75mm. The NDAs cover purified corticoptropin gel (40 units/mL and 80 units/mL) and corticotropin zinc hydrozide (40 units/mL). (Jan.)

The deal was first announced in September 2015, and now gives ANI an opportunity to share the corticotropin space with **Mallinckrodt**, which sells the drug under the brand name *Acthar* and recognized $1bn in sales for it in 2015. Corticotropin is a cyclic adenosine monophosphate (AMP) stimulant marketed for a variety of conditions including multiple sclerosis, rheumatoid arthritis and other rheumatic diseases, ophthalmic and dermatologic conditions, and allergic/edematous conditions.

ARBOR PHARMACEUTICALS INC.
DEBIOPHARM GROUP
Debiopharm International SA

Debiopharm International SA licensed **Arbor Pharmaceuticals Inc.** exclusive rights to commercialize sustained-release triptorelin 22.5mg in the US for central precocious puberty (CPP). (Jan.)

Debiopharm will manufacture the drug for Arbor. Once approved for CPP, Arbor will sell triptorelin to pediatricians and pediatric endocrinologists. Gonad-

otropin-releasing hormone antagonist-dependent CPP is characterized by puberty occurring before the age of 8 and 9 in girls and boys, respectively. Triptorelin pamoate is currently available in one-, three-, and six-month formulations for various indications including prostate cancer, endometriosis, and female infertility. Debiopharm has several partners in place for the drug including **Dr. Reddy's** and **Ipsen**.

ARENA PHARMACEUTICALS INC.
BOEHRINGER INGELHEIM GMBH

Boehringer Ingelheim GMBH and **Arena Pharmaceuticals Inc.** agreed to jointly identify and develop candidates for schizophrenia and other CNS indications. Arena will receive up to $262mm in commercial milestones, including an up front payment and research funding. (Jan.)

Arena will receive up to $262mm in commercial milestones, including an up front payment and research funding. The focus will be on an undisclosed G protein-coupled receptor (GPCR). Arena will give Boehringer exclusive rights to all of its internal novel compounds and IP for an orphan CNS receptor and the two companies will then jointly research additional candidates for various indications. BI will have the exclusive worldwide rights to develop, manufacture and commercialize any products that result from the collaboration.

ASTRAZENECA PLC
MedImmune LLC
MODERNA THERAPEUTICS LLC
OnKaido Therapeutics Inc.

Building on a successful relationship that began two years ago, **AstraZeneca PLC** and **Moderna Therapeutics LLC** have come to the dealmaking table again, this time to develop immuno-oncology therapeutics. (Jan.)

In 2013, the pair joined forces to use Moderna's *messenger RNA Therapeutics* technology to discover and develop cardiometabolic, renal, and cancer treatments. Now, Moderna will utilize its protein engineering expertise and, through its oncology focused division **OnKaido Therapeutics Inc.**, fund and carry out preclinical work on two specific immuno-oncology programs, with the goal of delivering an IND application-ready molecule for each program. AZ's **MedImmune LLC** unit will lead early clinical development, and Moderna and AZ plan to share the costs of later-stage trials. Under a 50/50 profit share agreement, the partners will co-promote resulting drugs in the US, while AZ leads ex-US commercialization (and hands over tiered royalties up to "substantial" double-digits). Moderna's platform involves using the body's ability to make proteins as a therapeutic mechanism. By injecting synthetic versions of messenger RNA into the body, cells can be prompted to produce effector proteins in vivo, avoiding the risks involved with gene therapy when the body launches an immune attack against foreign mRNA. Other partners taking advantage of the technology include **Alexion Pharmaceuticals** and **Merck & Co.** (Concurrent with the AZ deal, Moderna and Merck announced the addition of a new vaccine program to their December 2015 alliance, which is centered around viral disease therapies.)

ASTRAZENECA PLC
INCYTE CORP.

AstraZeneca PLC and **Incyte Corp.** have come together again, this time to study a combination of Incyte's INCB39110 with AZ's *Tagrisso* (osimertinib) for non-small cell lung cancer. (Jan.)

In May 2014, Incyte and AZ's **MedImmune LLC** division announced a collaboration surrounding the combination of MedImmune's anti-PD-L1 inhibitor MEDI4736 (darvalumab) and Incyte's IDO1 inhibitor INCB24360 for metastatic melanoma, NSCLC, squamous cell carcinoma of the head and neck, and pancreatic cancer. Now, AZ and Incyte will determine if INCB38110 and *Tagrisso* together would be an effective second-line treatment for patients with metastatic NSCLC who have already been treated with a first-generation EGFR tyrosine kinase inhibitor and developed the T790M mutation. INCB39110 is a JAK1 inhibitor in Phase II trials for myelofibrosis, NSCLC, B-cell lymphoma, and pancreatic cancer, while *Tagrisso*, an EGFR kinase inhibitor, was recently approved for NSCLC. The companies will collaborate on a Phase I/II study (Phase I for dosing and Phase II for safety and efficacy), which will be conducted by Incyte.

ASTRAZENECA PLC
MILLENDO THERAPEUTICS INC.

AstraZeneca PLC handed off global rights to its polycystic ovary syndrome (PCOS) candidate AZD4901 to **Millendo Therapeutics Inc.** (formerly Atterocor Inc.) (Jan.)

Millendo will pay money up-front in addition to development and sales milestones, plus royalties; AZ also takes an undisclosed equity stake in the company. AZD4901 (which Millendo will develop as MLE4901) is a neurokinin-3 receptor antagonist in Phase II for PCOS, one of the most common endocrine diseases in women that results in excess levels of male hormones, menstrual irregularities, and infertility. The candidate works by lowering rates of GnRH hyperpulsatility and luteinizing hormone pulse frequency to balance hormone levels and reduce symptoms. Millendo concurrently announced a $62mm Series B round; funds will go towards development of the in-licensed compound, and will also support trials of its other pipeline project ATR101, in Phase I for adrenal cancer.

ATHERSYS INC.
HEALIOS KK

Athersys Inc. announced public Japanese regenerative medicine company **Healios KK** as its new *MultiStem* cell therapy partner in Japan. This comes shortly after Athersys ended its March 2015 *MultiStem* alliance with **Chugai Pharmaceutical**, which returned all rights to Athersys in October 2015 after the candidate failed to achieve the primary or component secondary endpoints in Phase II for stroke. (Jan.)

In the current deal, Healios gets an exclusive Japanese license to develop *MultiStem* for ischemic stroke indications, plus an exclusive option to develop it (in Japan) in two additional indications: acute respiratory distress syndrome (ARDS; where Phase II trials are currently underway in the US and the UK) and the orthopedic area. This option is exercisable following successful completion of *MultiStem* trials in ARDS. Healios also gains an exclusive license to incorporate Athersys' technology into its own organ bud technology, which uses iPSC-derived organ progenitor cells. Currently in development (in collaboration with **Yokohama City University**) for transplantation to treat liver disease or dysfunction, the indications for the organ bud technology may be expanded if Healios exercises the option for the two additional *MultiStem* indications. In exchange for the rights and options, Athersys gets a $15mm up-front fee; development and regulatory milestones up to $30mm plus commercialization and sales milestones up to $185mm million for achieving objectives within the stroke indication; and tiered, double-digit sales royalties increasing into the high teens (*Strategic Transactions* estimates 10-19%). If Healios exercises its option to expand the partnership to ARDS and orthopedic indications, Athersys gets another $10mm, plus further related potential development and commercialization milestone payments. Athersys retains manufacturing rights to *MultiStem*, but could receive reimbursement for these costs from Healios under a manufacturing supply arrangement. The Chugai deal, had it been continued, could have brought in over $201mm in pre- and post-commercialization money for Athersys, but since the termination, Athersys kept just the $10mm up-front payment. The addition of a late-phase compound in new potential therapeutic areas enhances Healios pipeline, which is focused mainly on organ transplantation and ophthalmology candidates.

AVALON PHARMACEUTICAL SA
MEDIWOUND LTD.

MediWound Ltd. granted **Avalon Pharmaceutical SA** exclusive rights to sell its burn treatment *NexoBrid* in Colombia, Peru, Ecuador, Chile, and Panama. (Jan.)

NexoBrid contains proteolytic enzymes enriched in bromelain (a protein extract from the stem of pineapples). The topically applied product removes eschar (dead or damaged tissue) from deep partial- and full-thickness burns in about four hours without damaging surrounding healthy tissue, and without the need for surgical excisions or autografts. Avalon will file for regulatory approval in the licensed territories and expects to receive the first authorization within at least a year. (*NexoBrid* is already approved and launched in Europe and Israel). Wound care appears to be a new market for Avalon; the company's business includes products for cardiovascular health (the *Stentys* line of stents), orthopedic care (*BonAlive* osteostimulatives for bone regeneration), and dental products (the *Sefdent* dental hygiene line).

BAXALTA INC.
SYMPHOGEN AS

Symphogen AS granted **Baxalta Inc.** options to exclusively license global rights to six immuno-oncology projects against undisclosed checkpoint targets. Specific targets and indications were not disclosed. (Jan.)

Baxalta pays $175mm up front and up to $1.6bn in option fees and milestones, plus royalties. Symphogen will develop (and fund) each monoclonal antibody therapeutic through Phase I trials, at which time Baxalta can exercise its options for all later development and commercialization on a product-by-product basis. The companies expect the first candidate to enter the clinic in 2017. Baxalta looks forward to expanding its oncology franchise--especially with immunotherapies--through the collaboration. Though cancer is an area of focus for the firm, it currently only has one launched product on the market (the acute lymphoblastic leukemia drug *Oncaspar* (pegaspargase) which it got from **Sigma-Tau** in May 2015); a number of other projects are in various stages of preclinical and clinical studies. The deal was announced amid speculation that **Shire PLC** is preparing to announce definitive plans to acquire the Baxalta; it made a hostile bid in August for $30bn, but industry reports suggest it could now offer about $32bn.

BIOGEN INC.
RODIN THERAPEUTICS INC.

Biogen Inc., concurrent with a $17.3mm co-investment it made with Atlas Venture in **Rodin Therapeutics Inc.**, is collaborating with the start-up to develop epigenetic modulators for CNS disorders. (Jan.)

The multi-year research collaboration aims to advance neurodegenerative candidates, specifically Rodin's histone deacetylase 2 (HDAC2) inhibitors, through clinical trials. Rodin's internal pipeline uses modulators of selective epigenetic processes (those that turn genes on and off) to restore cognitive function in degenerative brain diseases. Histone acetylation controls genes relevant to brain cell function and stimulates snyapses; when this process is reversed (deacetylation) by HDAC enzymes, crucial gene processes related to memory and learning are shut off. While HDAC inhibitors have shown in preclinical studies to improve cognitive function, they're limited by side effects. Rodin is developing isoform-selective compounds that block the HDAC process (but also address the side effects). Rodin is first focused on Alzheimer's disease, but also believe its compounds have potential in Parkinson's disease and post-traumatic stress disorder. Biogen has the option to acquire Rodin at certain pre-negotiated terms, including up-front and milestone payments of up to $485mm. One of Biogen's key areas is neurology, including a few projects in AD. The addition of Rodin's preclinical epigenetic modulators (expected to enter the clinic in two-three years) would boost Biogen's pipeline of ten CNS candidates.

BIOLINERX LTD.
MERCK & CO. INC.

BioLineRx Ltd. and **Merck & Co. Inc.** entered into an agreement to evaluate the combination of Merck's *Keytruda* (pembrolizumab) with BioLineRx's BL8040 as a potential immunotherapy for metastatic pancreatic adenocarcinoma. (Jan.)

Keytruda is a PD-1 antagonist marketed by Merck for melanoma and non-small cell lung cancer; it is also in over a half-dozen Phase III trials for cancers including renal, bladder, head and neck, and breast, as well as earlier trials for other solid and blood tumors. BL8040, a CXCR4 antagonist, is in Phase II studies for myeloma, non-Hodgkin's lymphoma, AML, and myelodysplastic syndrome, and radiotherapy/chemotherapy-induced anemia and neutropenia. In combination, the companies have a Phase II trial planned for mid-2016, which will be sponsored and run by BioLineRx. The partners can opt to extend the collaboration to additional trials including a pivotal registration study.

BIOTEST AG
Biotest Pharmaceuticals Corp.
KEDRION SPA
Kedrion Biopharma Inc.

Biotest Pharmaceuticals Corp. granted **Kedrion Biopharma Inc.** exclusive rights to sell the immunodeficiency therapy *Bivigam* (human intravenous immune globulin, 10%) in the US. (Jan.)

Bivigam was approved by the FDA in December 2012 and is marketed for primary humoral immunodeficiency. Kedrion plans to start selling it immediately. Kedrion's business includes plasma-derived products for hemophilia, Rh sensitization, and immune system deficiencies. In 2012, Kedrion got rights from **J&J**'s **Ortho-Clinical Diagnostics** division to *RhoGAM*, *RhoGAM* Rho(D) immune globulin (human), and *MICRhoGAM* ultra-filtered Plus Rho(D) immune globulin (human), which are sold in the US to prevent Rho hemolytic disease in newborn babies.

BRISTOL-MYERS SQUIBB CO.
DUAL THERAPEUTICS LLC

Dual Therapeutics LLC licensed **Bristol-Myers Squibb Co.** exclusive global rights to develop and sell its small molecules for cancer and other diseases. (Jan.)

Dual is a 2013 start-up, and Bristol represents its first major partner. The biotech will receive money up front, reimbursement for development costs, more than $255mm in development and regulatory milestones tied to multiple indications, and sales royalties. Dual's small-molecule candidates modulate protein phosphatase 2A (a key tumor suppressor enzyme), leading to blocked growth and survival pathways in certain tumors (including prostate, lung, and acute lymphoblastic leukemia) without affecting healthy cells. The company's research came out of **Mount Sinai Medical Center (NY)**'s **Icahn School of Medicine** and **Case Western Reserve University**. BioMotiv and the Partnership Fund for New York City have provided funding to Dual. The current deal's focus on small molecules is somewhat of a departure for Bristol, as most of its recent partnerships have focused on immuno-oncology, including most recently an agreement with **Neon Therapeutics** to combine Neon's neoantigen vaccine with *Opdivo*. A few days before the Dual Therapeutics deal, Bristol did, however, announce a macrocyclic (small-molecule) drug discovery collaboration with **Oncodesign**.

C4 THERAPEUTICS INC.
ROCHE

C4 Therapeutics Inc. agreed to develop targeted protein degradation (TPD) drug candidates for a group of proteins chosen by **Roche**, which holds an option to license resulting products. (Jan.)

Once C4 meets preclinical milestones, Roche has the option to continue additional preclinical testing and eventually commercialization. The Big Pharma makes an up-front payment and is responsible for development, regulatory, and sales milestones per target, plus commercialization milestones and tiered royalties. In all, the deal could be worth over $750mm. TPD candidates are small molecules derived from C4's *Degronimid* platform, which **Dana-Farber Cancer Institute**'s **Bradner Laboratory** developed and licensed to the biotech. (C4 simultaneously launched from Dana-Farber and completed a $73.5mm Series A financing from 55 investors.) TPD molecules are labeled with ubiquitin, allowing them to bind to disease-causing proteins and prompting their destruction and clearance from the cell via the ubiquitin/proteasome system. Ubiquitin/proteasome is a natural pathway that is critical for degrading cell cycle regulatory proteins and misfolded proteins. **Arvinas** has a similar technology, called PROTAC (proteolysis-targeting chimera), that's also using the ubiquitin/proteasome pathway in targeting protein degradation; under an October 2015 deal, Roche's **Genentech** holds rights to PROTAC drug candidates.

CAMURUS AB
RHYTHM PHARMACEUTICALS INC.

Rhythm Pharmaceuticals Inc. received worldwide rights to use **Camurus AB**'s *FluidCrystal* injection depot technology in a new formulation of its setmelanotide (RM493). (Jan.)

Rhythm will handle worldwide development, manufacturing, and commercialization of the setmelanotide *FluidCrystal* once-weekly subcutaneous injection. In return, Camurus could receive up to $65mm in up-front and milestone payments (the majority of which are related to sales). The firm is also eligible for tiered mid to mid-high single-digit royalties (*Strategic Transactions* assumes 5-7%). Camurus' *FluidCrystal* injection technology delivers drug dosages over extended periods--days to months--by encapsulating the drug compound in the nanopores of the depot matrix and then transforming it into a liquid crystal gel matrix at the subcutaneous injection site. The system can be used with peptides and small molecules and avoids problems such as high initial drug release on injection, poor drug stability, and complex processing. Setmelanotide is a melanocortin-4 receptor (MC4R) agonist for treating obesity caused by genetic deficiencies in the MC4 pathway. Rhythm got the candidate (then known as BIM22493) from **Ipsen** in March 2010. Rhythm plans to initiate a Phase I clinical trial of the setmelanotide *FluidCrystal* formulation after completing GMP manufacturing. A non-*FluidCrystal* subcutaneous injection of setmelanotide is in Phase II for Prader-Willi syndrome and pro-opiomelanocortin deficiency obesity.

CELGENE CORP.
JUNO THERAPEUTICS INC.

Following its $132mm purchase of cell sequencing firm **AbVitro Inc.**, **Juno Therapeutics Inc.** and **Celgene Corp.** agreed in principle to enter into a deal in which Celgene could get a subset of the assets Juno obtained from AbVitro. (Jan.)

Celgene could also get options to potential products that Juno develops using AbVitro's IP. AbVitro, a **Harvard** spin-out, has a technology that allows for the identification of fully human natively paired T-cell receptors (TCRs) and chimeric antigen receptor (CAR) T binders from cancer patients. The platform generates binders that recognize known targets and is also useful in the discovery of novel cancer antigen targets. Juno bought the firm to expand upon its CAR and TCR offerings, and at the same time agreed to share some of the IP wealth with Celgene, whom it has been partnered with since the pair signed a $1.1bn cancer/autoimmune CAR/TCR deal in mid-2015.

COMPLIX NV
MERCK & CO. INC.
Merck Sharp & Dohme Ltd.

Complix NV agreed to use its *Alphabody* protein therapeutic discovery platform to develop Cell-Penetrating Alphabodies (CPABs) against up to two intracellular cancer targets for **Merck Sharp & Dohme Ltd.** (MSD). (Jan.)

MSD paid an up-front fee and could make up to $280mm in development milestone payments, plus tiered royalties. It has an option to license exclusive global rights to resulting candidates. The *Alphabody* platform allows for the development of small protein drugs that have features and benefits associated with antibodies, but lack the challenges associated with the larger molecules. They are highly target-specific and stable, and have the capacity to enter many different types of tumor cells and remain stable in the cell for up to 24 hours after administration to modulate intracellular protein-to-protein interactions and disrupt cancer progression. The deal with Merck is the first large partnership for Complix, which was founded in 2008 and has raised about $24mm through two venture rounds.

ENGENE INC.
TAKEDA PHARMACEUTICAL CO. LTD.

Takeda Pharmaceutical Co. Ltd. and **enGene Inc.** will work together to develop new gastrointestinal disease therapies based on enGene's "Gene Pill" oral delivery platform that delivers therapeutic genes to cells of the gut lining. (Jan.)

EnGene's non-viral vector platform utilizes a nontoxic biocompatible polymer as a carrier for nucleotides locally to the colon to stimulate expression of therapeutic proteins by gastrointestinal mucosal cells. The company will use the technology to develop up to two targets selected by Takeda through preclinical proof-of-concept and IND-enabling studies, at which time Takeda will have an option to license exclusive global rights. If it exercises the option, Takeda pays an up-front fee, reimburses R&D costs, and is responsible for development, regulatory, and sales milestones, plus tiered royalties. The companies also agreed to work together on the development of a gene pill to orally deliver antibodies; Takeda gets an exclusive option for first negotiation rights to up to three antibody targets.

ENTEROME BIOSCIENCE SA
JOHNSON & JOHNSON
Janssen Biotech Inc.

Enterome Bioscience SA is teaming up with **Janssen Biotech Inc.** in discovering targets and bioactive molecules from the gut microbiome for use in creating therapeutics for Crohn's disease. (Jan.)

Janssen will have an option to license exclusive global rights to any resulting therapies. Enterome stands to receive an up-front payment and R&D funding. The **Janssen Human Microbiome Institute** will assist in the collaboration. Initial findings which are the basis of the collaboration were discovered by the **French National Institute for Agriculture Research**. They found that symbiotic bacteria trigger anti-inflammatory effects in the human gut. Using its metagenomics tools and screening technologies, Enterome has identified bacterial strains and genes having immunomodulatory and anti-inflammatory properties and seeks to validate their therapeutic potential and create new Crohn's therapeutics. In late 2014 Enterome partnered with **AbbVie** to develop noninvasive monitoring tools of the gut microbiome in Crohn's disease patients.

FORTRESS BIOTECH INC.
Checkpoint Therapeutics Inc.
TEVA PHARMACEUTICAL INDUSTRIES LTD.

Checkpoint Therapeutics Inc. licensed exclusive worldwide rights to develop and commercialize CEP8983 (along with its small molecule prodrug, CEP9722) from **Teva Pharmaceutical Industries Ltd.** (Jan.)

CEP9722 is an oral poly adenosine diphosphate ribose polymerase (PARP)-1 and 2 inhibitor currently in Phase II trials for solid tumors (including non-small cell lung cancer) and lymphoma. Checkpoint will develop the candidate both as a mono-therapy and in combination with other anticancer agents, including its own checkpoint inhibitor antibodies.

INNATE PHARMA SA
SANOFI

Building on a successful relationship that began last year, **Innate Pharma SA** and **Sanofi** entered into a new partnership, this time focusing on the discovery and development of cancer immunotherapies. (Jan.)

In April 2015, Innate agreed to use its bacterial transglutaminase enzyme-based antibody-drug conjugate platform with Sanofi's antitumor antibodies. Now, the companies will use another of Innate's platforms together with Sanofi's tumor targets and proprietary bispecific antibody format to develop up to two bispecific NK cell engagers that will be able to kill tumor cells through the NKp46 activating receptor. (NKp26 is expressed on all natural killer cells and is the most specific of all human killer cells.) Sanofi pays up to €400mm ($434mm) in development and commercialization milestones, plus royalties, and gets development, manufacturing, and sales rights to resulting compounds.

JOHNSON & JOHNSON
Janssen R&D Ireland
GLAXOSMITHKLINE PLC
ViiV Healthcare

Janssen R&D Ireland and **GlaxoSmithKline PLC**'s **ViiV Healthcare** are once again partnering to develop a combination HIV therapy. (Jan.)

In June 2014, the firms teamed up to develop and commercialize a single-tablet HIV that combines Janssen's non-nucleoside reverse transcriptase inhibitor rilpivirine and ViiV's integrase inhibitor dolutegravir. In the current tie-up, the parties will investigate a long-acting injectable drug containing rilpivirine and ViiV's HIV integrase inhibitor cabotegravir. If the therapy is successfully developed and approved, HIV patients will be able to maintain viral suppression with just six injections of each drug per year. A Phase III trial is expected to commence in mid-2016.

KAIROS THERAPEUTICS INC.
ZYMEWORKS INC.

Zymeworks Inc. made an undisclosed equity investment in **Kairos Therapeutics Inc.** and holds an option to merge with the antibody-drug conjugate developer. (Jan.)

Kairos was spun out of the **Centre for Drug Research & Development** (CDRD) in 2013, and is developing therapeutics based on a novel toxin/linker/site-specific conjugation platform it licensed from CDRD. The company is working on cancer treatments that can be dosed with high potency while maintaining a low risk of toxic side effects. Zymeworks is interested in integrating Kairos' work with its own antibody technologies, including *Azymetric* (for the development of IgG-like bispecific antibodies), *AlbuCORE* (drug development based on multi-valent human albumin serum scaffolds), and *EFECT* (Fc gamma receptor modulation to tailor antibody effector function).

MANNKIND CORP.
RECEPTOR LIFE SCIENCES INC.

New company **Receptor Life Sciences Inc.** licensed **MannKind Corp.**'s *Technosphere* dry powder delivery platform to develop inhaled formulations of undisclosed Receptor compounds. (Jan.)

The *Technosphere* technology--which allows for pulmonary administration (for systemic absorption) of previously only injectable therapeutics--uses microparticles, which are formed through the pH-induced self-assembly of the small molecule fumaryl diketopiperazine (FDKP). The goal of the collaboration is to use *Technosphere* to deliver regulated doses of multiple inhaled Receptor candidates to treat chronic pain, spasticity, and inflammatory diseases, including rheumatoid arthritis. The companies will work

together on clinical development, with MannKind in charge of initial formulation studies and Receptor handling development costs as well as manufacturing and commercialization tasks. MannKind could receive up to $102.25mm in development and commercialization milestones, plus tiered royalties ranging from mid-single digits to low-double digits (*Strategic Transactions* estimates 4-30%), depending on sales volumes of resulting products. MannKind recently announced a new initiative in which it will also actively pursue additional partnerships that employ this proof-of-concept business model to out-license *Technosphere*; it could enter licensing agreements with companies other than Receptor for development of different active compounds. Internally MannKind is evaluating *Technosphere* for use with palonosetron, trepostinil, and epinephrine. Although little is known about the recently formed stealthy Receptor, MannKind confirms the Seattle area start-up is funded by a strong investor group and supported by well-known industry leaders.

MERCK & CO. INC.
QUARTET MEDICINE INC.

Merck & Co. Inc. is partnering with translational medicine start-up **Quartet Medicine Inc.** to develop drugs for chronic pain from Quartet's pipeline of small-molecule compounds that modulate the tetrahydrobiopterin (BH4) pathway. (Jan.)

BH4 is a metabolite known to play a role in peripheral nerve dysfunction and immune cell regulation. Quartet aims to develop modulators of the BH4 synthesis pathway using translational BH4-based biomarker tools to establish a human target and preclinical disease models for indication discovery. Its lead program involves sulfasalazine and related sulfa drugs, which have been used in approved products to treat autoimmune disorders and are inhibitors of sepiapterin reductase (SPR); an enzyme in the BH4 de novo synthesis pathway). Quartet's goal is to link SPR's clinical activity to BH4 synthesis modulation to restore BH4 levels back to normal; candidate selection is expected in 2H15. In exchange for $10mm up-front and another $10mm for an undisclosed development milestone--both of which Quartet will apply to fund its program through Phase IIa in pain--Merck received an exclusive option to purchase the company. If Merck exercises this option, Quartet will receive an option exercise fee and up to $575mm in development, regulatory, and sales earn-outs. Merck optioned pain candidates from Australian drug discovery biotech **Bionomics** in 2013 and has since taken a 5% stake in the company and signed a second partnership in cognitive impairment.

MERCK KGAA
PFIZER INC.
SYNDAX PHARMACEUTICALS INC.

Merck KGAA, **Pfizer Inc.**, and **Syndax Pharmaceuticals Inc.** entered into an agreement to explore a combination of the anticancer therapies avelumab and entinostat for patients with heavily pre-treated recurrent ovarian cancer. (Jan.)

Under a 2014 deal, Merck and Pfizer have been co-developing avelumab (MSB0010718C), a fully human anti-PD-L1 IgG1 monoclonal antibody. It is in Phase III studies for non-small cell lung, bladder, stomach, esophageal, and ovarian cancers, and earlier trials for additional solid and blood tumors. Syndax is working on entinostat, a histone deacetylase inhibitor, and has the compound in Phase III trials for breast cancer, Phase II for NSCLC and renal cell carcinoma, and a Phase I combination trial with **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) for NSCLC and melanoma. In the current collaboration, Syndax will run a Phase Ib/II avelumab/entinostat trial.

NESTLE SA
Nestle Health Science SA
SERES THERAPEUTICS INC.

Seres Therapeutics Inc. licensed **Nestle Health Science SA** exclusive rights to develop and commercialize outside the US and Canada candidates aimed at Clostridium difficile infection (Phase II SER109 and preclinical SER262) and inflammatory bowel disease, including ulcerative colitis (Phase I SER287) and Crohn's (SER301--unknown phase). (Jan.)

Nestle will pay $120mm up front (Seres will use the cash to fund its pipeline development), up to $660mm in development and commercial milestones, and tiered royalties ranging from the high single-digits to high-teens for each drug (*Strategic Transactions* assumes 8-19%). Total sales milestones could reach up to $1.125bn. Seres, which will manufacture the drugs for Nestle, expects to receive $30mm in milestone payments during 2016, tied to the commencement of a Phase 1b study for SER262 and Phase III for SER109. The most advanced compound in the collaboration, SER109, has orphan drug status and breakthrough therapy designation. Seres will fully fund the ongoing Phase II trial of SER109 along with Phase III trials. For SER262, it will pay for Phase I and II, and 67% of Phase III. For the IBD candidates, Seres will fully fund clinical trials up to and including Phase II and pay 67% of Phase III costs for Phase 3 (Nestle will fund the reminder). Seres will also fund US and Canadian approvals, while Nestle will pay for those activities in all other territories. For all products, Seres will fund US and Canadian approvals, while Nestle will pay for those activities in all other territories. The licensed candidates are ecobiotic therapies designed using Seres' *Microbiome Therapeutics* platform. Nestle Health Science was the sole investor in Seres' January 2015 Series D financing, and also contributed funding to the firm's $143mm IPO, which closed in June 2015.

NOVARTIS AG
SURFACE ONCOLOGY

Novartis AG and **Surface Oncology** are collaborating on the development of next-generation cancer immunotherapeutics. The start-up's approach--meant to benefit more patients and treat a wider range of tumors--involves a broader set of immune processes (in areas other than checkpoint inhibitors). (Jan.)

Surface aims to improve the process in which the immune system recognizes and rids itself of cancer cells through a method intended to increase the effectiveness of antigen presentation to the adaptive immune system, inhibit suppressor cell activity in the tumor microenvironment (where tumor and immune cells interact), and counter the immunosuppressive environment that accumulates in and surrounds the tumor. Novartis will gain exclusive worldwide rights to Surface's current pipeline of cancer immunotherapies, and the option (exercisable at the time of IND filing) to license up to three additional programs from the existing pipeline. (The company has five preclinical programs.) Surface has its own option to co-develop and co-commercialize in the US half of the programs under the agreement; it could receive up to $170mm--consisting of an up-front payment, equity, and near-term milestones--plus clinical and commercial milestones, and up to double-digit sales royalties. Surface was formed in 2014 and is currently headed by Detlev Biniszkiewicz, PhD--former head of oncology strategy at **AstraZeneca** (and an executive at Novartis prior to AZ). Novartis research arm **Novartis Institutes for BioMedical Research** and a couple other Big Pharmas (**Lilly** and **Amgen**) participated in the company's Series A round in January 2015. Since acquiring **GSK**'s cancer business in April 2014, Novartis has signed alliances within the immuno-oncology space with both **Arduro Biotech** (immunomodulating cyclic dinucleotides) and **Intellia Therapeutics** (CRISPR/Cas9) and bought **Admune Therapeutics** (cytokines).

SANOFI
X-CHEM INC.

X-Chem Inc. agreed to use its DNA-encoded discovery engine to identify new lead molecules against multiple targets for **Sanofi**. The deal could include compounds for cancer, diabetes, rare diseases, and other conditions. Sanofi has an exclusive option to license resulting candidates. (Jan.)

X-Chem's DNA-encoded X-Chem (*DEX*) library (which has over 100 billion small-molecule compounds) utilizes DNA tagging to record a molecule's synthetic history and chemical structure during combinatorial synthesis processes. The compounds are barcoded and can therefore be easily and quickly identified using DNA sequencing. X-Chem has similar discovery agreements with other major partners including **Janssen Biotech** (for inflammation; January 2014); **Alexion Pharmaceuticals** (ultra-rare diseases; December 2014); and **Pfizer** (inflammation and orphan diseases; June 2014).

SERVIER SA
Servier Canada Inc.
SPECTRUM PHARMACEUTICALS INC.

Continuing on the path to focus on its core projects, **Spectrum Pharmaceuticals Inc.** granted **Servier Canada Inc.** exclusive rights to develop and sell four of its cancer products in Canada. All have been approved and launched in other countries, but not yet in Canada. (Jan.)

Spectrum gets $6mm up front, plus undisclosed development milestones and royalties. Included in the deal are the lymphoma treatments *Zevalin* (ibritumomab tiuxetan), *Folotyn* (pralatrexate), and *Beleodaq* (belinostat), and *Marqibo* (liposomal vincristine) for acute lymphocytic leukemia. The drugs are the first cancer projects in the works for Servier Canada; it currently offers treatments for cardiovascular conditions and diabetes, and will commence operations of **Servier Canada Oncology** to work on the in-licensed compounds. For Spectrum, the deal (along with other prior similar out-licensing transactions) affords the company greater bandwidth for core candidates including SPI2101 (entering Phase III for chemo-induced neutropenia), poziotonib (Phase II for various solid tumors), apaziquone (Phase III for non-muscle invasive bladder cancer), and *Evomela* (melphalan; awaiting approval as a conditioning treatment prior to stem cell transplant in myeloma patients).

SINO BIOPHARMACEUTICAL LTD.
Chia Tai Tianqing Pharmaceutical Group Co. Ltd.
JOHNSON & JOHNSON
Janssen Pharmaceuticals Inc.

Chia Tai Tianqing Pharmaceutical Group Co. Ltd. licensed Janssen Pharmaceuticals Inc. exclusive rights to develop and commercialize outside of China undisclosed immuno-modulating agents to treat chronic hepatitis B virus. (Jan.)

Terms of the deal were not disclosed. Janssen has been looking to build its HBV pipeline. Two months ago it acquired HBV therapeutics developer Novira Therapeutics Inc., gaining a Phase I direct-acting antiviral. The Janssen-Chia Tai collaboration was announced on the same day that Johnson & Johnson penned 21 other alliances across the consumer, medical device, and pharmaceuticals sectors in various therapy areas including cardiovascular, cancer, and musculoskeletal diseases.

UPSHER-SMITH LABORATORIES INC.
Proximagen Ltd.
SANIONA AB

Upsher-Smith Laboratories Inc.'s Proximagen Ltd. CNS division and Saniona AB will together collaborate on the development of small-molecule therapeutics to treat neurological disorders. (Jan.)

Saniona will contribute its expertise in ion channel discovery and related technology platforms (combining medicinal chemistry, ADME, and in vitro and in vivo pharmacology) that identify and modulate the passage of charged ions across cell membranes. The deal will focus on one of Saniona's early-stage discovery programs. In exchange for Proximagen's exclusive worldwide license to develop, manufacture, and commercialize resulting therapeutics, Saniona will receive $1.1mm in up-front and research funding; research, development, and regulatory milestones up to $30mm; plus tiered royalties on net sales. Fully acquired by Upsher-Smith in 2012 (it had previously taken minority equity stakes in 2008 and 2010), Proximagen's pipeline contains two Phase II candidates in epilepsy and Parkinson's disease, as well as several preclinical programs in pain, PD, and dyskinesia. The alliance also comes at a good time for the Danish start-up as Pfizer--its partner under a 2014 deal--recently ended the $52mm potential partnership due to internal restructuring. This deal also incorporated Saniona's ion channel platform for the development of CNS therapeutics, and resulted in the achievement of preclinical proof-of-concept as well as a pathway to identify a new candidate.

Financings
/Pharmaceuticals

ACADIA PHARMACEUTICALS INC.

Acadia Pharmaceuticals Inc. (develops drugs for neurological and psychiatric disorders) netted $282 mm in a public offering of 10.3mm shares at $29. The company will use the proceeds to fund commercialization of *Nuplazid* (pimavanserin)--accepted for priority review by the FDA with a PDUFA date of May 1, 2016 in Parkinson's disease psychosis--and continued development of pimavanserin in additional indications; the candidate is also currently in Phase II for schizophrenia. (Jan.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Cowen & Co. LLC; HC Wainwright & Co.; JMP Securities LLC; JP Morgan & Co.; Ladenburg Thalmann & Co. Inc.; Needham & Co. Inc.

ACCELERON PHARMA INC.

Acceleron Pharma Inc. (cellular growth and repair) netted $141mm in a follow-on offering of 3.75mm common shares at $40 (partner Celgene purchased 800k of the shares). The company will use the proceeds for clinical trials of ACE083 (clinical stage candidate for muscle growth and function) and other candidates including antibodies and proteins from the *IntelliTrap* platform, and to expand R&D. (Jan.)

Investment Banks/Advisors: FBR & Co.; JMP Securities LLC; Leerink Partners LLC; Morgan Stanley & Co.; UBS Investment Bank

ADAMAS PHARMACEUTICALS INC.

In its first public offering since its April 2014 IPO, Adamas Pharmaceuticals Inc. (memantine-based CNS drug development) netted $54mm through the sale of 2.5mm shares at $23. The company intends to use the proceeds to expand its R&D programs for other potential CNS indications. Adamas recently announced positive top-line Phase III results for lead candidate ADS5102 for levodopa-induced dyskinesia (LID), a complication associated with Parkinson's disease. (Jan.)

Investment Banks/Advisors: Cowen & Co. LLC; JMP Securities LLC; Piper Jaffray & Co.; Trout Capital LLC; William Blair & Co.

AGILE THERAPEUTICS INC.

Women's health company Agile Therapeutics Inc. (transdermal contraceptive patches) netted $33mm in a follow-on offering of 5.5mm shares at $6.35. (Jan.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; FBR & Co.; Janney Montgomery Scott Inc.; RBC Capital Markets; William Blair & Co.

AKEBIA THERAPEUTICS INC.

Akebia Therapeutics Inc. (uses inhibitors of hypoxia-inducible factor, a regulator of red blood cells, in its development of therapeutics for anemia and other diseases) netted $61mm in a follow-on offering of 7.3mm shares at $9. The company concurrently initiated a Phase III trial in non-dialysis patients with anemia related to chronic kidney disease for its vadadustat (formerly AKB6548), which it licensed just last month to Mitsubishi Tanabe in Japan, various other Asia Pacific regions, and India. (Jan.)

Investment Banks/Advisors: Brean Capital LLC; JMP Securities LLC; Morgan Stanley & Co.; Needham & Co. Inc.; UBS Investment Bank

ARDELYX INC.

Ardelyx Inc. (therapies for gastrointestinal and cardiorenal diseases) netted $81mm through the follow-on offering of 8.6mm common shares (including the overallotment) at $10 each. Proceeds will help with Phase III trials of tenapanor for irritable bowel syndrome, end-stage renal disease, and hyperphosphatemia, and RDX022 for hyperkalemia. Additional money will support the IND filing for RDX009 and R&D activities for earlier-stage programs. (Jan.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Citigroup Inc.; JMP Securities LLC; Ladenburg Thalmann & Co. Inc.; Leerink Partners LLC; Wedbush PacGrow Life Sciences

BAVARIAN NORDIC AS

Danish firm Bavarian Nordic AS has filed for its initial public offering of American Depositary Shares. The company will trade on the Nasdaq Global Select Market under the ticker BAVN. (Jan.)

Investment Banks/Advisors: Cowen & Co. LLC; Nomura Securities International Inc.; Piper Jaffray & Co.

CASI PHARMACEUTICALS INC.

CASI Pharmaceuticals Inc. (therapies for cancer and other serious diseases; marketing efforts focused on China) grossed $10mm through the sale of 8.5mm common shares at $1.19 (a 4% premium to the market average when the deal was preliminarily announced in September 2015). Investors also purchased 1.7mm three-year warrants (exercisable at $1.69) for $0.125 per warrant. A Chinese investment fund manager affiliated with the management team of CASI's largest shareholder IDG-Accel China Growth Fund III LP was the sole buyer, and is expected to purchase another 12.2mm shares at some point in the future under terms of the original agreement. (Jan.)

CEMPRA INC.

Antibiotics developer Cempra Inc. netted $94mm through a follow-on offering of 4.17mm common shares at $24 each. Some of the proceeds will support the US launch of solithromycin for community-acquired bacterial pneumonia once the drug gets FDA approval. Additional funds will help additional development of solithromycin for gonorrhea, and *Taksta* for acute bacterial skin and skin structure infections and refractory bone and joint infections. (Jan.)

Investment Banks/Advisors: Cowen & Co. LLC; JP Morgan & Co.; Jefferies & Co. Inc.; Ladenburg Thalmann & Co. Inc.; Needham & Co. Inc.; Stifel Nicolaus & Co. Inc.; WBB Securities LLC

CLEARSIDE BIOMEDICAL INC.

Ophthalmic-focused Clearside Biomedical Inc. filed for its initial public offering. (Jan.)

Investment Banks/Advisors: Needham & Co. Inc.; RBC Capital Markets; Stifel Nicolaus & Co. Inc.; Wedbush PacGrow Life Sciences

CORVUS PHARMACEUTICALS INC.

Corvus Pharmaceuticals Inc. (checkpoint inhibitors for cancer) filed for its initial public offering. (Jan.)

Investment Banks/Advisors: BTIG LLC; Cantor Fitzgerald & Co.; Cowen & Co. LLC; Credit Suisse Group; Guggenheim Partners LLC

EDITAS MEDICINE INC.

Editas Medicine Inc. filed for its IPO on the Nasdaq, with initial plans to sell 5.9mm shares. Proceeds will be used to fund the company's trials for LCA10 (Leber Congenital Amaurosis type 10; genetic progressive form of blindness), for preclinical studies with the candidate under its Juno Therapeutics collaboration (entered into in May 2015), and for expansion of platform technology. (Jan.)

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

EPIZYME INC.

Epizyme Inc. (epigenetic cancer therapies) netted $130mm through the public sale of 15.3mm shares

(including the overallotment) at $9. Proceeds will fund ongoing development of lead project tazemetostat outside of Japan (including Phase II trials for non-Hodgkin lymphoma, INI1-negative tumors, and synovial sarcoma, and planned studies for diffuse large B-cell lymphoma, B-cell non-Hodgkin lymphoma, and mesothelioma) and the initiation of activities supporting the eventual market launch of the compound. (Jan.)

Investment Banks/Advisors: Citigroup Inc.; HC Wainwright & Co.; JMP Securities LLC; Leerink Partners LLC; Maxim Group LLC; Mizuho Bank Ltd.; RBC Capital Markets; Wedbush PacGrow Life Sciences

ESSA PHARMA INC.

Oncology firm **ESSA Pharma Inc.** raised $15mm through the private sale of 4.5mm units at $3.30 each (a 23% discount). Each unit consisted of one common share, one seven-year cash and cashless warrant, and one-half of one two-year cash exercise warrant, exercisable at $3.30. Clarus Lifesciences led (and holds a 9.4% stake following the transaction, before warrant exercise) and was joined by Special Situations Fund, Deerfield, and four other undisclosed buyers. (Jan.)

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

GALENA BIOPHARMA INC.

Galena Biopharma Inc. (oncology) publicly sold 19.8mm shares at $1.10 for net proceeds of $20mm. Buyers also received five-year warrants to purchase 11.86mm shares at $1.42. Some of the proceeds will fund the ongoing Phase III PRESENT trial of *NeuVax* (nelipepimut-S) for HER2/NEU-expressing cancers. (Jan.)

Investment Banks/Advisors: FBR & Co.; Maxim Group LLC; Noble Financial Capital Markets; Raymond James & Associates Inc.; Roth Capital Partners

HALOZYME THERAPEUTICS INC.

Halozyme Therapeutics Inc. (targeted cancer treatments) entered into a $150mm non-dilutive debt financing with funds managed by Pharmakon Advisors and Athyrium Capital Management. The per-year interest rate is 8.75 percent plus the three-month LIBOR rate (with the LIBOR rate subject to a floor of 0.70% and a cap of 1.5%). (Jan.)

MOBERG PHARMA AB

Swedish pharmaceutical company and distributor **Moberg Pharma** issued a five-year senior unsecured bond for $36mm (SEK300mm). The bond will bear a floating interest rate of three month Stibor (Stockholm Interbank Offered Rate) + 6%, will mature on January 29, 2021, and has a total framework of $72mm (SEK 600mm). The company intends to use the proceeds to apply for a listing on The Nasdaq Stockholm. (Jan.)

Investment Banks/Advisors: Carnegie Investment Bank AB; Swedbank

OTONOMY INC.

Otonomy Inc. (otology therapies) netted $108.1mm in a follow-on public offering of 5.75mm shares (including full exercise of the over-allotment) at $20. The company will use the proceeds for commercialization expenses and ongoing clinical trials of *OTIPRIO* (ciprofloxacin otic suspension for pediatric otitis media); for clinical development of OTO104 (including completion of Phase 3 US trials, initiation and completion of a Phase 3 EU trial, and safety studies in Ménière's patients); for completion of Phase 1 trials for OTO311 and Phase 2 trials in tinnitus patients; and for preclinical development of Program 4 targeting sensorineural hearing loss. (Jan.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Cowen & Co. LLC; Piper Jaffray & Co.; Sanford C Bernstein; SunTrust Banks Inc.

REATA PHARMACEUTICALS INC.

Reata Pharmaceuticals Inc. filed for its IPO on the Nasdaq. The Texas-based biopharmaceutical company will raise up to $80mm in the proposed offering. Proceeds will be used to fund further clinical trials. The company has raised over $100mm in venture funding to date through seven rounds. (Jan.)

Investment Banks/Advisors: Citigroup Inc.; Cowen & Co. LLC; Piper Jaffray & Co.

SAGE THERAPEUTICS INC.

SAGE Therapeutics Inc. (CNS drug development focused on selective allosteric GABAA and NMDA receptor modulation) netted $141mm in a public offering of 3.2mm shares at $47.50. The company intends to use the proceeds to progress clinical trials for lead candidate SAGE547, which has orphan and fast track status and is currently in Phase III for super-refractory status epilepticus (SRSE; a rare disease marked by persistent seizures), and ongoing development of other pipeline candidates for potential CNS indications. SAGE217 is in Phase I for seizure conditions including Dravet and Rett syndromes and SAGE689 is in non-clinical development for epilepsy; a Phase I trial was delayed following the FDA's November 2015 request for additional study data. (Jan.)

Investment Banks/Advisors: Canaccord Genuity Inc.; Cowen & Co. LLC; Goldman Sachs & Co.; JP Morgan & Co.; Leerink Partners LLC

SPRING BANK PHARMACEUTICALS INC.

Spring Bank Pharmaceuticals Inc. (infectious diseases) filed for its initial public offering. (Jan.)

Investment Banks/Advisors: BTIG LLC; Wedbush PacGrow Life Sciences; William Blair & Co.

THERAPEUTICSMD INC.

Women's health company **TherapeuticsMD Inc.** netted $117.5mm by publicly selling 15mm shares at $8.25. Most of the money will go towards future commercialization activities for Phase III TX004HR, an applicator-free vaginal estradiol softgel capsule for vulvar and vaginal atrophy in postmenopausal women. (Jan.)

Investment Banks/Advisors: Cowen & Co. LLC; Goldman Sachs & Co.; Guggenheim Partners LLC; Stifel Nicolaus & Co. Inc.

VISTERRA INC.

Visterra Inc. (infectious disease vaccines) filed for its initial public offering. (Jan.)

Investment Banks/Advisors: Leerink Partners LLC; Needham & Co. Inc.; Stifel Nicolaus & Co. Inc.; Wedbush PacGrow Life Sciences

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

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FDA Quality Metrics Proposal Sparks Objections, Disarray

Bowman Cox bowman.cox@informa.com

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

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

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

Support – and resistance

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

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

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

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

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

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

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

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EXECUTIVESUMMARY

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Orphans Should Live Alone

BY ALAIN J. GILBERT, ANNE-SOPHIE DEMANGE AND MARK RATNER

The organization and culture of a rare disease specialist company or program is distinct from that of a traditional pharma or biotech. Commercial success is driven by a patient-centric model focused on access and interactions with KOLs and less on selling features and benefits. An ability to connect with rare disease patient communities and physicians at the level of senior management is paramount, giving an advantage to companies of small size: it is the kind of representation a large company cannot afford for a relatively small product line. With size and diversity of markets also often comes more rigidity and standardization of practices. Many more processes are in place at large firms and decision-making is often dominated by a committee structure, which makes alignment with a successful rare disease model difficult. It may be easier for larger firms to acquire ultra-rare disease firms after they have become successful, as Sanofi did with Genzyme – initially leaving it alone to preserve the benefit of the asset. We therefore believe orphan drug franchises should live alone – at least until they reach a level of maturity to be able to withstand structural organizational pressures.

SUMMARY OF ARTICLE FROM PAGE 18

The Birth Of An Orphan Biosimilar Market

BY PAUL ZHANG, TRIONA BOLGER, VARUN RENJEN, BRIAN SATTIN, ANNY LIN AND ADITYA VENUGOPAL

Biosimilar regulatory pathways have been paved, complex mAbs biosimilars have been approved, a wave of patent expiries are sweeping across the product landscape and the first batch of biosimilars are establishing safety and credibility with physicians and patients. Investments made by major biologics companies and start-ups alike will unmistakably accelerate and intensify the growth of biosimilar markets. In this context, while orphan disease presents a unique set of unknowns to biosimilar players such as the availability of clinical study subjects, KOL loyalty and payer activism, the law of pharmaceuticals will prevail in the end. If the orphan biologic has revenue over $250 million, it will likely attract imitators. Pricing strategy and payer effectiveness will be the most critical consideration in its commercial success, while a less strenuous clinical development program will make the path to market that much more favorable.

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Glaukos Holds Lead In Microinvasive Glaucoma Surgery

BY TOM SALEMI

A wave of microinvasive surgery companies are looking to create a new market for the treatment of glaucoma, which affects roughly 80 million people worldwide. Glaukos Corp. is the reigning leader in the emerging field of microinvasive glaucoma surgery (MIGS), as it's the only company with an FDA-approved product. But the gap between Glaukos' iStent and rival technologies may be closing as new technologies are approved. CEO Tom Burns shares his thoughts on the MIGS space and explains where he thinks Glaukos is headed.

SUMMARY OF ARTICLE FROM PAGE 32

Medtechs Bet On Transcatheter Mitral Valve Repair

BY JENNY BLAIR

The success of transcatheter aortic valve replacement has generated optimism that the much larger pool of mitral regurgitation patients can be similarly served. Big medtechs made a number of mitral valve replacement M&A deals in 2015, while other companies, including start-ups, are betting on mitral valve repair, a market that may be four times larger than TAVR. But the road for new mitral interventions may be rockier than it was for TAVR. Among aortic stenosis patients, it is much more obvious who needs TAVR, whereas for MR patients indications often are unclear. Due to the complexity of the mitral valve, it's likely that multiple minimally invasive devices will share the space in the future, perhaps in a stepwise or combination fashion.