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SEPTEMBER 2018

DRUG DELIVERY

From novel mechanisms and new technologies to patient adherence solutions

Drug Delivery Outsourcing In A World Of Pharma's Shifting Sands

Microbiome Drug Development: An Investigation Into Challenges And Pipeline Approaches

Bringing The Clinician's Rationale Into The Heart Of Strategic Decision-Making At Boston Scientific

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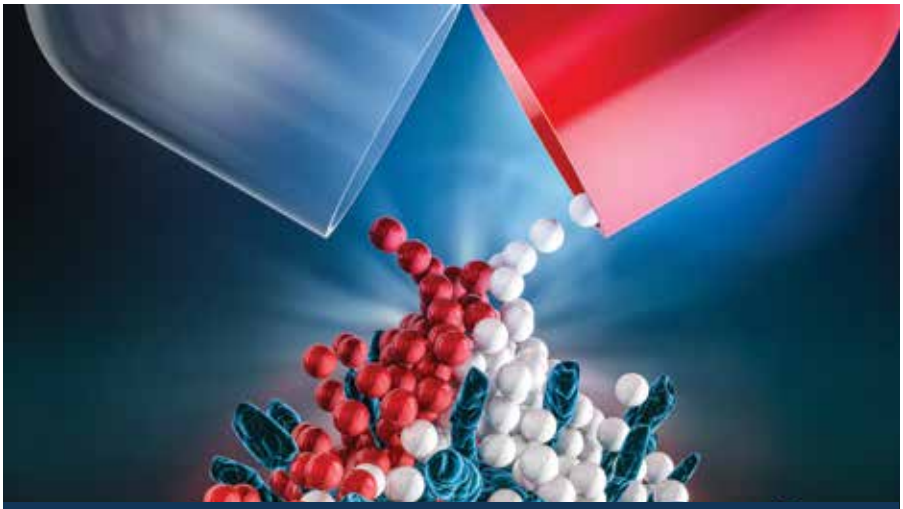
September 2018



THE DRUG DELIVERY ISSUE

In Vivo
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September 2018

DEPARTMENTS

EXCLUSIVE ONLINE CONTENT

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From The Editor

LUCIE ELLIS

Summer is over, and the life sciences sector is gearing up for the forthcoming conference season. For September, *In Vivo* is examining the theme of drug delivery – exploring the multiple faces of delivery, from the contract services perspective to new modes of action for therapeutic treatments, and strategies for growth in the device delivery space.

Drug delivery is currently a key focus area for pharma and medtech stakeholders because of the rapidly evolving science and shifting commercial ground around new approaches to treating disease. Developments for the pharmaceutical industry are causing ripple effects across the broader health care sector.

In this issue, William Looney speaks to the chief operating officer of Spark Therapeutics, John Furey, about the drug delivery challenges for gene therapies, a class that represents a whole new world of potential curative treatment for genetic conditions. Furey compares the current situation for novel gene therapies to the journey made by monoclonal antibody developers in the past – a class that took years to emerge as an accepted delivery platform for patients in the clinical setting.

Meanwhile, in an exclusive interview with drug delivery technology specialist Consort Medical, Ashley Yeo uncovers more about the company's plans to remain at the front of the pack for drug delivery and device manufacturing. Consort, a global market leader in valve technologies, is expanding its delivery manufacturing into nasal and auto-injectable devices. Consort CEO Jonathan Glenn discusses the company's recent acquisition of Aesica Pharmaceuticals Ltd., and how he was convinced early on that acquiring a pharma CMDO was the next stage in ensuring a competitive future in a segment where Consort's delivery business has dominated for five decades.

This month, *In Vivo* also features an in-depth look at the pipeline for novel microbiome therapeutics and an analysis of the challenges for delivering these drugs to patients; and exclusive interviews with Boston Scientific's new chief medical officer, Ian Meredith, and Cornell Stamoran, vice president of strategy and corporate development at contract drug delivery group, Catalent.

In Vivo is also pleased to announce that two new members have joined its Editorial Advisory Board. They are Annalisa Jenkins, CEO of Plaque Tec, and Sara Jane Demy, CEO and founder of the life science-focused events business Demy Colton. Furthermore, Ranjini Prithviraj, PhD, associate director of publications at DIA (Drug Information Association), has joined the advisory board in place of Barbara Lopez Kunz.

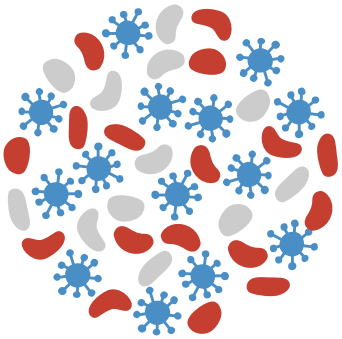
Up-Front

SNAPSHOTS FROM SEPTEMBER'S CONTENT

There is not one type of company that is a drug delivery company today. The center of gravity and aggregation of businesses is falling into the contract development manufacturing organization (CDMO) sector. **PAGE 14**

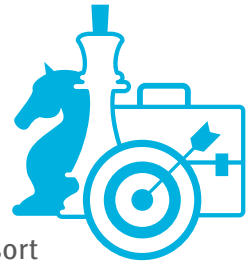
"Gene therapy has been compared to a multi-functional team sport, where careful coordination is necessary to build unique capabilities across a wide spectrum of activities."

JOHN FUREY, CHIEF OPERATING OFFICER OF SPARK THERAPEUTICS, SPEAKS EXCLUSIVELY TO *IN VIVO*. **PAGE 8**



Informa Pharma Intelligence's Pharmaprojects database has tracked trends in drug development from 1980 until present. These data reveal a boom in the development of the microbiome.

PAGE 26



Drug delivery technology specialist Consort Medical has capitalized on device respiratory expertise for 50 years, but a renewed focus on strategic expansion has seen it make an IP play and target other delivery formats for global pharma customers.

PAGE 32

"The confluence of digital health and medical technology will change the face of how devices are seen and used."

– IAN MEREDITH
Global CMO
Boston Scientific

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Around The Industry

Aptar's Focus On Digital Connectivity Presents New Drug Delivery Opportunities

Drug delivery specialist **Aptar Pharma** has a clear view on an increasingly acute problem for the global health care sector: the system cannot continue to pay out and not know who is taking the medicine, or if it is being effective. Part of the solution is to embrace digital capabilities, the company believes.

The Crystal Lake, IL group's portfolio includes standard devices, electronic devices, preventive devices (such as e-Lockout, the first fully-integrated electronic nasal drug delivery device with time-interval properties approved in the US or EU), and it is now taking that continuum further, going from electronic to connected devices. Its recently strengthened partnership with, and strategic investment in, digital therapeutics company **Propeller Health** (May 2018), will provide the platform for this activity.

This digital medicine platform will cover inhaled, injectable, nasal and dermal medicine delivery. Madison, WI-based Propeller and Aptar will co-market the platform, with Propeller managing the digital services and Aptar the device development, manufacturing and supply chain. The deal, accompanied by a $10 million investment in Propeller, followed the May 2017 investment in and partnership with Kali Care, covering digital and sensor technology in the ophthalmic space, and the tools to help pharma companies in their clinical trials. Aptar now has digital ambitions for all its established delivery routes.

Sai Shankar, Aptar Pharma's director of business development for connected devices, describes Propeller as a good partner, having already proved itself in the market with an e-respiratory and digital medicine platform. Speaking to *In Vivo*, he said Aptar Pharma's partnership expansion with Propeller Health (the two initially partnered in 2016 on the development of the world's first fully-integrated connected metered dose inhaler, cMDI) was another way of showing the market that Aptar is serious about digital health care and digital therapeutics.

> "Technology has democratized the idea of what can be done."
> – Sai Shankar
> Aptar Pharma

"We want to go beyond respiratory and into other disease areas, and Propeller was a logical partner for us. The rationale is compelling. The entire industry is moving towards digital health care and connectivity is integral to that," says Shankar. Aptar wants to participate in this health care space, and rivals, too, are making a huge push, with disruptors also making their presence felt. "The IoT is quite omnipresent now – connectivity is pretty much everywhere in day-to-day life, and it must happen in health care too, in ways that give patients more control over their health."

Digital connectivity is the next logical next step for the health care ecosystem, industry and for Aptar, where Shankar has been overseeing a dedicated strategy for the past year. As of September 1, 2018, Aptar has a new leader, Gael Touya, formerly president of Aptar Food + Beverage. Touya will continue to report to AptarGroup CEO Stephan Tanda, and is expected to continue the strategy driven by previous incumbent Salim Haffar, and champion Aptar's innovation and sustainability initiatives.

Aptar Pharma already provides drug delivery systems in inhalation, nasal, dermal, ophthalmic and injectables across several disease areas. Shankar says, "Our coverage is quite wide, but the point is that, with each drug delivery route, you can have a multitude of therapeutic areas to cover. Our idea for connectivity is to look at activity and the therapeutic areas where we believe we could really bring true value for the patient and the health care system."

BRINGING VALUE MORE IMPORTANT THAN TECHNOLOGY

Shankar is keen to stress that Aptar Pharma will not do connectivity for the sake of connectivity, which he says would be "pointless," rather he reiterates that the company will pursue connectivity where it can actually change lives, bring value to health care systems, reduce costs and make therapies more effective.

The Propeller deal will focus on developing solutions in areas that need a high level of compliance, i.e. substantially any areas of chronic or acute care where connectivity will help patients. The patient education piece is a huge part of the digital transition, Shankar adds. "Connectivity is also about behavioral issues," he says. "It's not just about taking a drug on time, it is the question of why patients do not take drugs as prescribed."

So the bigger issue as Shankar sees it is how to best leverage digital health to try to change that behavior and bring about change.

Aptar is not alone in broaching this challenge, but Shankar does not see any one player as having taken the lead. Many are experimenting with the possibilities,

given that "technology has democratized the idea of what can be done." In many ways, the industry is still finding its feet in terms where the value of connectivity lies. "We've approached this in terms of creating partnerships that are meaningful and logical," says the Aptar Pharma executive, observing that many players who would have been considered erstwhile competitors are now potential partners for collaboration.

Shankar does believe that Aptar has a unique approach to the connectivity solution – which is to take a broad approach. "Our idea of connected care is not to focus on one device or therapeutic area, but to provide connectivity meaningfully across the therapeutic spectrum." Disease states, for instance diabetes and cardiovascular disease, need to be looked at together, not in isolation. Insurance companies tend to look across the entire health space, not at individual diseases. Most companies, he believes, are focusing on one or two therapeutic areas. "To make it meaningful you have think much broader than one disease area."

DIGITAL EVANGELIST

Aptar's policy is that connectivity must add value to the patients' lives and improve outcomes. Its business priorities for the next few years have been shaped to fulfil this aim. It intends to continue rolling out its current technologies and create more partnerships with clients and implement programs with them. It will also focus on continuing its portfolio developments. Thirdly, it will continue to evangelize the idea of digital connectivity in therapeutics.

The fact that other companies are bringing programs and devices to market is "great news" for the sector, says Shankar, as it all serves to educate patients, providers, and clinicians about the value it can bring to health care. There is still an element of the population that is skeptical about digital, and look at it as adding to costs.

A good partner, as Aptar sees it, is a player who is well versed and understands the value of digital medicine. A potential collaborator might already have run a program similar to what Aptar does, understand pharmaco-economic values, and be receptive to the idea of implementing another program. By the same token, Aptar says it is also useful to work with newcomers and disrupters. "We should not be looking at this in a myopic way; start-ups have done a fantastic job disrupting the market with their novel ideas. Our philosophy is never to isolate one or the other." In fact, Aptar is doing work now with start-ups, with the world's largest pharma company, and with insurance companies, among others.

Its focus on the ecosystem is where Aptar feels it is different. "It is very important to make sure we have the right channel partner(s) – when you get that right, you can create the right digital ecosystem."

But it requires a lot of work still. These are early days in the space, but a lot is at stake. Excluding currency translation effects, Aptar Pharma's sales rose by 8% in 2017, and has similarly seen sales grow 10% through the first half of 2018 with an expected long-term range of 6-10% annually. The end consumer market in which it works is valued at $35 billion, with CAGR of 4.1%, according to Aptar internal data, McKinsey & Co and other sources. Prescription sales make up 53%, and consumer health care and injectables 28% and 19%, respectively, of year-to-date 2018 sales. Aptar Pharma's markets are the US and Europe principally, but China, India and South America sales are increasing fast, Shankar observes.

Another key part of the brief is Thought Leadership, which it promotes via its co-organization of the world's largest respiratory drug delivery conference RDD Europe and RDD Asia, and knowledge sharing and collaboration facilitating via webinars and conference appearances. It can also leverage its regulatory expertise, which has been used to help over 170 prescription drugs get on the market worldwide.

In a competitive market, all assets and expertise need to be exploited, and in the IoT era, that means maximizing health connectivity to demonstrate value to the system by improving outcomes and reducing costs – an area where Aptar Pharma is currently busy building a position.

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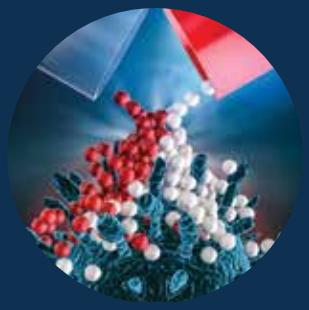
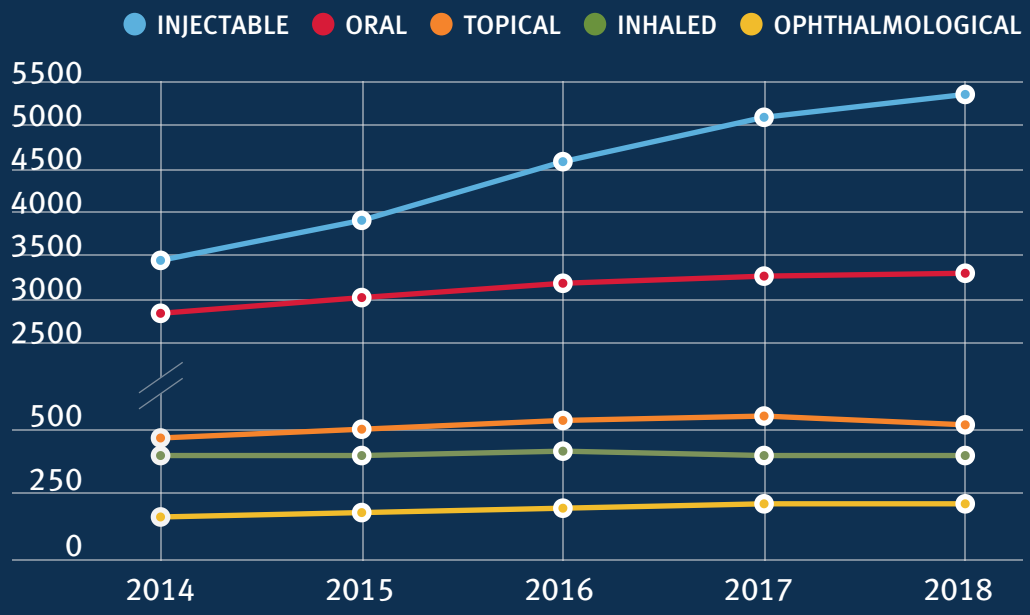
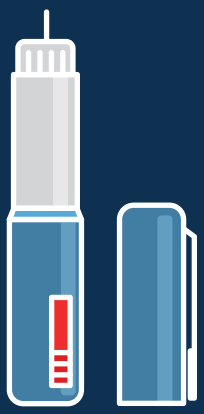


DRUG DELIVERY

Exploring route of administration, mode of action, clinical trial and therapy area trends across the biopharma pipeline.

Top Five Treatment Delivery Routes For Investigational Pharma Pipeline





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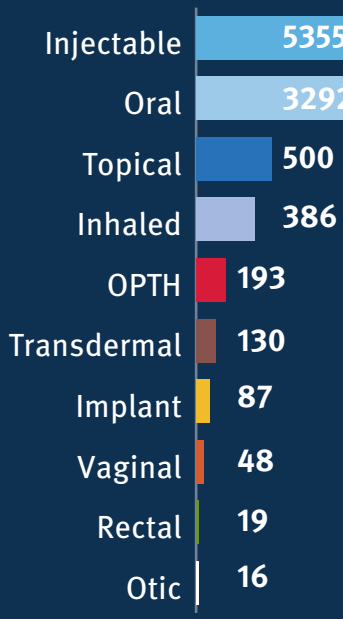
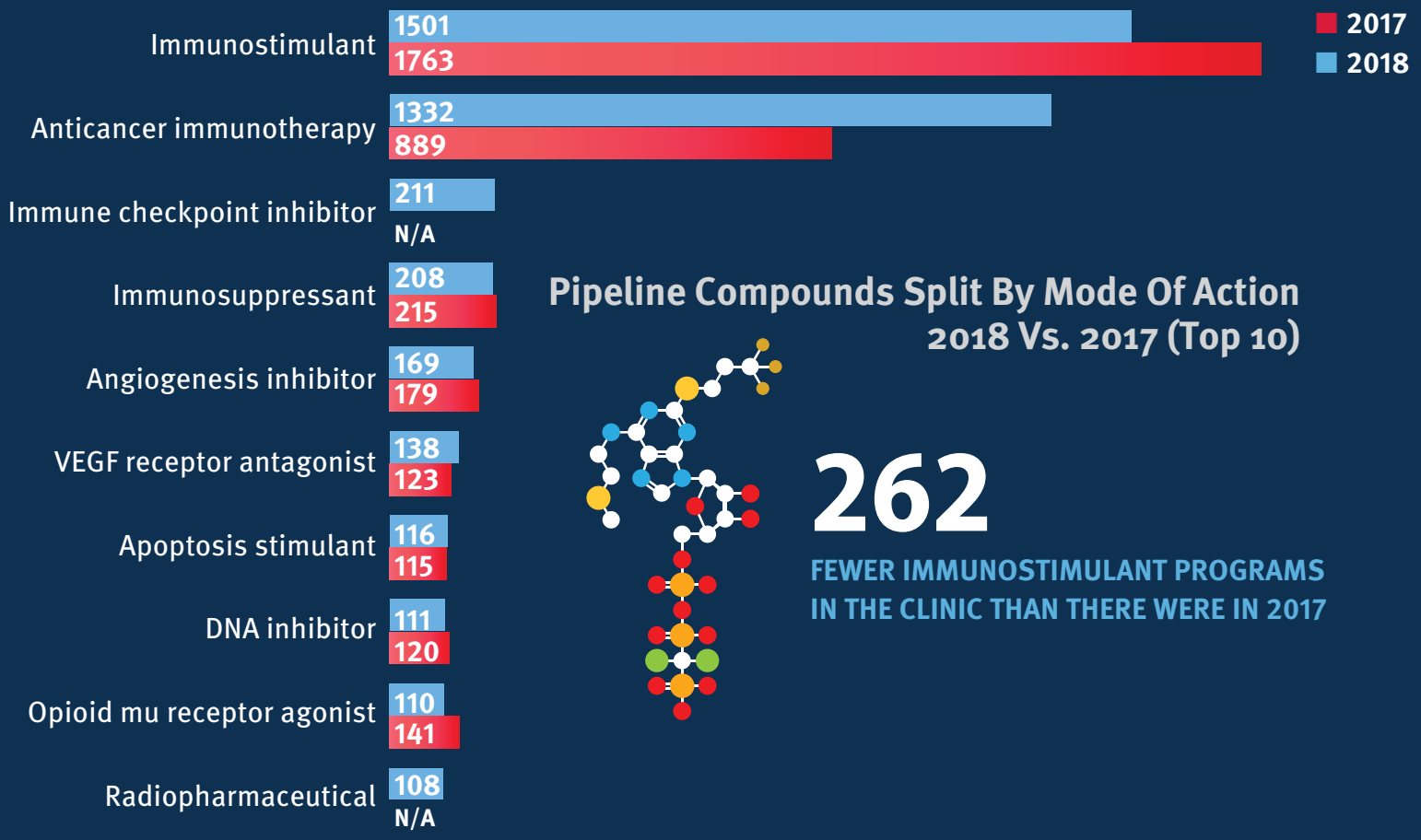
INCREASE IN THE NUMBER OF INJECTABLES FROM 2016 TO 2018



Route Of Administration Methods Across Pharma Pipeline In 2018

5150

TOTAL NUMBER OF ACTIVE COMPOUNDS IN THE 2018 PHARMA PIPELINE VS. 4540 IN 2017 (TOP 10 LISTED)

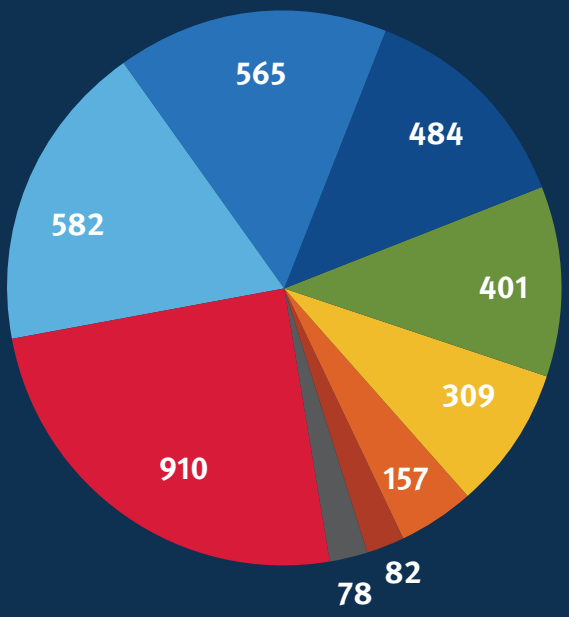


Pipeline Compounds Split By Mode Of Action 2018 Vs. 2017 (Top 10)

262

FEWER IMMUNOSTIMULANT PROGRAMS IN THE CLINIC THAN THERE WERE IN 2017

Industry-Sponsored Trial Count By Therapeutic Area - 2017*



- Oncology
- Autoimmune/Inflammation
- CNS
- Metabolic/Endocrinology
- Infectious Diseases**
- Cardiovascular
- Vaccines
- Ophthalmology
- Genitourinary

* Trials may span multiple therapeutic areas
** Does not inlcude vaccine trials

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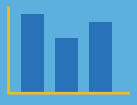
For more in-depth analysis and interactive data visit **Drug Delivery:**

https://bit.ly/2OcNAmt



SOURCES: Trialtrove; Pharmaprojects Pharma Intelligence, 2018

Gayle Rembold Furbert

Gene Therapy: Spark Charts A Course From Science To Payer And Patient Satisfaction

JOHN FUREY, COO, SPARK THERAPEUTICS

Gene therapy's promise depends on the ecosystem now being built to deliver real product to patients – safely and at quantities that match the soaring expectations fed by the curative potential of the science. To assess the state of play, *In Vivo* talks to the man who leads the team responsible for bringing forward the first US-approved gene therapy to treat an incurable, inherited genetic condition: John Furey, chief operating officer of Spark Therapeutics.

BY WILLIAM LOONEY

Spark Therapeutics Inc.'s extensive outreach to payers is bearing fruit: nine months after launch, 80% of commercial lives certified for the *Luxturna* (voretegene neparvovec-ryzl) RPE65 mutation treatment for inherited retinal blindness are receiving the product through insurance.

So what? Payers are proving receptive to non-traditional evidence on the value of high-priced cures from gene therapy. Spark's stats on US civil damage jury awards in cases resulting in blindness showed average compensation amounts many multiples higher than the price tag for Luxturna – a societal measure of value that resonates.

***In Vivo:* Drug delivery is undergoing significant changes as the basic science behind cell and gene therapy open new pathways for medicines that can prevent or cure a wide range of deadly genetic disorders. As chief operating officer (COO) of a company that secured the first FDA approval of a directly administered gene-based drug for a rare inherited retinal disease, you occupy center stage in the effort to make this novel technology an integral part of medical practice – one that is safe, efficacious and accessible to patients. What's your assessment of the industry state of play in realizing the promise of Luxturna and the more than 600 additional gene therapies now in clinical development?**

John Furey: Gene therapy today faces many of the same issues the industry had to confront 30 years ago with the advent of another revolutionary technology: the monoclonal antibody. These biologic drugs marked a major departure from the familiar world of solid dosing. Whether the industry had sufficient capacity to manufacture monoclonal antibodies was unclear, the supply chain for these complex medicines still had to be charted, while the need for a different approach to pricing and reimbursement helped spawn the rise of a whole new class of specialty drug distributors. Fast forward to today and the challenges are equivalent, if not more daunting, because with gene therapy we are talking about a disruption in how we approach disease. We are transitioning from treatments that ebb and flow over time to one-time administration of a drug that will prevent or reverse a singular genetic defect – potentially for good. Our business model at Spark Therapeutics is to deliver such therapies to eligible

patients safely and seamlessly, through a one-time clinical intervention accompanied by follow-up care appropriate to each patient. Given that Luxturna is the first US gene therapy product approved for an inherited disease, we take this mission very seriously, as evidenced by the years we spent perfecting our manufacturing, supply chain and market access capabilities prior to receiving final FDA go-ahead last December. We tackled basic questions like how do you manufacture in a scalable, repeatable way a very complex product, unique in its physical properties, placing genetic material into an inactivated viral vector consistently, without degradation of that material, to produce the dramatic improvement in vision established through data from randomized controlled trials? To us, delivering a gene therapy is not a trivial pursuit. It represents a reversal from the old days of the chronic care small molecule drug, where manufacturing was an adjunct activity that could often be handled by others. In gene therapy, manufacturing is a strategic core competence; an innovative activity in its own right; and a differentiator against the competition, posing a challenge to those who lack the commitment to invest and persevere. Success in this area is going to depend on mastering the fundamentals around manufacturing and capacity controls.

The Learning Curve

It took a number of years for monoclonal antibodies to emerge as an accepted delivery platform for patients in the clinical setting. Can we expect the same gradual build-up for gene therapy? Are you predicting a competitive hierarchy characterized by companies who have the requisite skills and capabilities in gene therapy, and those who do not?

I expect ramping up manufacturing and supply chain activities in gene therapy will be quicker than it was for monoclonal antibodies. That is because many of the people now working in this space began their careers studying how to optimize the monoclonal platform. There is a history there and an awareness that to prevail in these complex therapy areas you need an early start. Industry groups have coalesced around a common agenda to address capacity and access issues. Gene therapy also benefits from an early proactive stance from the FDA, which has prepared written guidance clarifying what "good" looks like in getting these new medicines into the hands of providers and patients. Finally, we have seen an influx of investment by CDMO firms to tackle the manufacturing and supply chain challenges to gene therapy than was the case when the monoclonal antibodies came on stream. Then, companies seeking to commercialize the science around these advanced biologics had to manage the transition alone rather than in partnership. The investment being made by CDMOs adds capacity and expertise to the in-house efforts of gene therapy companies. This allows companies to de-risk their expensive gene-based drug programs by providing incremental resources from outside.

Are you confident you have a handle on the capacity problems that may emerge as the demand grows for new cell and gene therapies?

I reiterate my comment that the industry is aware of the experience we had with the introduction of monoclonal antibodies. We are prepared with the knowledge that there will be cycles of over- and under-capacity in the vectors and other raw materials used to make gene-based drugs. We now have procedures and planning in place to make sure we are one step ahead of them.

Do you still see a separation emerging between companies with real know-how in gene therapy and the "wannabes" who are seeking a way in to the field?

Gene therapy has been compared to a multi-functional team sport, where careful coordination is necessary to build unique capabilities across a wide spectrum of activities, from pre-clinical discovery to vector choice and design, then on to process development and manufacturing and ultimately to commercialization. Bench-strength in managing these functions could probably fill in the back-end of the gene therapy pipeline, but not so much on the front end, where properties have characteristics that are unique and not easily replicable. And one of the biggest lingering problems in gene therapy is the shrinking labor pool – the human capital deficit. It stands to reason that companies retaining the best talent will have a competitive advantage against those who do not.

Regulatory Ramp Up

As a veteran of the Luxturna registration process, what can you add about the FDA's role in gene therapy? Are there areas where a higher profile is needed? FDA support is essential now that it is reported that manufacturing fulfillment standards comprise more than half the contents of a gene therapy drug's registration package.

Spark Therapeutics did have the experience of interacting with the FDA due to our status as the first directly administered gene therapy approved in the US. It was a strong collaboration, especially with regard to our CMC portion of the filing. Their advice proved crucial to bringing Luxturna successfully past the post. We continue to see useful guidance coming out of the agency and I expect that as the number of products submitted for approval grows, some elements of the process will get tougher. Certainly, one of these will be the ability to show comparability of product from that supplied during the clinical trial to full-scale capacity intended for the actual clinical setting. Expect more detailed guidance from the FDA on that. The FDA and other regulators will also need to invest in recruiting more talent with expertise in evaluating a whole new range of engineering and technical issues. One big lesson we drew from Luxturna is that "core competency" in gene therapy involves much more than just manufacturing expertise. Good analytics are almost equally critical to obtaining marketing approval. That is because many of the methodologies and assays needed to evidence the robustness and consistency of the manufacturing process are unique to gene therapy. The conclusion? Companies destined to be successful in gene therapy will not only have the requisite capabilities in manufacturing scale and yields, but also in building out a verifiable, analytical dashboard able to demonstrate to regulators – and ultimately to patients – that

the process of manufacture is safe and predictable in preparing the product for clinical use.

COO: Spark's Sweet Spot

You hold the title of Chief Operating Officer (COO) at Spark. Many biopharma companies no longer include this position as part of the c-suite leadership team, preferring instead to include relevant functions in the portfolio of today's endlessly accountable CEO. How do you define the role of COO and what are your principal duties as a member of the Spark leadership team?

If you went out and asked 10 people on the street what a COO does, you'd likely get 10 different answers. That's understandable because as I look at my peers in different organizations, from the smallest to the biggest biopharma players, I find their list of responsibilities and spans of control are different too. Organizational needs offer the readiest clue to the priorities of a COO. Gene therapy is defined by a complex relationship with diverse parts of the organization. In my case, Jeff Marrazzo, our CEO, required a colleague who had the broad exposure necessary to interact productively with commercial, IT and other activities outside the clinical development space. It was natural we would want to aggregate these responsibilities to achieve the goal of transforming Spark Therapeutics from an emerging R&D organization into a fully integrated commercial enterprise with products to market and sell. I possessed the background and qualifications to bridge this gap, with experience leading multi-functional teams for large multinational drug companies combined with mastery of technical and process issues involving manufacturing and the supply chain. In sum, my capabilities happened to be what Spark needed as it prepared to launch its first product. If an organization finds that its vertical functional structures are strong and can stand alone without the need for more integration, then maybe the COO role will no longer be relevant. It all depends on the needs of an organization as it evolves to meet successive rounds of challenges.

> *"One big lesson we drew from Luxterna is that "core competency" in gene therapy involves much more than just manufacturing expertise. Good analytics are almost equally critical to obtaining marketing approval."*

You have line management exposure at three major multinational drug makers – Pfizer, Baxter International, and Baxalta. What's your assessment of the Spark culture so far?

Spark is a young company with a singular mission: to challenge the inevitability of genetic disease by discovering, developing and delivering treatments in ways unimaginable until now. We've made a strong start with the launch of Luxturna in ophthalmology and we are moving forward with another ophthalmologic gene therapy candidate, this one for choroideremia, which is also a progressive inherited retinal disorder. In addition, we have two gene therapy drugs in testing stage for inherited hemophilia A and B; in the latter case, our candidate is progressing in partnership with Pfizer, which has commercialization rights to the product after launch. There is also some promising work we are initiating to find a genetic treatment for Pompe disease, a metabolic condition that damages muscle and nerve cells. This intense focus on what are presently incurable conditions imbues the Spark culture with an awareness that, should we succeed, the consequences for patients – and society – will be phenomenal. Blindness, for example, has a huge impact on economic productivity in that the vast majority of people with vision problems are unemployed. No one here doubts that this company has been built on the foundations of great science, as evidenced by us being the first to receive approval for a gene-directed therapy in the US. The fact alone is a great recruiting tool for talent.

Spark also has deep roots in academia. How does that shape the company culture?

We do not have to reach out to the laboratory – its right here, represented in our senior leadership. Dr. Kathy High, president and head of R&D, spent her early career studying the genetic roots of hemophilia, which led eventually to her establishing the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia (CHOP). The Center produced significant work on how knowledge of the genetic origins of disease could be applied in the clinical setting, which was a compelling rationale for building a company capable of doing just that. Spark was basically founded as a spin-out from CHOP, going public in 2015 and taking those gene therapy assets from CHOP forward to the commercial space. Today, most of our science and the development strategy behind it derives from the CHOP Center team, many of whom, like Dr. High, now work at Spark. Where I come in is to bolster that excel-

lence in academic science with expertise in the commercial, downstream functions like supply chain, manufacturing, market access and regulatory. Overall, we are up to 350 people today at Spark, all of us dedicated to creating a business active in all stages of the product cycle.

Operation's Three Pillars

Your role as COO incorporates three main areas of activity – commercial affairs, technical operations and technology. Can you highlight what that entails?

Commercial is, at present, the most important part of my portfolio. It covers marketing, including product launch, sales, manufacturing and the supply chain, and market access issues like P&R. I also manage a Luxturna group on diagnostics, which reflects the special approach we take to positioning a gene therapy in the market. This is not traditional "push" or "pull" marketing focused on things like share of voice. Because Luxturna is a "once and you are done" individualized treatment, we want to make the experience for each patient as pleasant and seamless as possible. We have invested heavily in our commercial team, which is organized in a series of national zones, and works jointly with our medical staff to identify and certify those patients with the right gene mutation profile to receive Luxturna; prepare patients, their care givers and providers for the injection procedure; staff and coordinate the medical centers where the administration of the gene therapy takes place; and manage the array of follow-up services required for patients, post injection. Another critical part of the process is helping to secure reimbursement for the procedure, which at the list price of $425,000 for each unit is a significant challenge. Outreach and dialogue with payers and insurers is a big part of what I do right now. We have launched a program called Spark PATH (Pioneering Access to Health Care), where we can contract with an insurer to buy Luxturna directly from us and then provide it as free issue to a hospital. The insurer can then do its own negotiation with the hospital to secure a fee for its covered patients, and by eliminating the middle-men in a standard transaction, this is usually advantageous for them.

Technical operations is another critical focus of my work. It entails oversight of the complex logistics in getting the product to the patient: vector and materials supply; manufacturing; the supply chain; quality control and assurance; and process development. I started on a solid foundation, as the team that came to us from CHOP already had its own vector lab along with relevant technical expertise in process development. That grounded expertise helped steer Luxturna to success. Since then, we have gone through inspections by both the FDA and the European Medicines Evaluation Agency (EMEA) satisfactorily. And we have been vetted by the contract manufacturing deals Spark negotiated with two of the largest pharma multinationals, Novartis and Pfizer. It is also important to note some aspects of technical operations sit with the R&D division under the mantle of Spark's president, Dr. High. Her group is responsible for selecting vectors and other materials used in manufacturing as well as all aspects of staging early preclinical work. Our job is really to take the constructs, scale them up and bring them through manufacture.

Technology is the third part of your COO remit.

This charge encompasses IT and keeping our infrastructure up to date. We have introduced a multi-year plan to invest in IT systems to keep pace with the growth of the company.

Mastery Of Manufacturing

What are the unique characteristics of a gene therapy that must be incorporated in your manufacturing template?

There is a need to move from an adherent cell line production platform of limited lot size to a sterile suspension process with larger, customized capabilities. Manufacturing these next-generation gene treatments requires much bigger production cohorts and increased amounts of viral vectors. Coming out of the CHOP laboratories, we relied on the roller bottle process to generate clinical material for the launch of Luxturna and we are still doing that today. But as we take our science to the next level, with possible cures for rare metabolic conditions like Pompe, it is necessary to convert all our manufacturing to a fully scaled-up and sequenced suspension platform. We have a new partnership with the CDMO **Brammer Bio** to help build capacity through this more robust suspension platform.

What about costs related to manufacturing gene therapies? Is reducing these costs an imperative to realize the potential of these therapies?

We are not yet at the point where efficiencies are pivotal to delivering on the promise of gene therapy. It is too soon to realize the kind of logistics and manufacturing cost reductions achieved over the course of 30 years in the monoclonal antibody solid dosage space. Certainly, we want to do this work at the lowest cost compatible with quality and safety standards, given the positive impact this could have on future profit margins. But for the short-term, a commitment to securing adequate supplies and getting to scale with yields that work, must be a priority, along with the analytical methods that validate our manufacturing is consistently safe and robust. I do look forward to the time when cost savings will move to the top of the "to do" list, as it will show we are well past the development phase of gene therapy in medicine.

Lessons From Luxturna's Launch

It's been nearly nine months since the formal launch of Luxturna in the US. What have you learnt from the rollout?

We were prescient in deciding to focus on identifying those patients whose genetic profile matched the RPE65 gene defect targeted by Luxturna. This required early, exhaustive cultivation and outreach to the ophthalmology practice community, which prior to Luxturna had nothing to recommend to patients with the defective gene beyond palliative care to ease the transition to low vision or blindness. It was up to us to convince ophthalmologists that a new frontier in science was at hand. We discovered amid the general pessimism some real pockets of neglect, especially older victims of the retinal defect. Their disease tended to

progress more slowly than in younger patients. Spark's response was to introduce, immediately at post-launch, a simple physician-administered diagnostic test to help ophthalmologists identify the genetic condition in their patients and initiate clinical management as necessary. It is physician education that made the difference in turning a niche product into a full-fledged launch success. But we also focused on the patient, with an extensive services network providing appropriate financial and emotional support not only to the individual but to family and caregivers as well. We helped privately insured patients and their families with travel costs to our designated treatment centers. We reimbursed co-pay costs required under various commercial health insurance plans. And that commitment extends to the second eye injection as well as the first. Overall, we become part of the patient's journey to restored vision. This includes a safety registry we operate as part of a pharmacovigilance agreement on Luxturna with the FDA.

Did you follow a stakeholder engagement strategy to build support for the Luxturna brand's value proposition?

We followed a deliberately inclusive approach to stakeholders. We decided one of our early dialogue targets would be the Institute for Clinical and Economic Research (ICER) in Boston. Spark initiated the conversation with them on grounds that ICER is known for its methodological rigor and commitment to transparency. Throughout this process, our goal was to raise understanding of the indirect impacts of a gene therapy like Luxturna, which, as a truly novel innovation, marked the beginning of a new era in health care. We have also initiated a productive exchange with Express Scripts, where we received considerable support for the economic arguments we put forward to justify our $425,000 per eye price point. We anticipate Spark's overall PATH approach could be the model for our access offerings in the hemophilia category, in the future.

Genes: Spark's Sure Bet In Biotech

Can you highlight the next phase in Spark's growth plan?

Next in line after Luxturna is our product (SPK-7001) for choroideremia, another inherited genetic disease. It is in Phase I/II. Our investigational therapy (SPK-9001, fidanacogene elaparvovec) for hemophilia B, which comes from our labs, is now being transferred over to our partner, Pfizer, which will manage the Phase III trial about to commence, as well as all future commercialization activities. Another investigational gene therapy (SPK-8011), for hemophilia A, is also in Phase I/II. We believe an early read out from the data last month has been sufficient to enable us to begin planning for a Phase III study for SPK-8011. Spark retains full ownership of this asset and our intent is to take it to market without a partner. Finally, we are pursuing several preclinical targets, the most important of which is a potentially ground-breaking investigational gene therapy (SPK-GAA) for Pompe disease. We hope to have some preclinical data soon to support application for an IND later in 2019. Finally, we are excited about the partnership with Novartis, which has assumed responsibility for regulatory and commercial for the Luxturna franchise outside the US. Under this arrangement, Spark and my team will manufacture and supply product to them directly. The Novartis deal represents a strong combination for us, given the larger company's commitment to building the gene therapy segment worldwide.

Does Spark have a position on acquisition?

We have no position, except to emphasize our focus is to make the company a fully-integrated enterprise geared to helping patients, with revolutionary advances in medicine. We think we can do that. And if we do it right, we will generate value for our shareholders too.

Can you hazard a guess on what to expect from the science of gene therapy over the next five to 10 years?

We will witness many new solutions to unmet medical needs. But what gene therapy will also do is advance the standard of care for conditions that currently have some treatments, such as hemophilia and liposomal storage disorders like Pompe disease. Given the number of new gene-based products in late-stage development, it can be expected that in 10 years the sector will have matured, not just from a clinical and commercialization perspective but on the technical and process side as well. We will solve the manufacturing and capacity issues that bedevil us today, getting bigger payloads into viral vectors that we can replenish as needed, in line with demand. Perhaps most important, the current view that gene therapy is a huge cost burden that society cannot afford will give way to a more balanced perspective. If you look at the emerging pipeline for gene therapies, many will be replacements for chronic care treatments that need to be taken for years, even decades. One-time cures from gene therapy will likely introduce significant cost offsets that complement the drive for value and efficiency in the health care system. Single-minded criticism will give way to a more nuanced policy approach to costs, as this new field begins to prove its potential in the clinic.

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Drug Delivery Outsourcing In A World Of Pharma's Shifting Sands

The contract drug delivery industry is facing disruptive influences from an evolving client base, the increase in biologics manufacturing, and specialty pharma needs. *In Vivo* speaks to Catalent's vice president of strategy, Cornell Stamoran, about the evolution of the industry and the continuous search for efficiency.

BY JOANNE SHORTHOUSE

The definition of drug delivery has changed over the last decade to be more inclusive of drug delivery devices, because of the increasing prevalence of biologics.

The fact that most biologics are not able to be delivered orally is challenging to those drug delivery contractors working in the oral space with small molecules. While biologics projects have been growing by 11% to account for about 40% of the pipeline, small-molecule projects have been growing at a slower rate of 6%.

So what? It is the formulation stage of drug delivery that has the biggest potential for improvement and enhancement, says Catalent's vice president of strategy, Cornell Stamoran. In an exclusive interview, he discusses the changing environment for drug delivery service providers.

The contract drug delivery market has evolved in line with several different factors: financing, client base, and product innovation. Once a vibrant sub-set of the outsourced offerings to the biopharmaceutical industry, three public companies dominated the space: **RP Scherer Corp., Elan Corp. PLC** and **Alza Corp.**

However, as the sector evolved, divergent strategies of the three largest companies changed the face of the contract drug delivery ecosystem, and by 2001 it was unrecognizable from the industry it had been just five years previously. Elan became a speciality pharmaceutical company when it bought **Athena Neurosciences Inc.** in 1995, RP Scherer was acquired by **Cardinal Health Inc.** in 1999, and Alza was bought by **Johnson & Johnson** in 2001, consequently becoming much less visible, externally.

As the millennium came and went, fewer companies were indulging in pure-play technology or platform technology, and more were progressing a lead candidate product toward the clinic or trying to get it partnered out. The investing community switched focus to product companies and away from platform technology-only companies. With a fundamental shift in the formation of the sector, and a corresponding shift from investors to product-focused drug delivery companies, when **Catalent Inc.** (formerly part of Cardinal Health) floated on the New York Stock Exchange in 2014 it had to do a lot of groundwork. "We needed to basically rebuild some investor understanding as to the role of advanced drug delivery technology in the marketplace," says Cornell Stamoran, Catalent's vice president of strategy. "Even though the technologies were still around, the visibility of the sector had fundamentally changed."

Catalent's journey over the past 25 years has been one that has differed from many of its competitors. While many companies in the clinical research space have been pub-

lic companies, and as such more visible to investors and the public, the largest drug delivery providers have mostly been divisions of larger companies. Catalent benefitted from Cardinal Health's prior efforts to bring together a broad range of proprietary technologies and dose-form development and manufacturing to broaden its capabilities in the drug development field, and is the first example of a roll-up in the drug delivery space.

It was part of the Cardinal Health business from 1999 to 2007, when it was divested from the firm and emerged as a private, independent company under The Blackstone Group. During the eight-year period of Cardinal Health ownership, it brought in the legacy company RP Scherer, an 80-year-old, oral drug delivery business that still forms the core of several of Catalent's business units today. It also acquired Automatic Liquid Packaging Inc., a blow-fill-seal technology company; SP Pharmaceuticals LLC, which worked in sterile fill/finish manufacturing and lyophilization for injectables; and International Processing Corp., to add oral solid coating and dose manufacturing to its burgeoning stable of expertise. (SP has since been divested.) In 2002, it entered the fee-for-service analytical chemistry market by acquiring Magellan Labs, a company focused on analytical science services for US pharma, and up to 2006 Cardinal continued to acquire more businesses, facilities and technologies in oral manufacturing and packaging, before deciding to refocus on downstream distribution activities.

Catalent has been involved with nearly half of all new drug approvals over the last decade, and produces approximately one in every 20 doses of prescription and consumer health products taken globally. Although the company might have been one of the first to aggregate proprietary and complex technologies, it certainly was not the last. **Patheon,** (acquired by ThermoFisher), for example, and Capsugel (spun out from **Pfizer Inc.**, now at **Lonza Group Ltd.**), provide dose activities and manufacturing.

There is not necessarily one type of company that is a drug delivery company today, explains Stamoran. Currently, the center of gravity and aggregation of businesses is falling into the contract development manufacturing organization (CDMO) sector. But even there, there is a bifurcation of companies, a difference between contract manufacturers and contract development in manufacturing organizations. "There's been a sub-sector emergence. About 90% of the new drug approvals, especially the new molecular entities, have been coming from about 10% of the CDMO-type companies, and those also tend to be the ones with more proprietary technologies, more know-how and complex development. Those that are at the core of drug delivery tend to have both development and long-term manufacturing involved," he says.

> *"The evolution of the market and the pipeline has increased the demand for people who know how to solve challenging, oral formulation problems for bio-availability."*
>
> *– Cornell Stamoran*
> *VP of Strategy*
> *Catalent*

Increase In Biologics

Whereas the industry has shifted in terms of company strategy and focus, what is defined as drug delivery has changed also to be more inclusive of drug delivery devices, because of the increasing prevalence of biologics. Around 40% of the pipeline is large molecule, according to Pharma Intelligence's *Pharmaprojects* database. "Drug delivery has broadened to include more focus on the devices involved, when devices are necessary for delivery, as well as the more traditional dose-form, formulation improvement, outcomes enhancement areas," notes Stamoran.

As any service industry, the drug delivery industry has shifted to meet the needs of a changing client base. Of the active projects in research and development, about two-thirds are coming from small, specialty or virtual companies, rather than large pharma companies, which is very different from 20 years ago. "More of those companies are likely to not have all the requisite formulation skills, especially when you're dealing with increasingly challenging compounds to deliver," Stamoran continues. "The evolution of the market and the pipeline has increased the demand for people who know how to solve challenging, all formulation problems, such as enhancing bio-availability. A higher proportion of the pipeline than ever – perhaps as much as 90% – need those kinds of solutions."

Although this evolving client base provides an opportunity for drug delivery service providers, there is also disruption for some in the market. The fact that most

biologics are not deliverable orally today challenges drug delivery contractors that only focus on oral delivery of small molecules. While biologics projects have been growing by 11% over the last five years to account for for about 40% of the pipeline, small-molecule projects have been growing at a slower rate of 6%. Companies working within the drug delivery space are looking at products such as peptides, vaccines and newer treatment modalities, and the ability to deliver those in less invasive means than infusion or injections. Stamoran describes this as "chipping away" at some parts of the large-molecule universe to adapt traditional technologies to them, often in new or different ways, thus "trying to take something which could potentially be disruptive and instead make it additive."

The shift to specialty products has also, to some of the niche players in the drug delivery and contract manufacturing space, been challenging because of a lack of diversification across products. For example, if 30% of a company's business is coming from one product and one customer, the increasing focus of the industry's eye on speciality products will require myriad new strategies, talent and technology to remain efficient, cost-effective and relevant in the contract services industry.

"We see a lot more volatility for individual products than in the past," affirms Stamoran. Drug launch uptake disappointments, reimbursement decisions, and earlier generic competition all make their mark on the drug delivery industry, especially the smaller players. "The impact of that volatility is felt foremost by our customers, but it also trickles back through the supply chain. Those delivery companies that have more diverse customer and product bases can weather this volatility more easily than some of the smaller companies," he explains.

This is especially important if the drug delivery services provider is looking for external investment, as many smaller contract manufacturing companies have done in the past two to three years. "Timing is everything because if you try to market your company when your lead compound is under patent challenge and that lead compound might account for a significant portion of your business or your earnings, it's very disruptive," Stamoran says.

> *"Change leadership is important, as we and other companies continue to adjust and anticipate changes in the end market conditions that our customers face."*

The combination of compound-focused specialty companies, the maturation of the external network of service providers, plus very strong venture capital activity means that specialty pharma will be a more sustainable customer for the drug delivery sector in the future, albeit a disruptive one for smaller companies.

The evolution in customer base has also meant a change in partnership agreement. A more diverse customer base that has a mix of smaller and traditional large pharma companies requires a different type of partnership agreement than normal. Whereas a traditional turnkey development agreement would commit a customer to four years of development activity in clinical supply, smaller companies that catalyze development by financing cycle have different commitments, and often can only commit to a phase of development up to their next milestone.

Stamoran concurs that the Catalent approach to partnering has evolved. "At heart, it is following the molecule, and contract-driven. We've certainly improved or evolved our approach to relationship and project management to become more sophisticated over the years as well."

Catalent calls it approach to partnering "follow the molecule," because once a molecule needs some type of intervention to bring it to market, such as an advanced formulation or dose form, or otherwise requires complex manufacturing, it is likely to need that type of solution through most of its commercial life. It could also need the same challenges addressed as a generic product, or as a consumer health product. Stamoran says this allows the company to bring an innovative product to market, while allowing "additional entry points" to provide services for the innovator or others who touch the molecule at various points in its life, including new indications or combinations of that molecule later. "We have many long duration relationships with molecules. With investors we use a case study about a 25-year relationship with a molecule that started out as a prescription product in one advanced dose form, went OTC in that dose form, and then led us to develop a second OTC line extension in a different form to meet certain consumer

preferences. We've got many examples of where following the molecule has really allowed us to provide solutions for long-duration periods of time," he recalls.

As with any industry, individual players have different approaches and this is no different in the contract drug delivery space. "There are slightly different ways to create space in this market," says Stamoran. "I would say there are more commonalities than differences from a partnering standpoint; we still tend to see long-duration relationships that are product-focused. And product-focused relationships that, especially when they are using proprietary technologies, may survive multiple transitions in product ownership from one company to the next. Because the product still needs the technology to reach its potential in the marketplace, that's still driving the relationship either way."

The Search For Efficiency

Traditional drug delivery formulation development is a trial and error approach that has "contributed to the delays in forward momentum on development of individual compounds," according to Stamoran. If those formulations did not sufficiently achieve the targeted biological result needed, gaps were identified and reformulation was required. This type of approach is also evident in different aspects of drug delivery work.

With this background in mind, Catalent's research, through its Applied Drug Delivery Institute, suggests that this trial and error approach contributes to companies settling for products that were suboptimally formulated for patients. The time lines involved to optimize formulation compete against companies' commercial imperatives to get products to market faster, and so they "may opt to proceed with a formulation that is *adequate* to achieve their target formulation profile, but may be suboptimal from a patient utility or usability standpoint," says Stamoran. Catalent, he explains, felt it was important from a process efficiency, right-first-time formulation standpoint, as well as for optimizing outcomes for patients, to develop more predictive tools that can be used at very early stages of development.

It is the formulation stage of drug

THE CREATION OF CATALENT

1999
Catalent is a unit of the Cardinal Health group

R.P Scherer and Automatic Liquid Packaging are acquired by Cardinal

2001
Cardinal adds SP Pharmaceuticals and International Processing Corp. to the business

2002
Magellan Labs is added to the Cardinal portfolio

2007
Cardinal's Pharmaceutical Technologies and Services segment is bought by Blackstone Group and branded Catalent Pharma Solutions

2011
Catalent acquires OptiForm

2012
Catalent buys clinical supply solutions company, Aptuit

2013
Catalent creates a new business unit, Advanced Delivery Technologies

2014
Catalent goes public on NYSE, IPO value reaches $871m

2016
Catalent acquires CDMO firm Pharmatek Laboratories and Canadian business Accucaps

2017
Catalent acquires Indiana-based Cook Pharmica

delivery that has the biggest potential for improvement via predictive tools, he believes, and Catalent has developed a best-in-class, evidence-driven, platform-agnostic approach that combines solid-state chemistry, predictive DMPK tools, high-throughput screening of alternative formulations, and algorithms built on Catalent's 80+ years of drug delivery experience to yield recommended optimal formulation approaches for the compound's specific needs. "Whether we're talking about delayed or controlled release, or bio-availability enhancements, formulation or even molecule variants, we look at which approach is likely to generate the best outcome from a successful formulation standpoint to achieve the target therapeutic profile, but also one that's designed to give the best real-world patient utility," he says.

While dosing and formulation are at the epicenter of the search for efficiency, both for the customer and the outsourcing services provider, regulatory compliance is also fundamental to making the process as smooth as possible for all concerned, with pre-approval inspection readiness essential to bringing products to market on time. The other key consideration is manufacturability. Catalent produces around one in 20 doses taken by patients globally, meaning that manufacturing effectiveness and efficiency is essential. The company has taken a lean six sigma approach to manufacturing; and over the last five years it has invested more than $500 million into its facilities or enhanced and expanded capacity for new processes and equipment that it thinks the market is going to need over the next five to 10 years. In 2018, Catalent produced 73 billion doses, and delivered 98% on time. This is a mark of efficiency, Stamoran asserts, and the company recognizes that at the other end of every shipment is a patient with a drug shortage risk if manufacturing is not correct and continuous.

Next Generation Of Talent

In a changing industrial and scientific environment, the right people "differentiate our ability to execute," says Stamoran, and Catalent has 10,000 of them. But in times when unemployment is at one of its lowest levels in decades, it is a buyer's market and candidates have many options.

Catalent is looking for a certain skill set among its newest recruits, a combination of hard and soft skills. First on its shopping list of attributes in new talent is relevant educational experience, through vocational and apprentice programs and university degrees. Increasingly, universities are focusing on multi-disciplinary degree programs, like biomedical engineering, which may better prepare candidates for today's drug delivery industry. "If you have a better understanding of the relevant biology, you may make different decisions than if you're more focused on the chemistry side," says Stamoran. "Or if you have an appreciation of devices, then you can understand the interaction between devices and drugs better."

Leadership skills are going to be a big differentiator in the future as companies become more complex across the services sector. Catalent is looking for people who can "collaborate across what will likely be more matrix organizations or more networked organizations, networked with customers in different ways and other external partners." The ability to work on, and lead, virtual teams effectively, to collaborate across sites, is also a big win for the potential employee.

"Change leadership is important, as we and other companies continue to adjust and anticipate changes in the end market conditions that our customers face," Stamoran says, with the ability to anticipate that change and therefore anticipate, design for, prepare for and implement the necessary skills to allow the company to remain competitive in a changing global environment.

Stamoran is one of the founders of Catalent's Institute and works closely with universities. He says that the graduate level of candidates is "really impressive." "Many of those are people who want to start their own companies and have great ideas for products or technology platforms. So, there's a huge amount of talent out there. Aligning career expectations and career paths and timing is important for them and for us."

The majority of Catalent's employees are involved in manufacturing, either in operations or quality. Getting people successfully into those jobs is critical and sometimes that means looking for tenured operating people; sometimes it means collaborating with local universities to create vocational programs, or internship programs to make sure the company is attracting enough of the right-skilled talent to continue to meet its high expectations, its on-time delivery, its high regulatory expectations, plus those of its clients.

Long-Term Value

As it stands today, through its various incarnations of the last 25 years, the drug delivery industry has demonstrated how much sustainable, long-term value there is from a drug delivery technology when a company gets it right. "It's a business model that provides important solutions that the market needs, with the potential to generate value flow from its operations over long periods of time. That's certainly been Catalent's experience," says Stamoran.

The drug delivery service provider industry, with an evolving pipeline, an evolving client profile and more challenging compounds on both the small- and large-molecule side is changing shape to fit the needs of the day.

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Bringing The Clinician's Rationale Into The Heart Of Strategic Decision-Making At Boston Scientific

IAN MEREDITH, MD, PhD

Boston Scientific Corporation

Boston Scientific Corp. has been back on the M&A trail in a big way in 2018, with a succession of strategic additions of various sizes that all have potential patient and shareholder impact across – and beyond – its established divisions. Chief medical officer of 18 months Ian Meredith explains the thought processes driving this policy, and the added dimension a CMO can bring to the overall question of strategy.

BY ASHLEY YEO

Boston Scientific has barely been out of the news in 2018, with a sustained program of M&A that continued into the second half of the year with three recent purchases, one of which brings TAVR adjunct technology into the group.

Former MonashHeart chief professor Ian Meredith, MD, PhD, has been global CMO at Boston since January 2017, and has the chance to help shape external portfolio development, as well as in-house trials policy and R&D, as Boston plans strategic moves in health care delivery.

So what? Attaining category leadership, assisted by meaningful innovation, is the aim at the Marlborough, MA, group, which is growing into new areas of device therapy while strengthening existing strongholds.

Boston Scientific Corp. has lit up the health care industry news pages arguably more than any other blue chip global medtech over the past 15 years – hugely acquisitive in 2004-2005, entering neuomodulation, working at the cutting edge of cardiovascular implant technology, stretching and stretching again to bring in Guidant in 2006, watching the share price dip below $5 in mid-2012, making ex-J&J's Mike Mahoney CEO in 2012, watching the share price recover, buying Vessix Vascular and Bard EP, and since spring 2018, bringing seven more innovative companies into the group.

Alongside organic R&D, M&A is clearly very important to Boston's growth, a fact that Ian Meredith, MD, PhD, appreciated long before Mahoney invited him to become EVP and global chief medical officer (CMO), succeeding Keith Dawkins, MD. Meredith shares the patient-centric values that Mahoney espouses, and saw at Boston an important role for himself not only in leading clinical and medical affairs and clinical trial strategy, but also increasingly as someone whose years of experience and insight would be brought to bear in strategic M&A decision-making, for example. And indeed, his input has been used to shape recent M&A activity, he told *In Vivo*.

Taking the job offered was not so straightforward, however, and Meredith needed 12 months to decide after first being approached. He finally agreed to start the role in January 2017. "You certainly do your due diligence!" Mahoney reportedly told Meredith, who identified wholly with the group's values, but had been unsure over whether he could leave practice or report to another boss. "When you've been a leader yourself for

a long time, you need to know the leader you would be under is aligned to your core values and principles."

Meredith already had a 28-year career in interventional cardiology and was accustomed to making his own decisions at Monash University's MonashHeart (Melbourne, Australia), a major regional cardiovascular service with over 40 cardiologists and cardiac surgeons (*see box*,**"***Leading Trials And Getting On Boston's Radar"*). Over time, he had risen to professor director, having come to MonashHeart from Brigham and Women's Hospital (US) in 1994. But even back then, Meredith had been ready to expand horizons, and he took an interest in the academic side of medicine and early device development, earned a PhD from the Baker Institute (Melbourne, Australia) and became deeply interested in the autonomic regulation of the heart.

His decision to move to Boston finally made, Meredith confides that it has been a fantastic transition, that Mahoney is approachable and that nothing is off the table for discussion. "It's given me the opportunity to amplify what I did in practice through training, education, doing first-in-human trials, and assisting in product development and iteration. And you can do that more in this role that you can from a hospital setting." What's more, he relishes the opportunity now to extend beyond the cardiovascular space into the other divisional activities at Boston. His are transferable skills. "The principles are the same in terms of the thinking and the product design around patient centricity, usability and solving meaningful problems in a fair and accessible way," Meredith points out.

Boston Comes Onto The Radar

Boston Scientific approached Meredith to be involved in early Taxus II trials, for CE marking studies, in 2003, and over the years he has worked on several Taxus and Platinum technologies and has been involved in structural heart devices. He had been managing early-phase DES trials for other strategics and start-ups too, and although his assignments in the period 2003 to 2015 were not all related to Boston Scientific, the Marlborough group often ended up acquiring the technologies utilized in his trials and bringing them to commercial success.

With all his experience, Meredith had reached a point where he knew instinctively what would and wouldn't work in trials. "You get to a stage where you can decide very quickly if something is practical or doable and whether it will translate into real-world practice." According to Meredith, medical technology comes in three forms: the "Why didn't I think of it type," which is so good and so obvious; the "Really good idea," but we need to modify and test it; and the "What were you thinking!" technologies, which no human would be able to use, or would be applicable only to a handful of patients.

Divisional Strengths And Openness To Change

At Boston Scientific, alongside several very strong, established divisions (see section below – "Unique Blend Of Divisions And Activities"), are two emerging focus areas – oncology and digital health – that inform work across the company. Meredith says, "It's inspiring and rewarding for me to be able to contribute to these other fields – and more importantly to come up to speed with the deep technology expertise that these divisions have."

He continues, "I've been able to support some of the other divisional activities, because of the approach to patient centricity and physician capability, and also help in the understanding of how and why things are done and what decision processes are going through the heads of patients and their caregivers." Often Meredith's contributions are around the design of the science and the quality of the clinical trial, and in understanding chronic disease management and the patient-physician aspect of the newer technologies.

And in other divisions, where there are developments, for example, in the pancreatico-biliary space with the CMOS camera technology *SpyGlass* DS visualization platform, Meredith brings extensive experience and insight in visually guided procedures and in understanding the simple manipulations of a device. "Many of the technologies are directly applicable in other spaces," he notes.

Half of his time is spent on cardiovascular/peripheral vascular and 30% on the other divisions. The remaining 20% is allocated to broader corporate functions, related to the global clinical structure: making sure that Boston has the right systems, processes and platforms in place across the globe, and that tasks are consistently conducted, high quality, reproducible, transparent and not duplicated. As CMO, Meredith wants to create a global center of excellence on clinical trial design, development and execution.

The CMO's Value At Big Decision Time

Meredith's science PhD brings to the role of Boston CMO a deep level of basic research, and an understanding of physics and the physiology underpinning medicine. His first-in-man experiences bring another dimension to the clinical cardiologist's role. But he sees in himself an ability to recognize the major challenges, and this has qualified him for a broader role and more senior overview of the business.

"When I came into the organization, I made it very clear that I didn't just want to be the talking head of products. That's not me. I am actually interested in contributing to every aspect of the product life cycle, from design through to commercialization, and making sure that we have a good value-proposition for the commercialized product." Products must be truly meaningful, not just marketing hyper-babble.

He is adamant that others who are not on the commercial front line should feel similarly empowered. "I've encouraged other physicians in the organization to see themselves as a shoulder-to-shoulder partner in every aspect of the daily life of the medtech industry, including iterations."

As to Meredith, CMO: "I see myself as a strategic collaborator for the organization, asking where we go next and what should Boston look like in 2025 or 2030, bearing in mind what's happening to the world's aging population." He devotes much time to understanding and talking about the burden of non-communicable diseases, especially the top five: cardiovascular disease, metabolic disease, chronic pulmonary disease, cancer, and mental health and cognitive decline.

These conditions will surely increase the burden on homecare and non-hospital-based care, and will elevate in

importance the ability to assess and treat patients remotely in a non-disaggregated way. They are a threat to well-being, and they are definitely coming, but Meredith takes a pragmatic stance, seeing an exciting time for the organization as well as a much more strategic role for himself. "The confluence of digital health and medical technology will change the face of how devices are seen and used." They won't merely be devices, but tools that provide significant biofeedback and closed control loops to manage conditions.

Stepping Up To The Challenges Ahead

Boston's communication channels seem to suit Meredith's modus operandi. He has developed a close working relationship with Boston's CIO, Jodi Euerle Eddy, who is also SVP of information technology, and with Boston Scientific's Digital Health Council, where the dominant theme is how health care will change going forward.

This was already on the Boston agenda, but Meredith's arrival has accelerated the urgency. "We are fortunate that at BSC you can have very radical conversations, as the leader's thinking is not simply constrained by the quarterly business objectives, and there are many broad and lateral thinkers in the organization."

As CMO, his role is to tailor conversations in slightly different ways, and magnify or accelerate ideas. Put another way, he's brought a structured approach to clinical problems, which Boston might solve via M&A,organic R&D or venture opportunities. Above all, the ethos is to be more patient-centric than solely business-focused, to meet health care needs both now and in the future.

"Radical conversations" is a favorite expression of Meredith's. As he says, put intelligent people into roles that require certain outputs but then miss out on the chance to encourage radical, lateral and imaginative thought, and that's equivalent to wasting opportunities. Another passage in the Meredith book of creative solutions would say, "The world is not disrupted by those who follow suit, but by those who actually reject convention and look for alternatives."

A top expression among Boston's leaders generally is "meaningful innovation," which Meredith defines as something that treats real problems in a practical and common-sense way. Innovation has to be available, accessible, reliable, acceptable, fair, safe, efficacious and within reach of everyone. A great idea accessible for a handful of patients has no interest for us whatever, he asserts.

> *"The confluence of digital health and medical technology will change the face of how devices are seen and used.*
>
> *– Ian Meredith Boston Scientific Global CMO"*

Each of Boston Scientific's recent acquisitions or investment enhancements has fit these criteria, and has sometimes appeared to move the group out of its traditional comfort zones. A brief look at the 2018 M&A activity shows monitoring and diagnosis as fields that Boston is looking to engage in more (s*ee Exhibit 1*).

Meredith has played a role in this M&A, as part of the "very broad-thinking, thoughtful, agile team." He says, "I think M&A activity is an incredibly important complement to BSC's growth, and the predominant focus is on opportunities that enable, attain or sustain category leadership positions. We want to be the best at what we do, and if we seek to do right by patients and physicians, we *should* be the best at what we do."

"Category leadership" is a concept that provides more of the framework within which Boston operates and sets its corporate goals. It is less about status, and more about the deep expertise and the comprehensive suite of offerings that the company leverages in each of its seven key disciplines.

Category leadership, Meredith explains, means "We are the choice, and we need to have that status so that physicians recognize Boston as the best and patients and families know they are receiving the greatest benefit from that therapy." To be a category leader requires a range of products and adjuncts to treat conditions.

A lot of Boston's M&A activity of late has been of near-field adjacencies to build out a complex portfolio for a series of conditions and to address unmet clinical needs. In July, for instance, the purchase of **Claret Medical Inc.** brought transcatheter aortic-valve replacement (TAVR) support/adjunct technology into the company. Category leadership, says Boston, is just as – if not more – relevant to patients, physicians and payers as it is to the company itself. It is also helping Boston to grow faster than underlying markets and most peers, claims Meredith.

A Role In Early Diagnosis

Diagnosis is an incredibly important area for Boston, says the CMO. We live in a new world of cancer therapies including emerging immunotherapies, checkpoint inhibitors and conjugated drugs, all of which define a personalized and precise therapeutic approach. And as a device company, Boston can be involved in adjunctive, ablative cancer therapies that might induce or enhance an immunological response. "One big area where we can play a meaningful role in cancer care is in early diagnosis."

But how does it develop technologies that allow it to make the earliest diagnosis of cell atypia or dysplastic changes, or indeed early *in situ* cancers?

Acquiring **EndoChoice Holdings Inc.** was a key step to building a platform of diagnostic capabilities at Boston. The

Exhibit 1.
Boston Scientific's M&A Activity 2018 (January–July)

TARGET	FIELD OF ACTIVITY	CONSIDERATION	DATES	MARKET*
Millipede Inc.	Mitral valve regurgitation device	$90m plus up to $450m on completion/ milestones	January 2018	n/a
EMcision Ltd.	Endoscopy – RF bipolar device	n/a	March 2018	Palliative option for 1 million worldwide pancreatico-biliary cancer patients
nVision Medical Corp.	Women's health diagnostics	$150m up front; up to $125m in milestones	April 2018	$500m–$2bn
NxThera Inc.	Urology – Rezum therapy for BPH patients	n/a	April 2018	n/a
Securus Medical Group Inc.	Electrophysiology – esophageal temperature monitoring	$40m cash and up to $10m in milestones	April 2018	n/a
Cryterion Medical Inc.	Single-shot cryoablation for AF by pulmonary vein isolation	$202m for remaining 65%	July 2018	Trending to $1bn in the coming years
Claret Medical Inc.	Cerebral embolic protection in TAVR patients	$220m cash plus up to $50m in milestones	July 2018	n/a
Veniti Inc.	Venous obstructive disease stent system	$108m for remaining 75% cash plus up to $52m contingent on FDA approval of the VICI stent system	August 2018	Over 1.1 million affected people in US and western Europe

*Boston Scientific estimates
SOURCE: Boston Scientific

$210 million transaction was finalized around the same time Meredith was announced as CMO designate, in September 2016. The company, with sales of $75 million (2015–16) develops solutions for gastrointestinal conditions, and has a portfolio of resection and retrieval devices, needles, graspers and infection control kits. It has strong positions in pathology services and imaging technologies, including the *Full Spectrum Endoscopy* (FUSE) colonoscope, which enables doctors to better see anatomy and find more lesions during colonoscopies.

nVision Medical Corp., acquired in April 2018, may lead to new diagnostic options for ovarian cancer. Meredith calls it "one of the most profound and interesting acquisitions that the company has made." He explains that it's only in recent years that studies have shown that much of ovarian cancer is derived from cells in the epithelial lining of the fallopian tube, from where it migrates. Accordingly, a technology has been developed to aspirate cells from the distal fallopian tube to be able to recognize *in situ* cancer.

There are no recommended early screening tests for this and, to date, there has been no effective minimally invasive way to biopsy or harvest epithelial cells in the distal fallopian tubes. As a result, women at higher risk for ovarian cancer often elect to have preventative removal of their ovaries and fallopian tubes to reduce the risk for developing the disease. "The idea of determining if a BRCA-positive woman, for example, is at risk for developing ovarian cancer by a very simple extension of a hysteroscopy is a very meaningful step forward," says Meredith.

"There is a role for Boston to play in these impactful, thoughtful, early-phase diagnostics that can lead to a change in how cancer or suspected cancer is managed in the early phase," he continues. The group is assessing several other early-phase cancer diagnostics in other fields, all under wraps for now.

Boston plans to look more closely at diagnostics, especially with cancer being one of the four giant non-communicable diseases. For the company, it would be a logical rounding out of a portfolio that already has ablative therapies and delivery catheters. The group has internal R&D underway that is in rudimentary phases, and is surveying externally for opportunities.

It is clear that much is happening in and across the divisions this year (not excluding the late spring *Wall Street Journal* report speculating on Boston and **Stryker Corp.** being in merger talks). But peripheral vascular intervention has yet to move center stage. This will be a very exciting year for peripheral intervention at Boston, with the release of the IMPERIAL results at the 2018 Transcatheter Cardiovascular Therapeutics (TCT) meeting. It will be the first true DES designed specifically for superficial femoral artery (SFA) atherosclerotic obstructive disease. Already with balloons and stents for SFA, Boston is now moving toward specific DES technologies for below-the-knee applications in chronic limb ischaemia. "If we can improve limb salvage, we'd all agree that that is meaningful innovation," says Meredith.

Unique Blend Of Divisions And Activities

Peripheral intervention accounted for 12% of Boston's 2017 group net sales of $9,048 million, $662 million (+7.9%) more

than in 2016 ($8,386 million). It is one of seven core businesses at Boston, along with interventional cardiology (27% of sales), cardiac rhythm management (21%), endoscopy (18%), urology and pelvic health (12%), neuromodulation (7%) and electrophysiology (3%).

These businesses are grouped into three reportable segments: Cardiovascular, Rhythm and Neuro, and MedSurg. MedSurg is benefiting from continued growth in urology/pelvic health. Electrophysiology was among the star revenue performers in the second quarter. Within Rhythm and Neuro, neuromodulation is seeing strong demand for *WaveWriter*, and Cardiovascular will be boosted by future US launches of the *Eluvia* DES, and *Ranger* drug-coated balloon (DCB), *Forbes* comments. It speculates that existing brands, the *Axios* stent, *Resolution* 360 platform and *LithoVue*, the company's single-use digital ureteroscope, are also expected to carry a lot of near-term growth.

Digital – From Transactional To Longitudinal Therapy

Digital health capabilities, bringing greater precision and patient power, is another layer of the offerings at Boston.

Its *HeartLogic* Heart Failure Diagnostic technology, built into ICDs, is a series of sensors that can reliably predict HF decompensation events, and classify patients at high- or low-risk for experiencing a future HF event. This not only allows the avoidance of hospitalization, but also prevents further deterioration of heart function. "This is a good example of a platform demonstrating the confluence of digital and devices – to improve patient care longitudinally," Meredith states. HeartLogic has been a 10-year commitment, "but it is a good exemplar of how we plan to use digital solutions to enable devices to provide much more than transactional care."

"Digital" moves device companies away from being time-based, transactional therapy companies, and toward becoming servicers of longitudinal pathways that run parallel to patients' lives. "The focus for me is always on the longitudinal aspect of care, and I see diagnostics, whether primary or secondary, as allowing us to play at different points in the natural history of a patient's care. We'll be providing devices that support care more longitudinally than transactionally," Meredith predicts.

Meantime, the wider industry and its role are undergoing transformation. Groups are providing targeted services and end-to-end patient solutions for diseases, as opposed to executing and delivering care within a hospital environment. For Boston, this is part of its value proposition, and value-based delivery means partnerships working sustainably. "We view value-based care holistically and see this as a critical element of our future role in the delivery of health care."

Meredith explains, "We have to partner, and share risk on outcomes with our partners." Maybe the concept would be better served if "value-based" was referred to as "impactful" health care, he reflects.

"That is the way forward. We can't just be a transactional company if we want to make a meaningful impact on health care." Boston's ADVANTICS health care is part of that too: a proposition to help organizations do procedures more efficiently, and enhance workflows and best practice.

The All Pervading Non-Communicable Disease Challenge

The challenge of delivering high-quality health care ever more efficiently is a big one, but dealt with in the right way, it is surmountable, in Meredith's view. He observes that the global aging trend means that for the first time in history, there are more people over 65 than under 5. "That highlights that we need to be thinking of age-appropriate focus. And think about what determines life and death in the 21st century: it's the big non-communicable diseases."

He adds, "If we are to make a meaningful contribution over the next 50 years, we must make it addressing those five areas. And Boston will aim for category leadership within the diseases that we target within those groups."

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LEADING TRIALS AND GETTING ON BOSTON'S RADAR

Returning to his native Australia after a period in the US in the early 1990s, Meredith opted to focus on first-in-human trials of new devices rather than be part of mega trials, given the few opportunities to run large, meaningful trials locally – where the vast majority are with the local center as a contributor rather than as the leader.

He managed first-in-human trials with bare-metal stents (BMS), drug-eluting stents (DES) and structural heart devices from atrial septal defect (ASD) closure to patent foramen ovale (PFO) to patent ductus arteriosus (PDA) closure; left atrial appendage occlusion and, ultimately, transcatheter (TC) aortic and mitral valve replacement. Leading these trials helped Meredith become known to the big strategics and also start-ups, which began to see him as someone whose results were quick, efficient, safe and reliable.

In a number of instances, Boston eventually acquired the technologies being trialed. Meredith joined Boston's strategic advisory board in 2005. It was a good fit, as Boston had patient-centricity and quality as core values, and there was alignment on patient safety, efficacy and transparency about the results, in addition to a readiness to iterate and change if a product was not working the way it should in early-phase trials. "What surprised me was the desire to get it right and the attention to detail," Meredith says of Boston's approach.

As of 2007, Meredith had led more first-in-human trials, in structural heart in particular, and Mike Mahoney eventually offered Meredith the chance to succeed Keith Dawkins as global CMO of Boston Scientific on the latter's retirement. Probably a no-brainer for most, but Meredith took time in making the decision, reflecting on a "good life as a clinician and good rapport with patients going back over 20 years."

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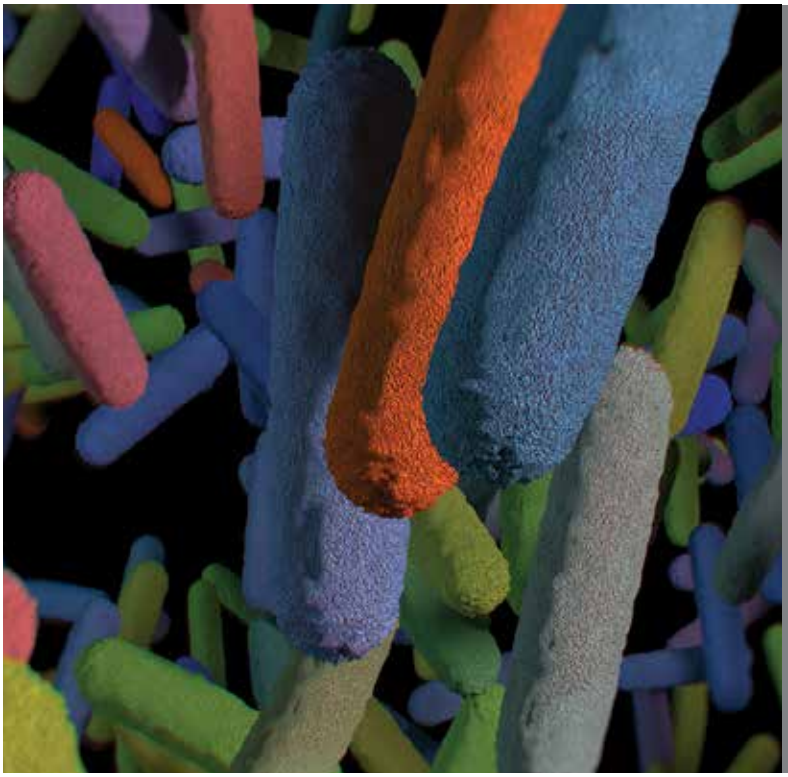
Microbiome Drug Development: An Investigation Into Challenges And Innovative Pipeline Approaches



The discovery and deep investigation of the microbiome has been one of the most cutting-edge advances in biomedical research of recent times, but as the science moves forward new hurdles are emerging for microbiome therapeutics.

BY HANNAH SALLY

Research is now very much focused upon investigating how exactly the microbiome's interactions within the body contribute to health and disease.

As a deeper understanding of these interactions is gained, the floodgates have opened for drug development companies to investigate the potential of microbiome therapeutics for the treatment of disease.

So what? With the microbiome being a new area of research, it brings new challenges. Specifically, development of technology to allow for effective delivery of these new therapeutics to the microbiome is an obstacle R&D teams must face.

Every human being hosts between 10 trillion and 100 trillion symbiotic micro-organisms, including bacteria, viruses and archaea. The collective genomes of these micro-organisms form what is known as the human microbiome. As research reveals more about the microbiome, the pharmaceutical industry can better understand how it may interact with different types of drug in the body, which in turn may affect the way the sector goes about developing drugs in the future.

The Microbiome In Health And Disease

In medicine, microorganisms have traditionally been considered in two categories: pathogens that cause disease; or commensal organisms that reside within the gastrointestinal tract of host individuals with no effect. However, within the last decade, an abundance of research has demonstrated that these organisms do interact with the host's physiological functions in multiple ways which may determine an individual's health or disease state.

The human microbiome is the aggregate of the genomes of all microbes that reside on or within the body. The microbiota population can become imbalanced because of dysbiosis, when there are more 'bad' pathogenic bacteria present than 'good' bacteria. Evidence suggests that the microbiome contributes to an individual's metabolic functions, provides protection against pathogens, interacts with immune system development, and can affect behavior through the gut-brain axis.

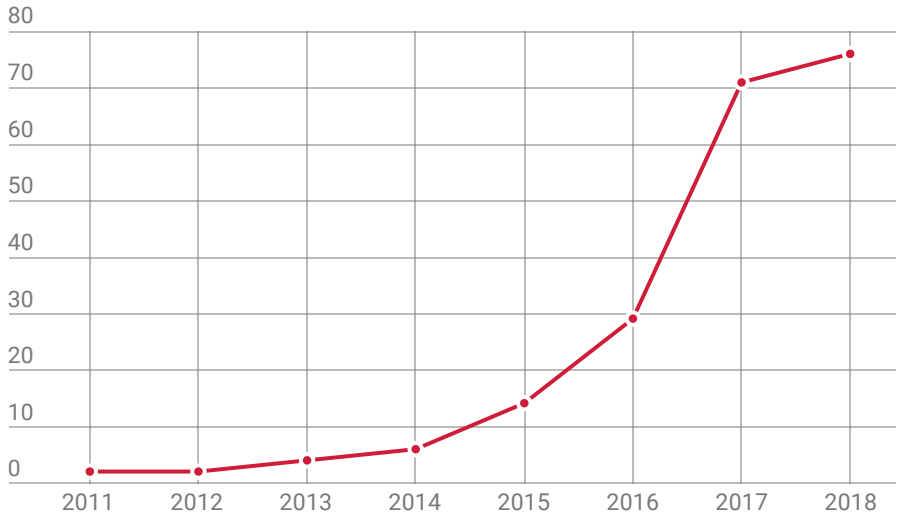
The gut microbiome has been a major focus of microbiome research. As noted in a 2013 paper in *Clinical Chemistry*, beneficial microbiota colonies within the gut help with the break-down of indigestible dietary fibers, and metabolize food to supply essential vitamins, nutrients and amino acids. Gut microbiota influences the way in which calories are extracted and stored from food, and in turn, our diet choices impact on the consortia of microbes that reside in the gut. Thus, the microbiome has the ability to influence metabolic disease states such as obesity and diabetes, as the microbiota consortia in obese and diabetic people differs to those observed in healthy individuals. Gut microbiota also act as an ally to the innate immune system and play an important role in regulating immune response. Dysbiosis of the gut microbiome is associated with autoimmune and inflammatory disorders, such as Crohn's disease and ulcerative colitis (UC), as it can lead to misdirected autoimmune responses. But, microbiome research is not solely focused upon the gut. The authors of a 2012 *Nature* review highlighted that microbiota also inhabits and has an impact upon a vast number of other human tissues, including the skin, oral cavity, esophagus, oropharynx, vagina, uterus, and ovaries. Due to their presence all over the body, imbalances in the microbiota could cause a range of illnesses, offering immense potential for microbiome therapeutics.

Within the area of microbiome therapeutic development, the aim is to leverage the microbiome and its interactivity with an individual's physiological processes to produce a therapeutic effect. Due to the vast amount of targets and physiological mechanisms associated with the microbiome, there are an abundance of drug mechanisms that can be classified as microbiome therapeutics. As summarized in the Mimmee et al. 2016 review in the journal *Advanced Drug Delivery*, microbiome therapeutics can be categorized as additive, subtractive, or modulatory.

Additive therapies are those in which a natural or engineered beneficial bacteria strains are introduced into a diseased individual to promote growth of a healthy bacterial consortia. An example of a natural additive therapy is fecal transplantation, which is the process of introducing fecal matter from a healthy donor into a diseased individual. The aim of this being to introduce healthy gut bacteria consortia to remedy the dysbiosis of the microbiome causing ill health in the recipient. Beneficial microbiota strains are being engineered for transplantation to achieve the same effect, but avoid some of the challenges of fecal transplantation (discussed in depth below). Subtractive therapies aim to eliminate unhealthy microorganisms that play a role in disease pathogenesis. Routinely, antibiotics have been used to rid the body of pathogenic bacteria, but antibiotic resistance is becoming one of the largest threats to global health. Antibiotics are not targeted to bad bacteria and they also kill good bacteria, which results in microbiome dysbiosis. The goal of subtractive microbiome therapies is to be targeted while preserving the microbiome consortia. Modulatory therapy involves administration of non-living agents, such as small molecule drugs or prebiotics, which positively influence changes in the composition of microbiota consortia that make up the microbiome.

Exhibit 1

Number Of Microbiome Modulators In Active Development, By Year, 2011–18



SOURCE: Pharmaprojects, July 2018

The Novel Therapeutic Development Landscape

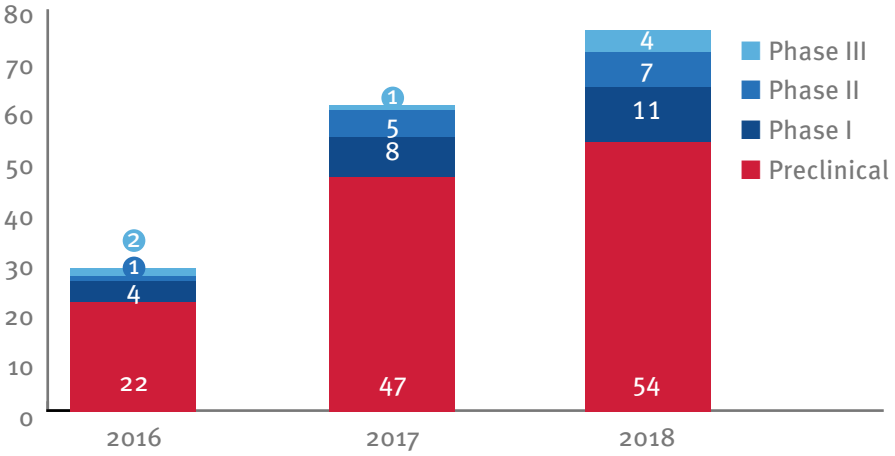
Informa Pharma Intelligence's Pharmaprojects database has tracked trends in drug development each year from 1980 until present. These data reveal a boom in the development of novel microbiome modulator candidates over the past seven years (*see Exhibit 1*). Industrial interest began in 2011, with two microbiome modulators in active development at that time. As of July 2018, the number of these drugs in development stands at 76. The sudden spark in industrial interest is recent, as seen by the 162% increase in the number of microbiome modulators being developed over the past two years.

The development of microbiome therapeutics is primarily at the early stages, with most candidates in preclinical development and fewer reaching clinical trials. The number of preclinical candidates has more than doubled in the past two years. Moreover, the number of candidates in the clinic has also increased, and there are currently more drugs at Phase III status than there ever has been before (*see Exhibit 2*). At this point in time, there are no drugs approved for use as human therapeutics, and therefore, the market is wide open in this space.

A total of forty-eight companies are involved in microbiome research. *Exhibit 3* shows that **Seres Therapeutics Inc.** is the leader in microbiome R&D, with 10 candidates in active development. This landscape is dominated by small to mid-size pharma companies, with only four big pharma companies (**Allergan PLC**,

Exhibit 2

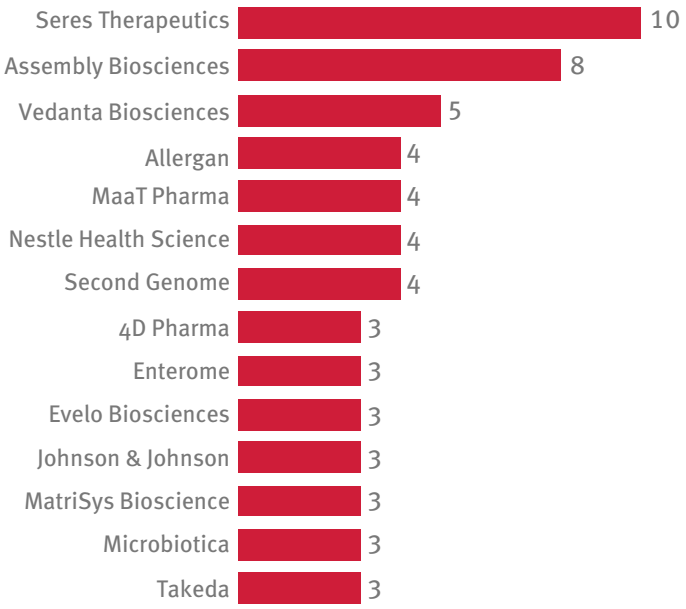
Number Of Microbiome Modulators At Each Development Phase, 2011–2018



SOURCE: Pharmaprojects, July 2018

Exhibit 3

Companies With Multiple* Microbiome Therapeutics In Development



SOURCE: Pharmaprojects, July 2018

Johnson & Johnson, **Takeda Pharmaceutical Co. Ltd.**, and **Bristol-Myers Squibb Co.**) appearing in the top 20 microbiome developers.

Microbiome therapeutics are being investigated in a broad range of therapeutic areas. *Exhibit 4* presents the percentages of drugs in development for diseases for each therapeutic area (TA). Presently, the largest focus area of drug development is for gastrointestinal (GI) disorders. Infectious disease is another big area of development, with a major focus on therapeutics for Clostridium difficile (*C.difficile*) gut infections. Other TAs under development include metabolic disorders, dermatology, oncology, and neurological disorders.

Microbiome therapeutics have great potential in treating an abundance of diseases, and pharmaceutical companies have obviously recognized this, considering the wide range of therapeutic areas in the current development landscape. This is a new area of development, and traditionally, drugs have been developed to target an individual's native physiological systems, rather than the microbial consortium interacting with these systems. As demonstrated in *Exhibit 5*, the clear majority of microbiome therapeutics are being formulated to be delivered orally. This is reflective of the fact that the most common therapeutic areas being investigated are localized to the gut or aim to treat metabolic disorders affected by digestion, such as obesity or diabetes.

It is important to assess the approaches to formulating and designing the delivery technology for additive, subtractive and modulatory microbiome therapeutics to treat disease. Moreover, considering increasing evidence that the microbiome plays a huge role in our metabolism and our health states, we must consider how drugs that interact with the microbiome have physiological side effects and whether bioavailability is affected by microbe metabolism. *In Vivo* has investigated the main challenges in developing orally delivered drugs for GI disorders, and highlighted innovative drugs in the pipeline targeting the microbiome.

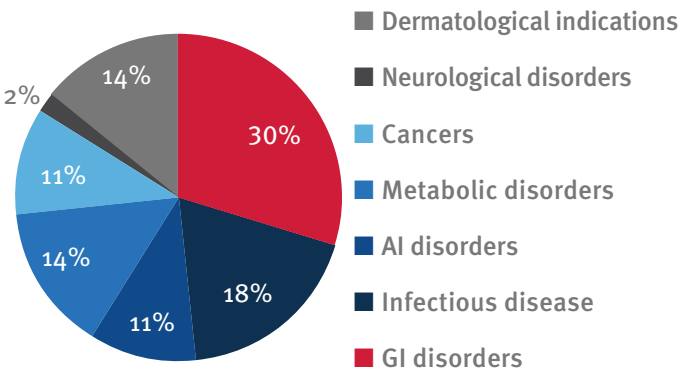
Subtractive Therapies: Eliminating Pathogenic Bacteria While Preserving The Microbiome

The misuse of antibiotics has led to the growth of antibiotic resistance, which is described by the World Health Organization as one of the biggest threats to global health and development today. The standard antibiotics we use today, kill off the beneficial bacteria residing in our bodies as well as the pathogenic target, which leads to dysbiosis of the microbiome. This creates an environment in which pathogenic drug-resistant bacteria can thrive as competition by other bacterial consortia is depleted. Moreover, an abundance of literature suggests that there is an association between the infant exposure to antibiotics and the development of inflammatory bowel disorders (IBD) such as Crohn's disease, due to dysbiosis and subsequent inflammation and autoimmune responses. Therefore, it is vital that preservation of the microbiome is considered when developing new targeted antibiotic drugs for infectious disease.

C. difficile is a common environmental

Exhibit 4

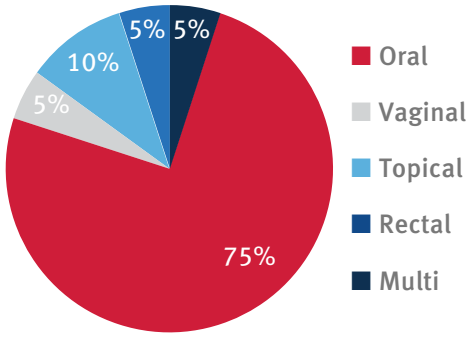
Breakdown Of Microbiome Drugs Being Developed In Each Therapeutic Area (%)



SOURCE: Pharmaprojects, July 2018

Exhibit 5

Proportions Of Investigational Microbiome Drugs By Delivery Route



SOURCE: Pharmaprojects, July 2018

bacterium, which most often resides in the bowel of both children and adults without causing any issues. However, in some cases it can act as an opportunistic pathogen and cause illness, ranging from mild diarrhea to more serious conditions such as pseudomembranous colitis, sepsis, and even death. *C. difficile* infection is commonly seen after broad-spectrum antibiotics have been taken for an unrelated issue, as the antibiotics remove both the protective resident bacteria as well as the pathogen targets, which allows for opportunistic infection and can cause so called antibiotic-associated diarrhea. Ironically, administration of alternative antibiotics is the standard treatment for *C. difficile* infection. But, various reviews available describe how the incidence of *C. difficile* is increasing due to the widespread use of antibiotics, and emergence of antibiotic resistant strains. Development of targeted subtractive therapies is therefore of utmost importance to stop the growth and spread of *C. difficile* superbugs.

Ridinilazole (SMT19969) is a great example of a novel subtractive antibiotic therapy, with targeted delivery to pathogenic bacteria in the gut. It is a narrow-spectrum, non-absorbable iminosugar antibiotic under development for the treatment of *C. difficile* infection by **Summit Pharmaceuticals International Corp.** The exact mechanism of action of this drug is unclear, but a study published in the *Journal of Antimicrobial Chemotherapy* in 2016 demonstrates that when ridinilazole is administered orally, it specifically targets *C. difficile* and significantly hinders the bacteria's ability to produce toxin A and B, which cause symptomatic inflammation of the gut. Preclinical study results show that this drug has minimal impact on the gut microbiome, and Phase I and II clinical studies have demonstrated that it is well tolerated by patients, and superior to vancomycin in reducing recurrent disease. Currently it is in Phase II, but Phase III trials are planned to be initiated within the first quarter of 2019.

Delivering Additive Microbial Therapies To The Microbiome Safely At Effective Doses

As understanding about the protective ability of the microbiome has increased, development efforts have been driven towards identifying ways in which we can change the composition of the microbiome for therapeutic effect. Fecal microbiota transplantation (FMT) is a procedure which involves delivering a solution composed of the feces from a healthy donor into a diseased individual. Due to the nature of this procedure, it can be viewed as very undesirable by patients and there are worries about the transfer of pathogenic or 'bad' bacteria from donors. Complications associated with the delivery of FMT is another concern.

According to Citeline's Trialtrove, as of August 2018, 93 trials investigating FMT treatment for a range of disorders have been completed. Half of these trials investigated the safety and efficacy of its use for the treatment of *C. difficile* infection. Due to the majority of evidence reporting efficacy for *C. difficile*, most experience of using FMT in medical practice is for patients with this indication. Other indications investigated in multiple trials include inflammatory bowel disorders (ulcerative colitis and Crohn's disease) and irritable bowel syndrome. According to limited long-term, follow up-studies, FMT is relatively free of severe side effects, but short term gastrointestinal symptoms have been reported such as; nausea, vomiting, diarrhea, and abdominal cramps. There have also been reports of transfer of norovirus and *E.coli* infection from donor to recipient. FMT must be delivered directly to the GI tract while a patient is sedated, most often through the anus in an endoscopic procedure, or via nasoduodenal tube in some cases. Complications associated with delivery procedures include bowel perforation, bleeding and risk of infection, fecal regurgitation, upper gastrointestinal tract bleeding, peritonitis, and enteritis.

Moreover, as this is relatively new procedure to be used in clinics, there is a lack of knowledge on the potential long-term effects of FMT. Infectious disease transfer, such as HIV, hepatitis A, B and C, and syphilis, is a worry. Furthermore, transfer of bad bacteria which may play a role in contributing to non-communicable disease risk, such as cancers, inflammatory bowel disorders, and metabolic conditions must be seriously considered. Therefore, donors must be thoroughly screened before procedure to ensure safety. The process of identifying donors and screening them for safety is therefore

laborious in the lead up to the procedure.

Although, the use of FMT for *C. difficile* treatment has increasingly been accepted by clinicians and patients as a natural therapy, there are many research groups looking into creating innovative synthetic versions of this additive therapy to avoid the potential risks discussed. For example, Seres Therapeutics are developing 'Ecobiotic' drugs for a range of indications. The company has built a proprietary library of thousands of microbial strains derived from human donors. Their research involves identifying the key microbial strains that are lacking or in abundance in microbiome dysbiosis states, to characterize the microbiota that need to be re-introduced into an unhealthy person in multiple disease states to achieve therapeutic effect. The 'Ecobiotics' are assembled combinations of specially selected key microbiota from their proprietary library that demonstrate beneficial properties. They are purified to improve their safety and eliminate risk of contamination. These drugs are being developed with both the natural biologically sourced microbiota, as well synthetically fermented bacterial species cultured *in vitro*. As they are compacted into a capsule form, they can be easily swallowed by patients, and no invasive procedures are necessary.

Developing Targeted Drugs To Positively Influence Microbiome Composition

While additive and subtractive therapies aim to directly alter the microbiome by introducing or eliminating certain bacteria, modulatory therapy involves indirectly influencing the composition of the microbiome to create an environment that promotes beneficial bacteria growth. Most commonly, probiotics and prebiotics used in conjunction to promote healthy bacteria growth in the gut. Probiotics are mixtures of live bacteria and yeasts with health benefits, which are added into various dairy products and fermented foods (e.g. yoghurt, kefir, kombucha, kimchi, sauerkraut etc.) or taken as supplements. Prebiotics are non-digestible dietary fibers which stimulate the growth and activities of beneficial gut microbiota. The most commonly consumed prebiotics include galacto-oligosaccharides and fructo-oligosaccharides, which are present in a variety of foods, including asparagus, leeks and onions. Many people struggle to consume enough probiotics and prebiotics through diet alone.

> *"There is plenty of evidence suggesting that the microbiome influences the way in which many marketed drugs already available to patients are metabolized."*

Probiotic and prebiotic supplements are widely available over the counter to help people to increase their uptake, but due to the fact they are rarely tested tested in clinical trials, it is difficult to assess the quality or efficacy of many brands. So, many important factors are not fully understood including; the exact dose of probiotic or prebiotics required to promote a healthy microbiome, how well they target the gut, and the shelf life of these supplements. Therefore, there may be an inadequate concentration of the biologically active substances in traditional probiotics and prebiotic supplements currently available. Moreover, despite a safe history of use, introducing a mix of live probiotics to the body may have negative effects in immuno-compromised or genetically vulnerable people. Every individual has a unique microbiome, which also differs depending on disease state, therefore these supplements may not necessarily be beneficial for everyone. Developing drugs which beneficially alter the microbiome composition, may have multiple advantages over the traditional supplements including; accurate delivery to targets in the gut, precision dosing, improved safety profile, and longer shelf-life. Moreover, there is the potential for them to be tailored for specific diseases.

Ritter Pharmaceuticals Inc.'s RP-G28, is an innovative example of a targeted prebiotic drug which is currently in Phase III clinical development for lactose intolerance. It is a novel galacto-oligosaccharide, formulated in a gel capsule, and it works to stimulate colonic bacterial adaptation which alters the population of anaerobic and microaerophilic bacteria. This increases intraluminal beta-galactosidase activity, which enhances digestion and reduces the production of fermentation product which has been demonstrated to significantly improve lactose digestion in lactose intolerant patients. Clinical trials have demonstrated that this drug improved overall tolerance to dairy products and reduced abdominal pain in patients.

Another interesting example is Xeno Biosciences' XEN-101, which is not technically a prebiotic, but works to create a beneficial environment to promote a healthy microbiome. It is an orally delivered small molecule microbiome modulator specifically targeted to treat obesity by delivering oxygen to the lower GI tract, to mimic the beneficial microbiome composition change observed when a patient undergoes gastric bypass surgery. Anatomical changes caused by gastric bypass allows more swallowed air to pass to the gut, which leads to increased growth of aerobic bacteria which help with metabolism of food and increased weight loss in obese patients. This pill aims to create this environment in the gut, without need for surgery.

Considering The Impact Of Microbial Metabolism On Pharmacokinetics

It is vital that the microbiome is considered when developing orally delivered drugs, not just because it is an important target for cutting-edge drug development, but also because research suggests that it may influence the way our body metabolizes drugs. When developing drugs and delivery systems for them it is important to consider how the drug will be metabolized in the body, to ensure that a safe and effective dose is absorbed into the blood stream. There is plenty of evidence suggesting that metabolism of marketed drugs already available to patients is influenced by the microbiome. A review published in 2016 in the *Yale Journal of Biology and Medicine*, provides multiple examples of where the microbiome influences the activation or inactivation, toxicity, bioavailability and uptake of drugs which have been widely used for many years including the following:

- Lovastatin is directly activated in the gut by the microbiota
- Uptake and bioavailability of simvastatin is influenced by the microbiota or by co-administration with probiotics
- Microbial beta-glucuronidase activity in the gut elevates the toxicity of irinocetan
- Paracetamol detoxification in the liver is inhibited by the gut microbial metabolite p-Cresol
- Digoxin is inactivated in the gut by the enzymatic activity of particular strains of Eggerthella lenta which resides in the gut

The above examples provide just a snapshot of the many drugs that are impacted by the microbiota, and with emerging research in this area the more we will understand about the exact mechanisms that allow the microbiota to influence drug pharmacokinetics. The microbiome differs massively from person-to-person, so pharmacokinetics may potentially vary depending on the individual. Modern drugs with improved delivery systems, such as sustained-release or enteric coatings, tend to reside in the gut for longer, so they have prolonged exposure to the gut microbiota. Therefore, in the development of new drugs and delivery systems, an increased focus on the impact of the microbiome during preclinical and early clinical studies may be of great importance to ensure efficacy and tolerability of drugs is improved.

In Summary

As a result of groundbreaking advances in microbiome research, industrial interest in this area has boomed. In the current drug development landscape, most therapies under investigation are orally delivered and targeted to the gut microbiome for treating gastrointestinal disorders. These therapies can generally be categorized as additive, subtractive or modulatory. There are a wide range of challenges in targeting the gut microbiome through each of these approaches and there are many disadvantages to established therapies such as antibiotics, fecal microbiota transplantation, and prebiotic or probiotic supplements. There are many examples of ground-breaking novel drugs that overcome the challenges discussed including; subtractive targeted antibiotics, engineered additive 'Ecobiotics', and modulatory pharmacotherapy. Moreover, it is vitally important that the gut microbiome is considered in the development of new drugs and delivery technologies due to its ability to influence pharmacokinetics.

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Broader Capabilities Keep Consort On Top At Device End Of Drug Delivery

Drug delivery technology specialist Consort Medical has capitalized on device respiratory expertise for 50 years, but a renewed focus on strategic expansion has seen it make an IP play, move into the pharma side and target other delivery formats for global pharma industry customers. Its enhanced capabilities will keep rivals on their toes.

BY ASHLEY YEO

In respiratory drug delivery devices, Consort Medical is a global market leader in valve technologies and is building on decades of experience to remain at the head of the field.

Cautiously acquisitive by nature, the company has entered the pharma CDMO market via the purchase of Aesica. Consort's CEO Jonathan Glenn has convinced shareholders that adding pharma capabilities to its technology expertise is the next logical growth step.

So what? With customers increasingly outsourcing development and manufacturing processes, as well as consolidating supply chains and dealing with fewer, broader partners, expansion into adjacencies makes sense. It is likely to continue at Consort, with nasal and auto-injectable techs already on the agenda, and potential US M&A on the watch list.

Bespak Europe Ltd., the UK-based drug delivery device specialist, changed its name to **Consort Medical PLC** in 2007, and Bespak is now one of two divisions of the group, following the 2014 purchase of Aesica, a contract development and manufacturing organization (CDMO) serving pharmaceutical companies. The move to acquire a pharma CMDO was carefully executed, even though Consort CEO Jonathan Glenn was convinced early on that it was the next stage in ensuring a competitive future in a segment where Bespak has dominated for five decades.

"All our major customers are trying to consolidate their supply chains, so being able to offer a service all the way from APIs, through development, to finished manufacture, together with the device, is pretty compelling offer to our customers," Glenn told *In Vivo* in an interview about Consort's expansion into the drug delivery sector. What the company had in mind played into what was happening in the market. But the management team proceeded with caution, looking at six candidates before settling on **Aesica Pharmaceuticals Ltd.**, a business built on sites formally run by a big pharma.

Four years on, two separate managing directors head twin managements teams at different sites, but integration has been happening: the first combined Bespak/Aesica deal was with Oxular Ltd, in February 2016.

Aesica was the beginnings of building of a drug and device capability business, but it did not happen without due deliberation: the strategic course had been laid down in 2012/2013, and the resulting acquisition was taking Consort into new territory, and this had to be carefully managed and communicated. "We couldn't go out and buy a CDMO that had all the capability we wanted, as we were limited. The £230 million ($304 million) Aesica deal was about as big as the shareholders could live with," Glenn says.

The preparation had been done in good time, Bespak having obtained the necessary drug handling license in 2013 prior to entering the pharma CDMO world. For Glenn, it was a fairly obvious step to look at doing the drug side, given the company's familiarity with similar regulatory environments and standards in devices. "We'd spent 50 years getting others to do the drug part, but then we thought we should look at doing that ourselves." Aesica covers oral delivery, and when a delivery device is needed, Consort can cover most of the field – with transdermal being the exception. It has positions in auto Injectors, assisted prefilled syringes, bolus injections, pressurized Metered Dose Inhalers (pMDI), valves and actuators, dose counting actuators, and intranasal technologies.

New Horizons For An Established Player

Stepping into the pharma world is indicative of the new horizons that Glenn is looking towards for a company that was founded almost 60 years ago as a developer of pumpsfor the cosmetics industry. In 1968, GlaxoSmithKline PLC asked Bespak to put a valve on its inhaled asthma rescue therapy, *Ventolin*, which proved to the beginnings of health care and the end of cosmetics for the company, which operated then, as now, at facilities in King's Lynn (Norfolk, UK).

Bespak/Consort is one of three companies globally to have developed pMDI valves, along with Aptar Pharma and 3M: Aptar and Consort roughly equally share 80% of the market, with Consort holding 35-40%, while 3M's share has declined in recent times. PMDI has driven Bespak's growth over the years, the company's technology is used in over 90 marketed products – all off the back of the original deal with GSK, for whom it still manufactures *Diskus* (with two other companies), and does generic *Advair* for Mylan.

The very high barrier to market entry means that there are just a few – but very high-quality – competitors. "Many have tried and failed to develop valves – there is a small suite of top competitors and a lot of companies below them that can't really do this technically complex job at scale and at the right quality." The other major route is the dry powder inhaler (DPI) – a valve-less device technology that incorporates a blister. Here, Bespak competes against five other key players: West Pharmaceuticals, Nemera, Nypro, Philips-Medisize and Gerresheimer.

The core of the business is a cash machine. "When we're on a product, we're on it for life, and it's a great business to build around." In respiratory, it takes about two years to get a valve to work with a new formulation to the level that's required, says Glenn. Consort also prepares the DMF (device master file) for the customer.

But Consort should think bigger, according to Glenn, who has been the company's CEO for more than 10 years (appointed in December 2007 after serving 15 months as chief financial officer). Asking the management team early in his tenure to define Consort's business, "respiratory" tended to be dominant answer. But to Glenn, Consort was a business that happened to have a dominant position in respiratory. His view of Consort's core skill set was in developing its own devices, and industrializing customers' devices for high-volume manufacture at FDA- or MHRA-standard certified facilities.

Glenn questioned why the company would focus just on respiratory if there is a core skillset to be manipulated for other growth areas. "Respiratory is very important, but in drug delivery, there are lot of other areas we could look at." For instance, the vast majority of biologicals need to be delivered by injection. Glenn observed that a lot are delivered by auto injectors, and that became the next drug delivery device space Consort looked to enter, after respiratory.

So, it made a "small" acquisition, of The Medical House, for £16.5 million in autumn 2009. This UK company specialized in the development and supply of delivery systems for injectable drugs. At the time of the purchase, Glenn said the expanding range of biological drugs should ensure strong sustainable growth for this segment of the market. It was really an intellectual property play, Glenn told *In Vivo*, but the company did bring with it two products for the clinic: the migraine treatment Dr Reddy's sumatriptan, using Bespak's Auto-Safety Injector technology; and UCB's Cimzia AutoClicks prefilled pen (developed by Bespak).

Cambridge R&D

Around the same time, Consort opened an innovation center in Cambridge, UK, costing £4-5 million a year, which had a brief of looking at drug delivery and how to do things differently. It was more or less a blank sheet of paper, and its output has been key for Consort. The R&D challenge with autoinjectors is that they were not developed to deliver viscous biological drugs through very fine-gauge needles with the normal spring mechanism.

The answer from Cambridge was a gas-powered autoinjector (with no spring) that delivers a consistent pocket of gas. It overcame the autoinjectors problems, and has attracted a lot of interest, including, in spring 2017, the first contract with a global biopharma company. But this too was another case of patiently watching the progress. "It addresses an unmet need, but we've been working for some five and half years on it with the customer." The point is that Glenn sees the injectables franchise for Consort as becoming "very material" in time. At some point, it will match Consort's respiratory business, given the market's medium-to long-term growth.

The company already had legacy nasal IP, and nasal delivery is now back in vogue. Consort's technology focuses on single-use, single-shot controlled doses. Nasal projects in Bespak's pipeline include NAS 020, with a global generics company; and NAS 030, an agreement with a pharmaceutical company to develop a nasal device, which is currently at an early stage.

A lot is happening in delivery technology. "We've really spent the past five years broadening the drug delivery capability at Bespak," said Glenn.

Drug Delivery Plus

But it has also diversified in a small way. In 2011, it made a foray into point of care (POC) diagnostics, taking a 16% equity stake in STD diagnostic developer Atlas Genetics. Consort manufactures the cartridge for this POC test. The technology is currently going through the final phases of development and should be on the EU and US markets in the next 12 to 24 months, as a combined chlamydia and gonorrhoea test. Hospital acquired infection diagnosis is next on the list of tests.

Glenn explains that many patients presenting for tests at STD clinics fail to return for the results, which can take five days to come back from external labs. It is a system not without faults: the risk of patients re-infecting during this waiting is obviously high (if they return at all); and the costs of sending out to an external lab are higher than for POC tests done in the clinic. For the latter, patients could wait the 30 minutes or so required to produce the result, and the treatment could start immediately.

The company also addresses "innovation on demand", which is when customers approach Consort to remedy a technology problem, one recent example being the case of a client requesting two drugs to be delivered in one injection device. In these cases, Consort retains the IP and charges the customer appropriate rates.

Bespak was the first real device company to make a move in response to the trends in the industry that is seeing pharma wanting to work more with single customers. "In the CDMO world, our peers would love our device capability; it is seen as a real advantage." Customers coming to Consort for formulation work are now aware that, even if they have a regular device manufacturer, they have the option of using Consort to keep the whole project – both drug and device elements – under one roof.

"In the CDMO world, our peers would love our device capability; it is seen as a real advantage.

– Jonathan Glenn
Consort Medical CEO"

Strategic Aims

The strategy now is to build on the acquisitions and expand the geographic footprint. "US customers are very US-centric, and it's very important for us to have a US manufacturer." Consort also wants to add to its capabilities around injectables, either in-house or by acquisition. "Our focus now is on nasal and auto-injectables, with respiratory accounting for around 80% of revenues and injectables and a small share of nasal accounting for the rest."

At maturity, the injectables franchise should be as large as the respiratory franchise. "A quick look at the biologicals landscape and pipeline, one signed customer contract already and potentially others to come, and that seems realistic," Glenn notes. If a client wants an MDI, the development will be a 12- to 18-month task. "Anything we win will be five to seven years away from being a commercial product," he says; revenues are generated during that period via charges through the clinic, but the real returns come with commercialized products.

GSK remains a very important customer for Consort, which aims to work across big- and medium-sized pharmas. Its long-term partnerships also include Mylan, Johnson & Johnson, Merck KGaA, Boehringer Ingelheim, Teva, Dr Reddy's, Chiesi and UCB. But as seen in the Aesica M&A initiative, Consort is selective and does not take punts in the dark. Moreover, it has no bad debts, and partners pay on time. "It's all about relationships," says Glenn, a phrase which now echoes around the industry.

Global Ambition

Those relationships extend outside the home market. India's Cipla has a 70% share of the local respiratory market and is a very significant customer of Consort's in terms of valves for MDI inhalers. The company also sells valves into China. "We supply to a large pharma at their site, and then they have the product licence for all over the world. For other customer groups, we do the supply globally." Consort sees itself as very international, albeit most of the 2,200 Consort employees are in the UK.

In the majority of cases, the company actively goes after the business, but in respiratory, the business tends to come to Consort. Nevertheless, it has business development staff placed in the developing markets and is selling hard in India, China, and Latin America, for instance. In China, the challenge is in the regulatory environment, with the local regulator continually "moving the goalposts," says Glenn, who adds that pricing, rather than reimbursement, is the main market access issue in China. Consort also sells into Russia and the Middle East. "If someone wants an MDI inhaler, we will sell it," he notes. As to Aesica's business, repeat business is vital, although business development staff are on location. "The device capability has given that business a whole new angle for sales."

Regulatory "Barriers"

Consort is deeply involved in regulatory affairs on pharma and device fronts. Drug

CONSORT TARGETS COMPLETE DRUG DELIVERY SERVICE, BUT RIVALS KEEP HEAT ON

Industry activity in the drug delivery device sector is characterized more by stability than speed. Consort Medical's recent strategic moves have been both deliberate and decisive. For these players, deals with pharma can be several years in the making.The results are worth the wait, however. Even though the nature of the process means that sales cycles can take many years and expansion through new projects can be slow, once established, there is a steady, predictable and defensive revenue stream.

Consort Medical CEO Jonathan Glenn stresses that the drug delivery industry's share of the pharma pie is small, but once a client is on board on a drug delivery project, the mutual relationship can be of long duration – partly due, at times, to the sheer complications and costs of changing horses mid-course.

By bringing Aesica on board, Consrot ensured its sales and product mix was able to set it apart as a top global supplier in the sector. By integrating pharma and device businesses and bringing two parallel processes under one roof, significant improvements can be made to process efficiencies.

Commercially, the addition of Aesica more than doubled Consort Medical's revenues. Bespak, the pre-existing device drug delivery technology activity, now accounts for just 41% of group sales of £311.1 million ($350 million) in 2017-2018. The division's £126.9 million sales last year were up 4.8%, but were not able to match overall growth (5.8%), driven by Aesica's sales performance (£184.2 million).

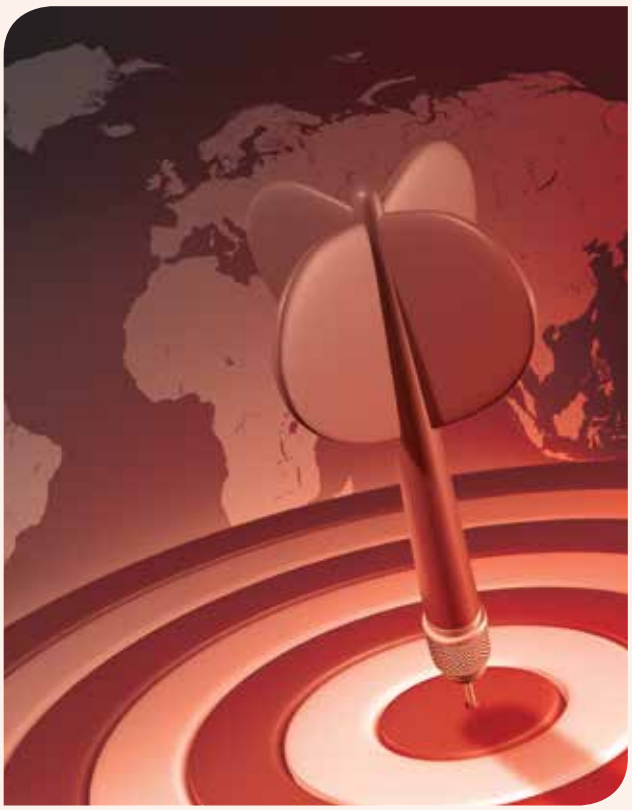
MARKET SIZES

The global market in which inhaled drug delivery devices play is forecast to reach $43 billion in 2024, growing at an estimated CAGR of 3.3% between 2016 and 2024. These products target mainly chronic therapy. To work, they need to be delivered directly into the lungs using inhalers that spray a specific dose deep into the airway.

The main methods for delivering drugs in this way are: Pressurised Metered Dose Inhalers (pMDI), where the drug is delivered in an aerosol form from solution; Dry Powder Inhalers (DPI), where the drugs are delivered as a cloud of small particles/powder; and nebulisers, where medication is converted into a mist that can be inhaled through a mouthpiece or a mask. Soft mist Inhalers are another, but lesser used, option.

Consort Medical is embarking on new projects that have the potential to drive long-term growth. The injectable franchise is one of the fastest growing at Bespak. Projects in development include a recently-signed master development agreement for *Syrina/VapourSoft* technology.

Consort is also developing nasal delivery products, where



its portfolio includes two projects for new devices. But the exact timing for progression of these remains unclear. The company also has work ongoing in the ocular space, via a 2016 agreement with **Oxular Ltd** to develop ophthalmic drug delivery devices.

The injectables franchise is the most advanced of these new activities, as underlined by recent product approvals and roll-outs of: **Dr Reddy**'s sumatriptan (migraine treatment), launched in 2014 that uses Bespak's Auto-Safety Injector technology; and **UCB Group**'s *Cimzia* AutoClicks prefilled pen.

Bespak currently has a small share of the injectables market, but it is estimated that some 40% of all new drugs in development will be delivered parenterally and may, therefore, require some form of auto-injector. The injectable drug delivery market is forecast to reach $625 billion in 2021, growing at an estimated CAGR of 11.5% between 2016 and 2021.

The nasal drug delivery technology market is forecast to reach $64 billion in 2021, growing at an estimated CAGR of 6.5% between 2016 and 2021. The global oral drug delivery market is forecast to reach US$100 billion in 2018, having grown at an estimated CAGR of 9.4% between 2013 and 2018. These forecasts are the estimates of Consort Medical.

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delivery is a two-reg filing, but the two parts sit hand in hand. Consort does the device filing on behalf of the customer. It does not manage clinical trials, rather provides the device or the drug, and lets the customer/CRO manage them. "Regulation is a key barrier to market entry," Glenn reiterates, "but we have a lot of our own IP. The real protection is 'knowhow' and scale."

Much is at stake. "If a company moves its business from us, they know they must reopen the regulatory file. No one relishes that, and it would take a rival two years to take our place." Glenn claims that Consort has a very strong position, and is quite often able to increase prices in a global environment where downward price pressures prevail. "We get cost pressures too, but we can manage the customer on a volume basis." If it's a technology that nobody else has, the company has a lot of leverage on what it can charge for the device.

Changing Times, Different Needs

Consort has made sure to shift with the fast-changing landscape. The move into injectables – where the major growth is happening – and tracking where drug delivery is heading, including into the nasal delivery space, has kept it ahead of the curve. In fiscal 2018, Glenn was able to point to significant progress on Bespak's innovative *Syrina/VapourSoft* auto-injectors, which came out of the Cambridge group, as well as continued growth of the respiratory business.

But keeping competitive has become harder. "When I joined, it was all around quality, and that remains crucially important, but now it's also around reducing stock levels at clients and the constant drive for delivery means we are doing much more for relentless quality. The pressure is on our own customers, and as such we are victims of our own success."

Moving with the landscape also means keeping irons in the M&A fire. Repeating the Aesica success with a candidate in the US, or adding capabilities that it so far lacks, are strategic aims. "We're up for acquisitions, absolutely, but we're pretty cautious," Glen notes. Between The Medical House and Aesica was a period of five years. Nothing happens with undue haste in Consort's world, and with reason: "We have such a good business and don't intend to just jump in – we don't want to ruin a 60-year legacy."

> *"It's a simple model: the better job you do for the customer, the more they give you.*
>
> *– Jonathan Glenn*
> *Consort Medical CEO"*

In fact, Consort can grow "very nicely" without an acquisition, although on May 25, Consort made a bid for Carclo PLC. A deal could create a leading drug-delivery CDMO business with expanded positions in injectables and diagnostics, a manufacturing footprint with a strengthened presence in Europe, and new geographies in Asia and North America. The offer is, at time of print, ongoing.

On the drug side of delivery, Aesica is one of some 630 pharma CDMOs globally. But it is a diverse and consolidating landscape, where quality is not necessarily the common currency. Quality puts a CDMO into the top 10% of the market.

Only one thing comes before quality for Consort, and that is health and safety, says Glenn, "even if it takes profits down." Similarly, "we wouldn't tolerate the non-acceptance of anything below GMP thresholds," he adds, listing the five Consort values: customer focus; results-driven; respect; integrity; and teamwork.

Time And Control – Factors Beyond The Company's Scope Of Influence

Which leaves the challenges. These are mainly technical, in Consort's world: for example, getting the device to work with the drug. "For us now, it would be unusual to come up against a technical show-stopper, but it's still time-consuming, and bumps in the road can add six months to a timeline."

Ironically, for a company that takes such pains to be in control of its business – building selectively and taking a conservative approach to M&A – the biggest concern for Glenn is not being in control of products once they are with the customer. "Everything we make goes to customers that have their own sales and marketing machinery – we can't control what happens then. Or if customers 'fall over' in the clinic: we never get a commercial return on that."

But it is the nature of the industry, says Glenn, pointing to good margins. In fiscal 2018 (year ended April 30), Consort reported a 5.8% increase in group revenue to £311.1 million (+4.4% underlying growth) and EBIT before special items of £42.7 million (+6.8%; and +5.3% at constant exchange rates).

"It's a pretty exciting time; business is upbeat at the moment. The Aesica deal was successful, we see huge opportunities in nasal and injectables franchises, and meanwhile the respiratory franchise keeps steaming along." The business is there to be won, has says. "It's a simple model: the better job you do for the customer, the more they give you."

Consort now has to ensure it is continuing to do the job right. The innovation center and moving into injectables look to be providing continuity. Brexit might be a fly in the ointment, but Consort has mainland European sites in Düsseldorf and Zwickau, Germany; and Turin, Italy. In fact, record volumes were manufactured at these facilities in 2017-2018, with investments being made in new production lines to support growth. Without them, Brexit could have led to lost business, but Consort might have that potential complication covered. Thinking ahead is vital, for all operation and strategic elements, and it is a 24/7 job, says Glenn. But he is ready for the challenges. "It's been a really interesting journey so far."

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Early Thinking Pays Off In Powerful Launch Labels

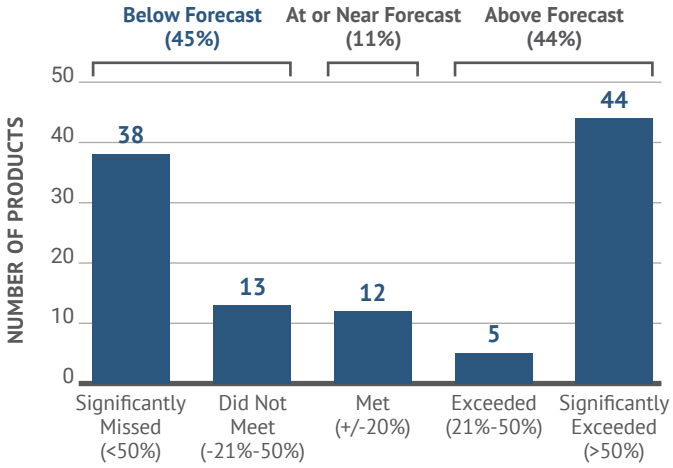
BY WENDY BALTER, KATHRYN BOHANNON, JESSICA LEE AND ROHIT SOOD

The first thing everyone wants to know about a new drug is, "how is it better?" The way the answer is worded in TV commercials, online promotion, and physician sales materials can be worth billions of dollars to a pharma manufacturer. And it all depends on what the FDA or the EMA allows in the label.

Yet, until recently, label language was not only one of the last documents submitted before approval but also among the last things on new-product planning team minds during early clinical trials. However, that is changing. Pharma has woken up to label optimization. Figuring out, in advance of your pivotal trial, what robust and compelling language you need in your label has become one of the most strategic issues in drug development.

For an early example, Eli Lilly's TV commercials for Cialis said outright that the product is "ready when you are" for men with erectile dysfunction. (Competitor Viagra's window of efficacy is just 4 hours). Observers familiar with development of Cialis say that as soon as Phase II studies showed a 17-hour half-life, the team began strategizing how to get competitive language about it into the label. "Improves erectile function compared to placebo up to 36 hours post-dose" became a key part of the Dosage and Administration section, helping propel Cialis to blockbuster sales. And even as the company was launching the product for PRN use, it was conducting studies to get a lower-dose, daily-use version approved, anticipating a whole new market.

Competitive masterstrokes like these happen less often than one might imagine. Many drugs launch with labels practically indistinguishable from those of competitors already on the market. Some spend millions reaching endpoints that lack resonance or urgency with audiences. Recent Syneos Health research shows that nearly two-thirds of all drug launches miss the expectations of their sponsors and industry analysts. A key reason according to the study: lack of meaningful data to build compelling label claims.



N=112 new molecular entity (NME) launch products with a forecast available the year prior to launch. Source: Evaluate Pharma pull of all product launches 2011-2014. Evaluate Pharma Forecast Report February. Launch Excellence at Syneos Health Consulting, 2015.

Blockbuster Label Or Lackluster Label? Pre-Planning Makes The Difference

A set of best practices has emerged starting at Phase II, or even earlier for orphan diseases and oncology drugs. Some call this process label optimization; our proprietary process for it is called Winning Label. Name it what you like, these steps bring strategic discipline and collaboration to the task of optimizing clinical trial design for competition, beyond simply getting to market faster.

Step 1: Convene a multidisciplinary team

A cross-functional team is a must. Commercial stakeholders such as portfolio managers, market analytics experts, brand managers, new product planning teams, and market access strategists keep close watch on market trends. They can share with R&D not only what features prescribers desire, but also language they use to describe these needs, language that ideally enters the label.

Step 2: Define the launch environment

Intelligence-gathering should be future-oriented. In our process, for example, we define the upcoming launch environment: how stakeholder expectations will evolve, new market entrants, generic ization and changes in clinical, access, and reimbursement guidelines. We look at how the FDA and the EMA accept new biomarkers and other efficacy/safety metrics. The goal: to identify label claims that will win this drug a compelling value proposition in the years following its launch half a decade from now.

We scrutinize word and phrase choices within all current competitive labels, section by section, which require analysts to have cross-functional experience within the desired indication and its market. For example, we seek signs that regulators may have reined in claims for lack of sufficient data – potential opportunities for you. Similarly, we look for exceptions both good and bad – clues to what your product is up against and what gaps you may be able to fill. In many ways it is more art than science.

We also review clinical trial designs for pipeline competitors. What outcomes are they measuring? What assumptions are they challenging? A deep understanding of audiences and their unmet needs drives this quest for unexpected, uncontested, or superlative label language that can prevail in current and future markets. As an example, for years marketers of hormonal birth control assumed a period-like monthly discharge was mandatory… until they listened to patients who clamored for freedom from the need for tampons, pads and PMS. An entire new category of "pills" and label claims emerged in Seasonale, Lybrel, and others.

Step 3: Think about the supportive data required

Imagine your drug being advertised to consumers on TV. What language would move them? What would they be indifferent to? Then ask how you will prove it. The road to launch is littered with skeletons of claims that never made it to the label for lack of sufficient evidentiary support.

Some factors we consider are:

- What primary endpoint addresses the desired claim in a clinically meaningful way? Is it a well-established endpoint? Are secondary endpoints such as patient-reported outcomes (PROs) needed to differentiate the product commercially? What is needed to prove controversial claims such as less abuse potential, efficacy in obesity, or improved compliance? Consider factors such as patient preferences for dosing regimen, or tablet size, or particularly unwelcome adverse events that PROs could document.

- What are our pivotal trial design options, especially regarding comparators? Out-performing a weak comparator will not be impressive if the market has already moved away from using it.

- Will use of novel emerging clinical trials designs (such as adaptive and basket trials) cause confusion to physicians and their patients?

- How would we quantify opportunities like the clinical impact of un-addressed administration, storage, and other management hurdles we can solve through form factors, packaging, or kinetics?

- What must be shown to claim an earlier place in a treatment sequence? In combination with other drugs, or as monotherapy?

- In our current environment, where patient convenience or tolerability do not always factor into reimbursement decisions, is there a safety signal that we could turn to potential advantage? Should our trials be designed a priori to compare a specific unwanted event and potentially claim superiority over a competitor, rather than rely on a posteriori comparisons that provide less compelling proof?

- How will the clinical trial patient population affect commercial use? Will inclusion or exclusion criteria expand or limit broader utilization in the elderly and/or children? Conversely, can we "own" an unmet need characterized by an underserved subpopulation of patients – for example, treatment-naive (or on concomitant therapy), or genetically distinct patient groups?

The team must let unmet needs, data and economics drive decisions about what can and cannot be included in the clinical

trial program. We model the potential market value of possible claims, running alternative scenarios. We also examine how claims should roll out over the product's life cycle. Some may be desirable, but not critical for launch – and could be deferred.

We look as well at practicalities. The more outcomes studied, the longer and more costly the clinical development program. Add in regulatory negotiation time if you use new biomarkers, endpoints, or non-standard metrics, and budgets and timelines may get be upended.

Prioritization is the key to finding the right balance and staying on track.

- What will each change in trial design and capture of additional data (e.g., resources, patient recruitment, timeline, reporting) cost?
- What risks accompany each trial design?
- What is each label expansion worth to us in incremental sales?
- How much can we spend?

Clinical colleagues can offer valuable counsel early on, while the team evaluates options and before it issues bid requests. They can suggest less costly approaches, advise on recruitment, and show how to capture data points that might be overlooked. For example, if shorter time to onset of effect is a potential claim, these experts can advise on how costly capturing data more frequently and/or increasing statistical power through large sample sizes would be.

Step 4: Align on the optimal critical path and execute

With answers in hand, the team can develop or revise a Target Product Profile (TPP) informed by market insights, organization strategy, and clinical feasibility. As the FDA puts it, "the ideal version of what the sponsor would like to claim in labeling [emphasis in original] guides the design, conduct, and analysis of clinical trials to maximize the efficiency of the development program."[1] Alignment within the team and top management buy-in to the TPP are essential, as changes beyond this stage can incur large costs and time delays. Yet flexibility is key, too: as important data emerge from trials or market conditions change, the team must re-examine the TPP and, if appropriate, change it accordingly.

Benefits Of Using This Process

A label optimization process such as Winning Label can deliver a strong return on investment for any drug, but it is particularly valuable for products entering rapidly-changing fields like oncology, in areas where real-world evidence is gaining acceptance, and for small/midsize companies with limited experience commercializing new drugs. Does your process include these best practices? The answer could have profound consequences for your product's bottom line.

Reference: [1] U.S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Guidance for Industry and Review Staff: Target Product Profile — A Strategic Development Process Tool. March 2007. *https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080593.pdf. Accessed 8/13/2018.*

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On the Move

Recent executive appointments in the life sciences industry

DANA ANDERSEN

ROY BAYNES

GJEST BREISTEIN

ILDIKO CSIKI

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Tobias Larsson Agervald	A1M Pharma AB	Chief Medical Officer	Astellas Pharma	Senior Medical Director	1-Dec-18
Anthony S. Gibney	Achillion Pharmaceuticals Inc	Chief Business Officer and Executive Vice President	Leerink Partners	Managing Director and Co-Head of the Biotechnology Investment Banking Team	15-Aug-18
Steven Zelenkofske	Achillion Pharmaceuticals Inc	Chief Medical Officer and Executive Vice President	UniQure	Chief Medical Officer	21-Aug-18
Lars E. Birgerson	Adlai Nortye	Chief Executive Officer, President,	Bristol-Myers Squibb	Senior Vice President, Medical R&D	6-Aug-18
Scott Burell	AIVITA Biomedical	Chief Financial Officer	CombiMatrix Corporation	Chief Financial Officer	16-Aug-18
Susie Jun	Allogene Therapeutics	Chief Development Officer	Abbvie	Vice President, Head of Development	14-Aug-18
James P. Tursi	Antares Pharma	Chief Medical Officer, Executive Vice President, Head of R&D	Aralez Pharmaceuticals Inc	Chief Medical Officer	6-Aug-18
Anderson Gaweco	APEIRON Biologics AG	Chief Medical Officer and Chief Scientific Officer	Innovimmune Biotherapeutics	Founder, Chief Medical Officer and Chief Scientific Officer	28-Aug-18
Jill Broadfoot	aTyr Pharma Inc	Chief Financial Officer	Emerald Health Pharmaceuticals Inc	Chief Financial Officer	31-Jul-18

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Take an interactive look at recent executive-level company changes and promotions in the biopharma, medical device and diagnostics industries.
Visit: invivo.pharmaintelligence.informa.com

SHONTELLE DODSON

ANTHONY GIBNEY

CHRISTOPHER MCNULTY

CHERYL SCHWARTZ

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
Filippo Petti	Celyad SA	Chief Financial Officer	Wells Fargo Securities	Vice President, Healthcare Investment Banking	3-Sep-18
Margo Roberts	Celyad SA	Director and Member of Scientific Committee	Kite Pharm	Senior Vice President of Discovery Research	1-Aug-18
Cecilia Danckwardt Lilliestrom	C-RAD AB	Chief Financial Officer	KPMG	Senior Manager	14-Aug-18
Chris D. Emery	Curetis USA Inc	President and Chief Executive Officer	Menarini Silicon Biosystems	Chief Commercial Officer	1-Sep-18
Dana Andersen	Denali Therapeutics Inc	Chief Technical and Manufacturing Officer	Genentech	Vice President, Global Head, Technical Development Project and Portfolio Management	7-Aug-18
Geno Germano	Elucida Oncology Inc	Chief Executive Officer and President	Pfizer Inc	Head, Global Pharma	14-Aug-18
Kurt Kruger	Emmaus Life Sciences Inc	Chief Financial Officer	WR Hambrecht + Co	Head, Life Sciences Investment Banking	26-Jul-18
Julie Anne Smith	E-Scape Bio	Chief Executive Officer, President and Director	Nuredis	President and Chief Executive Officer	23-Aug-18
David Macdonald	First Light Biosciences Inc	Chief Executive Officer, President and Director	Agendia	Chief Executive Officer	7-Aug-18
Iain Mackay	GlaxoSmith-Kline plc	Chief Financial Officer and Director	HSBC	Group Finance Director	14-Jan-19

COMPANY CHANGES

EXECUTIVE	TO COMPANY	NEW ROLE	FROM COMPANY	PREVIOUS ROLE	EFFECTIVE DATE
E. Lynne Kelley	Histogenics	Chief Medical Officer	Senseonics	Chief Medical Officer	31-Jul-18
David Stover	i2 Pharmaceuticals	Chief Executive Officer	Agensys Inc	Senior Vice President and Head of Site	1-Jul-18
Samuel Agresta	Infinity Pharmaceuticals Inc	Chief Medical Officer	Agios Pharmaceuticals Inc	Vice President and Head of Clinical Development	7-Aug-18
Robert J. Marshall, Jr.	Lantheus Medical Imaging	Chief Financial Officer	Zimmer Biomet Holdings Inc	Vice President, Americas Finance	24-Sep-18
David K. Lee	Les Laboratoires Servier	Chief Executive Officer, Servier Pharmaceuticals (US)	Shire plc	Head, Global Genetic Diseases and Oncology	16-Jul-18
Gjest Breistein	Lytix Biopharma ASA	Chief Financial Officer	Pricewaterhouse-Coopers	Auditor and Consultant, Capital Markets	20-Aug-18
Christian Chavy	MedDay Pharmaceuticals	Chief Executive Officer	Stallergenes	Chief Executive Officer	27-Aug-18
Albert P. Parker	Oncocyte Corporation	Chief Operating Officer	GC Legal Advisors	Managing Shareholder	9-Aug-18
Ernie Meyer	Portola Pharmaceuticals Inc	Chief Human Resources Officer, Executive Vice President and Member of Executive Committee	Celgene	Executive Vice President, Human Resources & Corporate Services	20-Aug-18
Jodi Ann Cook	PTC Therapeutics Inc	Head, Gene Therapy Strategy	Agilis Biotherapeutics Inc	Chief Operating Officer	24-Aug-18
Mark Pykett	PTC Therapeutics Inc	Chief Innovation Officer	Agilis Biotherapeutics Inc	Chief Executive Officer	24-Aug-18
Ildiko Csiki	Sensei Biotherapeutics	Chief Medical Officer	Inovio Pharmaceuticals Inc	Vice President, Immuno-Oncology Clinical Development	21-Aug-18
Murthy Simhambhatla	SetPoint Medical	Chief Executive Officer and President	Evolus	Chief Executive Officer and President	13-Aug-18
Peter P. Pfreundschuh	UroGen Pharma	Chief Financial Officer	Sucampo Pharmaceuticals Inc	Chief Financial Officer	20-Aug-18
Christopher McNulty	VBI Vaccines	Chief Financial Officer and Head, Business Development	Invivo Therapeutics	Senior Vice President, Business Development and Investor Relations	13-Aug-18
William Brodie	Vigilant Biosciences Inc	Chief Executive Officer	Vital Connect	Chief Commercial Officer	7-Aug-18
Namir Hassan	Zelluna Immunotherapy AS	Chief Scientific Officer	Immunocore Ltd	Vice President	13-Aug-18

PROMOTIONS

EXECUTIVE	TO COMPANY	NEW ROLE	PREVIOUS ROLE	EFFECTIVE DATE
Shontelle Dodson	Astellas Pharma US	Senior Vice President, Health Systems	Senior Vice President, Medical Affairs, Americas	22-Aug-18
Todd A. Norbe	BIOLASE Inc	Chief Executive Officer and President	Director and Member of Compensation Committee	8-Aug-18
Chris Boerner	Bristol-Myers Squibb Company	Chief Commercial Officer and EVP	Head, International Markets	28-Aug-18
Cheryl Schwartz	EMD Serono	Head, US Fertility and Endocrinology	General Manager, US Biosimilars	31-Jul-18
Gregg H. Alton	Gilead Sciences Inc	Chief Patient Officer	EVP, Corporate and Medical Affairs and Interim Head, International Commercial Operations	14-Aug-18
Rehan Verjee	Merck KGaA	Global Head, Innovative Medicine Franchises and President, EMD Serono	Executive Vice President, Chief Marketing and Strategy Officer, Healthcare	1-Sep-18

DIRECTORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Dambisa F. Moyo	3M Co	Director and Member of Audit and Finance Committee	13-Aug-18
Cynthia Smith	Akebia Therapeutics Inc	Director	28-Aug-18
Michael E. Greenberg	Allergan plc	Director	8-Aug-18
Neil Flanzraich	Alzheon Inc	Vice Chairman	6-Aug-18
Carrie S. Cox	Array BioPharma Inc	Chairman and Member of Audit and Corporate Governance Committee	10-Aug-18
Jeffrey Henderson	Becton Dickinson and Company	Director	16-Aug-18
Michael Lee	Fate Therapeutics Inc	Director	6-Aug-18
Roy Baynes	Natera Inc	Director	31-Jul-18
Jon Ellis	Orchard Therapeutics	Director	2-Aug-18

ADVISORS

EXECUTIVE	TO COMPANY	NEW ROLE	EFFECTIVE DATE
Moshe Gomori	Aspect Imaging	Advisory Board Member	20-Aug-18
James L. Gajewski	Avalon Globocare Corp	Head, Scientific and Clinical Advisory Board	14-Aug-18
Arnold I. Chin	CardioVascular BioTherapeutics Inc	Scientific and Medical Advisory Board Member	30-Aug-18
David M. Ornitz	CardioVascular BioTherapeutics Inc	Scientific and Medical Advisory Board Member	30-Aug-18
Congjian Xu	Esperance Pharmaceuticals Inc	Scientific Advisor	14-Aug-18
Thomas Siklosi	Formycon AG	Advisory Board Member	13-Aug-18
Gary Blick	Immune Therapeutics Inc	Advisory Board Member	23-Aug-18
Trevor Champagne	MedX Health Corp	Medical Advisory Board Member	9-Aug-18

Deal-Making

Covering deals made August 2018

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

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

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IN VITRO DIAGNOSTICS

Mergers & Acquisitions

Bruker buys majority interest in **Hain**

Alliances

Exact Sciences, **Pfizer** co-promote *Cologuard*

Financings

Public offering nets $117.5mm for **NeoGenomics**

MEDICAL DEVICES

Mergers & Acquisitions

Boston Scientific to acquire the rest of **Veniti** for $108mm plus earn-outs

Wright Medical pays $435mm in cash for **Cartiva**

Avista buys **Organogenesis** for $92mm

Varian buys **humediQ**

Alliances

Antares, **Pfizer** develop drug-device combo product

RTI Surgical to distribute **Aziyo**'s *ViBone* in the US

Biotronik to distribute **InfoBionic**'s *MoMe Kardia* in the US

Covalon pens deal with undisclosed device partner

HemoCleanse and **Specialty Renal** partner to develop dialysate filtration system for hemodialysis

Financings

Covalon enters $Cdn17mm banking facility with HSBC

Endologix enters $210.5mm convertible debt financing

IntriCon nets $89.2mm through follow-on offering

PIPE grosses $10mm for **Obalon**

Public offering nets $109.3mm for **Tandem Diabetes**

TSO3 gets $20mm in debt financing from Courage Capital

Public offering nets $141mm for **ViewRay**

Wright Medical nets $423.5mm via follow-on

PHARMACEUTICALS

Mergers & Acquisitions

Amid bankruptcy proceedings, **Aralez** signs LOI to divest *Toprol-XL* assets to Deerfield

Astellas buys gene therapy start-up **Quethera**

Emergent acquires overdose and addiction treatment-focused **Adapt** for up to $735mm

Emergent pays $270mm in cash for **PaxVax**

Nuvo stands to raise $112.5mm in debt from Deerfield to fund proposed **Aralez** transaction

Aralez signs LOI to divest Canadian spec pharma operations to **Nuvo**

Portage buys I/O firm **SalvaRx Ltd.** for $71.7mm in stock

Alliances

AbbVie, **Tolero** enter AML trial collaboration

Acadia gains NA license to **Neuren**'s trofinetide for Rett syndrome

Acorda enters into settlement with **Mylan** for generic *Ampyra*

Affimed signs innate cell antibody engager deal with **Genentech**

Ambys finds its first strategic partner in **Takeda**

BioNTech, **Pfizer** ally in infectious disease vaccines

Gritstone and **bluebird bio** enter cell therapy partnership

Regeneron and **bluebird bio** enter cell therapy pact

BI licenses Western EU rights for generic *Spiriva* to **Glenmark** for COPD

Boehringer secures option for cystic fibrosis gene therapy from **Oxford BioMedica**

Glaukos, **D. Western Therapeutics** ally in glaucoma

Poxel licenses NASH project from **DeuteRx**

Evotec, **Novo Nordisk** pen small-molecule agreement

Vertex and **Genomics PLC** ink collaboration for precision medicines

Gilead off-loads momelotinib in deal with **Sierra Oncology**

Harbour BioMed gets rights to **Glenmark**'s bispecific antibody

Roche partners discontinued inclacumab with **Global Blood Therapeutics**

GtreeBNT, **YuYang** form **Lenus** JV to develop EB candidate RGN137

Harbour BioMed licenses **Kelun**'s PD-L1 antagonist; pays up to $350mm

Urovant gains global rights to **ICI**'s gene therapy for OAB

PTC gets two rare disease therapies from **Akcea**

Sarepta licenses Pompe program from **Lacerta**, options two CNS candidates

Perrigo to bring **Merck**'s *Nasonex* OTC in the US

Rexahn enters trial collaboration with **Merck** for breast cancer tx

Luoxin gets *Trulance* rights in China from **Synergy**

United Therapeutics settles patent litigation with **Watson Labs**; licenses rights to generic *Tyvaso*

Financings

Public offering nets $43mm for **Acer Therapeutics**

Adamis nets $37.8mm via FOPO

Ampio Pharmaceuticals nets $7.4mm in follow-on

Aridis nets $24.2mm via IPO

Aveo nets $5.4mm through latest public offering

BeiGene nets $875.5mm via Hong Kong IPO

BioCryst nets $54mm via FOPO

Critical care focused **Citius Pharmaceuticals** nets $9.2mm in FOPO

Emergent BioSolutions secures $450mm in committed debt financing contingent on **Adapt** acquisition

Entasis files for IPO

Exicure grosses $22mm via PIPE

Gritstone attempts initial public offering

Kiadis enters €20mm debt financing agreement with Kreos

Krystal Biotech brings in $10mm through PIPE

Principia Biopharma files for its initial public offering

Progenics nets $70.5mm through public offering

Protagonist Therapeutics nets $21.8mm via PIPE

RedHill Biopharma nets $23.7mm through FOPO

REGENXBIO nets $189.7mm through latest follow-on offering

Resverlogix grosses $Cdn26mm in PIPE

Sierra Oncology enters $15mm debt facility with SVB; draws down $5mm up front

Public offering nets $35mm for **Spring Bank Pharmaceuticals**

Vaccinex nets $37.2mm through IPO

Y-mAbs files to go public

Zogenix FOPO brings in $293mm

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

Financings

BioNano nets $19mm through Nasdaq IPO

IN VITRO DIAGNOSTICS

Mergers & Acquisitions

BRUKER CORP.
HAIN LIFESCIENCE GMBH

Bruker Corp. is acquiring an 80% stake in German infectious disease diagnostics firm **Hain Lifescience GMBH** for an undisclosed sum. (Aug.)

Bruker has the option to buy the remaining 20% of Hain after 2021. Hain offers various molecular diagnostic solutions for microbial and viral pathogens, antibiotic resistance testing, and genetic diseases. It specializes in tuberculosis and other mycobacterial infections. Specific product lines include the *GenoType* diagnostic assays for tuberculosis, sexually transmitted disease (STD) testing, and HIV viral load testing; the *Fluorocycler* XT real-time PCR system which incorporates *Liquid Array* syndromic panels; and *GenoXtract* for the efficient extraction of nucleic acids. The acquisition expands Bruker's microbiology offerings beyond its mass spec-based *MALDI Biotyper* system. Hain co-founders and managing directors David and Tobias Hain will retain their roles post-transaction with Bruker's microbiology and diagnostics business. For 2018, Hain expects to bring in $38mm in revenues.

Alliances

EXACT SCIENCES CORP.
PFIZER INC.

Exact Sciences Corp. has signed on **Pfizer Inc.** to co-promote its *Cologuard* in the US and Puerto Rico. (Aug.)

Pfizer will begin co-promoting *Cologuard* starting in Q4, and the deal term will extend through 2021. Exact Sciences will handle all manufacturing activities. Both firms will equally share profits and expenses. After expiration of the deal term, Exact agrees to pay Pfizer the following royalties tied to revenue achievements for twelve consecutive quarters: 1% for revenues between $200mm and $400mm; 2% on revenues greater than $400mm and less than $600mm; 3% on revenues exceeding $600mm. The firms will establish a joint steering committee comprised of three representatives from each. Exact will provide Pfizer with adequate training and materials relating to *Cologuard*. *Cologuard* is the only FDA-approved non-invasive stool DNA screening test for colorectal cancer, which is one of the most preventable forms of cancer yet the second leading cause of cancer deaths in the US. Current colorectal cancer screenings such as colonoscopies are invasive and require unappealing prep for patients. Exact and Pfizer hope to bring the product to more people in an effort to reduce colon cancer deaths.

Financings

NEOGENOMICS INC.

NeoGenomics Inc. netted $117.5mm through a public offering of 9.8mm common shares at $12.75. The company offers genetic testing for cancer and companion diagnostic/pharma services, and will use the offering proceeds for business growth and working capital. (Aug.)

Investment Banks/Advisors: Benchmark Co. LLC; Craig-Hallum Inc.; First Analysis Securities Corp.; Janney Montgomery Scott Inc.; Leerink Partners LLC; Stephens Inc.; William Blair & Co.

MEDICAL DEVICES

Mergers & Acquisitions

BOSTON SCIENTIFIC CORP.
VENITI INC.

Boston Scientific Corp. agreed to paid $108mm in cash up front to acquire the remaining 75% of cardiovascular stent developer **Veniti Inc.** that it does not already own. The deal also includes up to $52mm in in earn-outs tied to FDA approval of Veniti's flagship product. (Aug.)

BS holds a 25% stake in Veniti following a $25mm investment in the company's Series D round in 2016. Veniti, which was formed in 2009, raised a total of $67.5mm through four venture rounds. The firm developed the *VICI VENOUS STENT*, a system comprised of a laser-cut self-expanding nitinol stent and a coaxial over-the-wire delivery system designed to protect the stent prior to deployment. The *VICI* stent is designed to withstand compression and is intended for use in the venous anatomy, delivered via either a jugular or femoral vein approach. It received the CE Mark in 2013 and is awaiting FDA approval in the

US. Under the BS umbrella, Veniti will see much wider physician and patient exposure for its device. *VICI* is complementary to BS's *AngioJet* pharmacomechanical peripheral thrombectomy device and the rest of the firm's venous product pipeline.

CARTIVA INC.
WRIGHT MEDICAL GROUP NV

Wright Medical Group NV is acquiring closely held orthopedic device maker **Cartiva Inc.** for $435mm in cash. (Aug.)

Wright gains the *Cartiva* synthetic cartilage implant, an alternative to fusion for treating arthritis of the big toe. The device, which incorporates a biomaterial, is designed to replace damaged cartilage and can be implanted in about 35 minutes to provide a smooth load-bearing joint surface. The product is approved in the EU, Canada, Brazil, Chile, and Australia; in the US it is the only product with premarket approval for treating great toe osteoarthritis. The technology behind the *Cartiva* implant has applications in high-volume foot and ankle procedures and will fit nicely into Wright's lower extremities business. Cartiva spun off from Carticept Medical in late 2011 and is backed by investors including New Enterprise Associates and Windham Venture Partners. Wright expects the acquisition to increase its 2019 net sales by approximately $47mm and non-GAAP adjusted EBITDA from continuing operations by about $20mm. Investment Banks/Advisors: JP Morgan & Co. (Wright Medical Group NV); Guggenheim Partners LLC (Cartiva Inc.)

ORGANOGENESIS INC.

Avista Capital Partners' public special purpose acquisition company Avista Healthcare Public Acquisition Corp. (AHPAC) is acquiring regenerative medicine firm **Organogenesis Inc.** for $92mm in cash. (Aug.)

AHPAC will fund the deal through cash, equity, and debt. Organogenesis will become an AHPAC subsidiary. Post-transaction, the expected initial enterprise value for the firm will be $673mm. Organogenesis was founded in 1985 with technology originating at the **Massachusetts Institute of Technology**. Until last year, the company had specialized in products for the wound care and sport medicine markets. With its 2017 acquisition of **NuTech**, Organogenesis gained a presence in the orthopedic surgical space by taking on NuTech's amniotic product line for soft tissue and bone applications. Organogenesis strives to bring to market healing products that significantly improve patient outcomes with reduced costs.

VARIAN MEDICAL SYSTEMS INC.
HUMEDIQ GLOBAL GMBH

Varian Medical Systems Inc. boosted its radiation therapy business through the acquisition of **humediQ Global GMBH**, a privately held firm developing motion management systems for use in radiation therapy suites. (Aug.)

HumediQ's flagship product *IDENTIFY* is an automated workflow station for SGRT (surface-guided radiation therapy). The system includes a palm reader for patient identification, a radiofrequency identification reader which verifies accessories used in a certain procedure as well as their placement on the table, cameras for patient positioning and motion monitoring, and synchronization with an oncology information system. *IDENTIFY* verifies setup for each patient, and directs the patient and radiation technician for proper body positioning. The platform is highly complementary to Varian's radiotherapy offerings, which include the *TrueBeam* and *VitalBeam* radiation systems, and the *ARIA* oncology information and image management system.

Alliances

ANTARES PHARMA INC.
PFIZER INC.

Antares Pharma Inc. and **Pfizer Inc.** are teaming up in the development and commercialization of a combination drug-device rescue pen. (Aug.)

The rescue pen will combine Antares' *QuickShot* auto injector and an undisclosed Pfizer drug. The Big Pharma will fund development activities and be responsible for all regulatory activities. Antares will supply the finished product to Pfizer, which gets US commercialization rights. Antares is eligible for sales royalties. The *QuickShot* device enables the fixed-dose delivery of viscous and aqueous formulations via a fine-gauge nonvisible needle. Under a 2014 agreement, Antares and **AMAG** partnered to create a combination product of *QuickShot* and AMAG's *Makena* (hydroxyprogesterone caproate) designed to reduce the risk of preterm birth in women who are pregnant.

AZIYO BIOLOGICS INC.
RTI SURGICAL INC.

Aziyo Biologics Inc. granted **RTI Surgical Inc.** exclusive rights to distribute its *ViBone* next-generation cellular bone matrix product in the US. (Aug.)

The *ViBone* allograft performs and handles more closely to autograft and is designed to protect the tissue environment with less disruption. The product is osteogenic, osteoinductive, and osteoconductive to provide enhanced bone formation. *ViBone* will join RTI Surgical's own family of allografts.

BIOTRONIK SE & CO. KG
Biotronik Inc.
INFOBIONIC INC.

InfoBionic Inc. licensed **Biotronik Inc.** exclusive rights to distribute its FDA-cleared *MoMe Kardia* cardiac arrhythmia monitoring system in the US. (Aug.)

MoMe Kardia is a software-as-a-service (SaaS) platform for remote cardiac monitoring. It replicates in-hospital monitoring and provides anytime access to 24-hour ECG data, thus allowing physicians to have real-time access to patient data so they can quickly diagnose and intervene when necessary. InfoBionic says the device is the only full disclosure transmitter on the market. Earlier this year Biotronik got rights to co-distribute **Aziyo Biologics'** *CanGaroo* bio envelope in the US.

COVALON TECHNOLOGIES LTD.

Covalon Technologies Ltd. licensed an unnamed medical device firm global rights to its patented antimicrobial coating technology. (Aug.)

In exchange, Covalon receives $3.5mm up front, $5mm in development milestones, fees for use of its technology development services and equipment, and sales royalties. Few details were disclosed regarding the collaboration. The licensee will use the antimicrobial coating with its own devices. Covalon's *Centaur* low-particulate coating is designed to improve the safety and functionality of intravascular medical devices, including vascular access catheters, by helping to prevent infections.

HEMOCLEANSE TECHNOLOGIES LLC
NEPHROS INC.
Specialty Renal Products Inc.

Renal care firms **HemoCleanse Technologies LLC** and **Specialty Renal Products Inc.** (a new subsidiary of **Nephros Inc.**) penned an agreement to develop a dialysate regeneration and filtration system for renal disease patients. (Aug.)

SRP gets global development and commercialization rights to IP and know-how pertaining to carbon-based sorbent technology in the treatment of renal disease, while HemoCleanse retains technology rights outside of the field of renal care. SRP plans to utilize the licensed IP to develop a filtration system to be used in tandem with disposable tubing circuit sets for continuous renal replacement therapy (CRRT) in ICU patients with acute kidney injury. In contrast to hemodialysis devices, which generate dialysate from ultrapure water and dialysate concentrate, CRRT requires bags of dialysate to be provided and changed out constantly during the procedure, and also results in excessive small molecule removal (requiring costly supplements to be added to the dialysate bags prior to administration). The carbon-based filtration system devised by SRP and HemoCleanse could allow for regeneration of a patient's own sterile dialysate, and could also result in the removal of more uremic toxins and middle molecules, improving overall patient response rate to therapy.

Financings

COVALON TECHNOLOGIES LTD.

Covalon Technologies Ltd. (advanced wound care, infection control, and medical device coatings) entered a $Cdn17mm ($12.7mm) banking facility with HSBC, which has provided the company with a $Cdn9mm acquisition demand line (repayable over five years), a $Cdn5mm revolving operating facility, and a $2mm bank guarantee facility. Proceeds will support Covalon's current acquisition plans. (Aug.)

ENDOLOGIX INC.

Endologix Inc. (minimally invasive devices for aortic disorders) announced a $210.5mm convertible loan facility with three undisclosed investors. The company also issued warrants. (Aug.)

INTRICON CORP.

IntriCon Corp. netted $89.2mm through a follow-on public offering of 1.7mm common shares (including the overallotment) at $55. The company designs and manufactures hearing aids, diagnostic monitoring devices, drug delivery solutions, and biotelemetry devices. Proceeds from the offering will be used to repay debt and fund the purchase of capital equipment for expansion of manufacturing facilities. (Aug.)

Investment Banks/Advisors: B. Riley FBR Inc.; Dougherty & Co. LLC; Stifel Nicolaus & Co. Inc.

OBALON THERAPEUTICS INC.

Obalon Therapeutics Inc. (devices for weight loss) grossed $10mm in a private placement of 5.5mm common shares at $1.82 (a 3% premium) to institutional investors, company management and board members, Domain Associates, and InterWest Partners. The company developed the only FDA-approved swallowable, gas-filled intragastric balloon system for obesity. (Aug.)

TANDEM DIABETES CARE INC.

Tandem Diabetes Care Inc. (manufactures and sells insulin pumps and glucose monitoring devices) netted $109.3mm through the public sale of 4mm common shares (including the overallotment) at $28.50. The company will use some or all of the proceeds to repay debt under an existing term loan agreement with Capital Royalty. (Aug.)

Investment Banks/Advisors: Oppenheimer & Co. Inc.; Robert W. Baird & Co. Inc.

TSO3 INC.

TSO3 Inc. (sterilization technology for medical devices) has entered into a $20mm debt financing with Courage Capital Management. TSO3 receives $15mm in the form of a 10% five-year non-callable note convertible into common shares at $0.82 each. (The company's shares averaged $0.62 at the time of sale.) The second $5mm consists of a 12% five-year term loan. The firm will use the proceeds for commercialization of its FDA-approved *Sterizone* VP4 sterilizer. (Aug.)

VIEWRAY INC.

ViewRay Inc. netted $141mm through a public offering of 16.2mm common shares at $9.25. Proceeds will support continued development and commercialization of the company's MRI-guided radiation therapy systems. (Aug.)

Investment Banks/Advisors: B. Riley FBR Inc.; Cantor Fitzgerald & Co.; Guggenheim Partners LLC; Jefferies & Co. Inc.; Mizuho Bank Ltd.; Morgan Stanley & Co.; Northland Securities

WRIGHT MEDICAL GROUP NV

Wright Medical Group Inc. netted $423.5mm through a follow-on public offering of 18.2mm ordinary shares priced at $24.60 each. The proceeds will fund Wright's concurrent $435mm cash acquisition of orthopedic device maker **Cartiva**. (Aug.)

Investment Banks/Advisors: JP Morgan & Co.

PHARMACEUTICALS

Mergers & Acquisitions

ARALEZ PHARMACEUTICALS INC.

Faced with bankruptcy, **Aralez Pharmaceuticals Inc.** signed a non-binding letter of intent (LOI) under a stalking-horse bid process to sell its *Toprol-XL* (metoprolol) franchise to Deerfield Management. (Aug.)

The LOI states Deerfield will pay Aralez an anticipated $140mm in cash at closing. Aralez first gained exclusive US rights to *Toprol-XL* and its authorized generic from **AstraZeneca** under an October 2016 alliance in which it paid $175mm up front. *Toprol-XL*, which had US revenues of $37mm for 2017 (and worldwide sales of $695mm for the same period), is a beta blocker marketed for hypertension, angina, and stable, symptomatic heart failure. In a separate concurrent LOI, Aralez also plans to divest the assets and operations of its Canadian spec pharma operations (formerly known as Tribute Pharmaceuticals) to **Nuvo Pharmaceuticals** for $110mm. Investment Banks/Advisors: Moelis & Co.

ASTELLAS PHARMA INC.
QUETHERA LTD.

Astellas Pharma Inc. is acquiring ophthalmic-focused UK start-up **Quethera Ltd.** (Aug.)

Astellas could shell out as much as £85mm ($109.3mm) in the form of up-front and earn-out payments. Post-transaction, Quethera will be an Astellas subsidiary. Three-year-old Quethera is a gene therapy company focused on eye diseases that result in blindness. It is initially working on treatments designed to reduce progressive visual loss conditions such as glaucoma that affect the optic nerve. Quethera uses recombinant adeno-associated viral vectors (rAAV) to introduce therapeutic genes into target retinal cells for glaucoma. Its lead program in preclinical studies has shown to improve the survival of retinal ganglion cells, which are damaged in glaucoma patients. As of now, all therapeutic approaches for treating glaucoma work by lowering the pressure inside the eye. Astellas says the rAAV program can provide a new treatment option for refractory glaucoma via an intraocular pressure-independent mechanism.

EMERGENT BIOSOLUTIONS INC.
ADAPT PHARMA LTD.

Emergent BioSolutions Inc. agreed to acquire private specialty pharmaceutical company **Adapt Pharma Ltd.** (focused on overdose and addiction treatments) for up to $735mm in cash and stock. Emergent expects the transaction will contribute additional revenues of $200-220mm in 2019. (Aug.)

Emergent will pay $635mm ($575mm in cash and $60mm in stock) and up to an additional $100mm in earn-outs (consisting of two possible $50mm payments); the first tied to Adapt exceeding a certain sales goal between January 1, 2018 through December 31, 2019 and the second upon Adapt surpassing certain sales thresholds during any single calendar year ending on or before December 31, 2022. Emergent will fund the transaction with cash on hand, an existing $200mm Wells Fargo senior credit facility secured in October 2017, and debt financing commitments of $600mm from Wells Fargo. Emergent is mainly interested in Adapt's only marketed product *Narcan* (naloxone HCl) 4 mg, a nasal spray for the immediate emergency treatment of known or suspected overdose of opioids, including prescription painkillers and illegal drugs such as heroin. Adapt in-licensed global development rights to the intranasal formulation of the opioid antagonist naloxone from Lightlake Therapeutics (now **Opiant Pharmaceuticals**) under a 2014 agreement. Although an injectable version was previously cleared by the FDA, the naloxone nasal spray offers the same dosage and onset of action in a needle-free and more convenient method of administration. Adapt's formulation was approved by the FDA in 2015 and by Health Canada in 2017. Founded in 2013 and headquartered in Dublin, Ireland (with US and Canadian locations), Adapt also has a pipeline of candidates with various delivery options, including AP002 and AP004 (regulatory filings expected this year) for

opioid overdose, and preclinical AP007, a potential opioid addiction treatment. Regulatory filings for AP003 and AP005, also for opioid overdose, are anticipated in 2019 and 2020, respectively. The acquisition supports Emergent's mission to provide civilian and military populations diverse offerings that address chemical, biological, nuclear, and infectious disease public health threats (the opioid crisis in this case) and will supplement Emergent's only-in-class medical countermeasure and emergency preparedness solution products across both government and commercial markets. Earlier this month Emergent bought infectious disease-focused **PaxVax** for $270mm in cash, a deal also enhancing its public health crisis programs with the addition of PaxVax's travelers' vaccines portfolio. Investment Banks/Advisors: Morgan Stanley & Co. (Emergent BioSolutions Inc.); Bank of America Merrill Lynch (Adapt Pharma Ltd.)

EMERGENT BIOSOLUTIONS INC.
PAXVAX INC.

Public **Emergent BioSolutions Inc.** is acquiring closely held infectious disease-focused **PaxVax Inc.** for $270mm in cash from its majority owner Cerberus Capital Management. (Aug.)

Founded in 2006, PaxVax's focus is on travelers' vaccines. Emergent gains PaxVax's lead products--the *Vivotif* oral typhoid fever vaccine and *Vaxchora* oral vaccine for cholera. Both are the only FDA-approved products for their respective diseases. In development, PaxVax has vaccines in Phase IV for pediatric cholera, Phase II for Chikungunya, Phase I for adenovirus Type 4 and Type 7, Phase I for HIV, and preclinical studies for Zika. Emergent also takes on cGMP biologics manufacturing facilities in Europe as well as around 250 PaxVax employees. The PaxVax acquisition positions Emergent as a worldwide leader in therapies aimed at public health concerns. Emergent believes the transaction will provide the firm with additional revenues of $70-90mm in 2019. Emergent has both marketed and development-stage programs aimed at various infectious diseases, including anthrax, botulism, influenza, and Zika. Last year the company paid $97.5mm for **Sanofi Pasteur**'s *ACAM2000*, the only FDA-licensed vaccine for active immunization against smallpox in high-risk patients. Investment Banks/Advisors: Perella Weinberg Partners (PaxVax Inc.)

NUVO PHARMACEUTICALS INC.

Nuvo Pharmaceuticals Inc., to support the proposed concurrent purchase of **Aralez Pharmaceuticals Inc.**'s Canadian specialty pharmaceutical business (Tribute) under a separate non-binding letter of intent, plans to receive a six-year, 3.5% senior secured debt facility of $112.5mm from Deerfield. Nuvo would issue Deerfield 43.6 mm common share purchase warrants exercisable at $3.53. The financing is contingent upon Nuvo's execution of a definitive agreement with Aralez by August 19, 2018. (Aug.)

NUVO PHARMACEUTICALS INC.
ARALEZ PHARMACEUTICALS INC.
Tribute Pharmaceuticals Canada Inc.

Nuvo Pharmaceuticals Inc. signed a non-binding letter of intent (LOI) under a stalking-horse bid process to acquire **Aralez Pharmaceuticals Inc.**'s Canadian specialty pharmaceutical business, formerly known as Tribute Pharmaceuticals Canada Inc., along with associated personnel and infrastructure. Aralez plans to negotiate with Nuvo to execute a definitive agreement by August 19, 2018. (Aug.)

The LOI states Nuvo will pay Aralez an anticipated $110mm in cash at closing, with Deerfield providing funding to Nuvo under a separate $112.5mm debt facility. (In another concurrent LOI, Aralez also expects to offload its US *Toprol-XL* (metoprolol) cardiovascular franchise to Deerfield for $140mm.) Attempting to restructure amid impending bankruptcy proceedings, Aralez is also involved in other ongoing negotiations to sell the assets not purchased by Nuvo or Deerfield and intends to discontinue its operations following the proposed sales. The former Tribute Pharmaceuticals (which merged with Pozen in 2015 to form Aralez, and was absorbed as an Aralez subsidiary) has a portfolio of more than 20 products, including *Cambia* (diclofenac potassium), an oral solution NSAID sold in Canada since 2012 for migraine, and *Blexten* (bilastine) antihistamine tablets for allergic rhinitis and chronic spontaneous urticaria symptoms, which received Canadian approval and was launched there in 2016. Under the deal, Novo would also gain multiple drugs that Tribute or Pozen had in-licensed over the years, including Canadian rights to *Resultz* (isopropyl myristate/cyclomethicone D5) over-the-counter head lice & egg elimination kit, sold as a class 1 medical device. (Nuvo already has worldwide rights in most other territories through a January 2018 deal with originator **Piedmont Pharmaceuticals**.) In addition, Nuvo gets global rights (including royalties) from licensee **Horizon** for *Vimovo* (esomeprazole magnesium/naproxen) for osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and global, ex-US product rights to MT400 (sumatriptan/naproxen sodium), currently sold as *Treximet* in the US by licensee **Pernix**, and to be marketed as *Suvexx* in Canada once approved there. (A new drug submission filing with Health Canada is expected by the end of this year.) The anticipated deal boosts the fellow Canadian company's portfolio and additionally expands its capabilities to acquire and launch additional products in Canada. Should the deal go through, Nuvo's pro forma 2017 revenues are predicted at approximately four times higher and 2017 pro forma adjusted EBITDA ten times higher than that reported for fiscal 2017. Since Nuvo's current CEO and CSO were former Tribute executives, they also provide strong knowledge of the products, the business history, and the key operations personnel. Investment Banks/Advisors: Moelis & Co. (Aralez Pharmaceuticals Inc.)

PORTAGE BIOTECH INC.
SALVARX GROUP PLC
SalvaRx Ltd.

Portage Biotech Inc. agreed to acquire immuno-oncology firm **SalvaRx Ltd.** from its parent **SalvaRx Group PLC**. Portage will issue 805mm of its common shares at $0.089 (an 18% discount), valuing the deal at close to $72mm. (Aug.)

SalvaRx was founded in 2014 with a business model based on investing in companies that work on new immuno-oncology assets and providing support to help its subsidiaries bring candidates through clinical proof-of-concept. Through the acquisition, Portage gains 10 early-stage projects from SalvaRx's pipeline. Portage operates similarly to SalvaRx; it currently has majority interest in five biotechs with disease areas ranging from ophthlamics, cancer, and kidney conditions.

Alliances

ABBVIE INC.
SUMITOMO CHEMICAL CO.
Tolero Pharmaceuticals Inc.

In a clinical trial collaboration, **Tolero Pharmaceuticals Inc.** is investigating a therapy that combines its own alvocidib with **AbbVie Inc.**'s venetoclax for relapsed/refractory acute myeloid leukemia (AML). (Aug.)

The parties will share all development expenses equally and post-transaction Tolero and AbbVie will each retain full commercial rights to their compounds. Alvocidib is a Phase II cyclin-dependent kinase 9 (CDK9) inhibitor which controls MCL-1 expression, while venetoclax is a B-cell lymphoma-2 (BCL-2) inhibitor. Preclinical studies have shown that MCL-1 and BCL-2 inhibition together can drive apoptosis. Alvocidib is in Phase II for AML and preclinical studies for myelodysplastic syndrome. Tolero got exclusive global rights to the candidate from **Sanofi** under a May 2013 deal. Venetoclax is sold for chronic lymphocytic leukemia in the US as *Venclexta* and EU under the *Venclyxto* brand, and is in pre-registration for AML. It is in various clinical trials for other cancers--myeloma and mantle cell lymphoma (Phase III); and non-Hodgkin's, B-cell and follicular lymphomas, myelodysplastic

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syndrome, and breast cancer (Phase II).

ACADIA PHARMACEUTICALS INC.
NEUREN PHARMACEUTICALS LTD.

Acadia Pharmaceuticals Inc. licensed exclusive North American development and commercialization rights to **Neuren Pharmaceuticals Ltd.**'s trofinetide (NNZ2566; a synthetic analog of the amino-terminal tripeptide of IGF-1) for Rett syndrome (a neurological disorder occurring primarily in females, caused by X chromosome mutations on the MeCP2 gene) and other indications, including Fragile X syndrome, another rare X-linked CNS disease. (Aug.)

In exchange, Acadia will pay Neuren $10mm up front, potential milestones up to $455mm ($105mm related to development achievements in Rett and Fragile X syndrome indications and $350mm upon the attainment of certain NA sales goals), and tiered, escalating, double-digit royalties on net sales within the licensed territory. (Acadia has a right of first negotiation to acquire a license outside North America.) In addition, Neuren is entitled to one third of the market value of any rare pediatric disease priority review voucher for trofinetide if awarded by the FDA upon approval of an NDA. Acadia will take over funding of and conduct remaining development for trofinetide in Rett syndrome in NA, except for the completion by Neuren of certain ongoing preparatory activities. The partners will form a joint steering committee to oversee development in all indications, including an upcoming Fragile X syndrome trial; any data or regulatory filings generated may be used by either party within their respective territories. Trofinetide received fast track status (in 2013) from the FDA and orphan drug designations (in 2015) in both the US and the EU for Rett syndrome, which affects the synapses of the brain responsible for cognitive, sensory, emotional, motor, and autonomic functions, and results in symptoms such as seizures, disorganized breathing patterns, scoliosis, and sleep disturbances. In Phase II trials concluded last year, trofinetide demonstrated safety and tolerability as well as clinically meaningful improvement in core Rett syndrome symptoms. A randomized, double-blind, placebo-controlled Phase III study is planned for H2 2019. Trofinetide also completed a Phase II trial in Fragile X syndrome (with a Phase III trial expected to begin this year) and is also in preclinical development for other cognitive impairments and neurodegenerative disorders. The candidate complements Acadia's CNS focus. Acadia's antipsychotic *Nuplazid* (pimavanserin), a selective serotonin inverse agonist (SSIA), was FDA approved in 2016 for hallucinations and delusions associated with Parkinson's disease psychosis. Acadia is also developing the SSIA for other psychiatric disorders.

ACORDA THERAPEUTICS INC.
MYLAN NV
Mylan Pharmaceuticals Inc.

Acorda Therpeutics Inc. entered into a settlement agreement with **Mylan Pharmaceuticals Inc.** which gives Mylan the right to market a generic version of Acorda's *Ampyra* (dalfampridine) in the US sometime in 2025 or earlier under certain circumstances. Simultaneously, Acorda signed interim agreements with **Teva** and **Hikma** concerning their respective patent litigation related to *Ampyra* regarding the period of time until decisions are reached. The drug, which was developed using **Elan**'s proprietary *MXDAS* technology, is currently marketed for the treatment of multiple sclerosis. (Aug.)

AFFIMED NV
ROCHE
Genentech Inc.

Affimed NV and **Roche**'s **Genentech Inc.** agreed to discover and conduct early- and late-stage research on innate immune cell--natural killer (NK) cell and T-cell--immunotherapies against certain Genentech-selected targets for various solid and hematological tumors. Genentech will take over clinical development and hold exclusive global commercialization rights; it is also responsible for related costs. (Aug.)

In return, Affimed gets $96mm in upfront and committed near-term payments (over the next 12 months); $250mm in development milestones; $1.1bn in regulatory milestones; $3.6bn in commercial milestones; and tiered sales royalties. Affimed was also granted nonexclusive, worldwide, and royalty-free rights to certain IP from Genentech. Each company will own IP that they solely develop, and new IP will be jointly owned. The partners plan to use Affimed's *Redirected Optimized Cell Killing* (*ROCK*) platform as part of the deal; *ROCK* produces NK cell and T-cell antibody engagers with tetravalent and multi-specific formats and variable pharmacokinetic profiles. The resulting candidates are designed to have improved abilities to destroy cancerous cells. There could be potential for combining such innate immune cell engagers with checkpoint inhibitors to help boost the immune system response to cancer. In fact, in 2016, Affimed signed an agreement with **Merck & Co.** to combine the former's *ROCK* agent AFM13, for CD+ malignancies, with the latter's *Keytruda* for Hodgkin's lymphoma. So likely, under the current deal Roche may evaluate combinations of the *ROCK*-generated therapies with its checkpoint inhibitor *Tecentriq*. **BMS**, another key player in the immunotherapy market, is also now evaluating innate system activators through its 2017 acquisition of IFM Therapeutics.

AMBYS MEDICINES
TAKEDA PHARMACEUTICAL CO. LTD.

In tandem with a Series A investment in the start-up, **Takeda Pharmaceutical Co. Ltd.** entered an option agreement with **Ambys Medicines** for new liver disease therapies. (Aug.)

Takeda invested $20mm in Ambys' $60mm Series A round, and also committed an additional $80mm through an alliance to help the young regenerative medicine firm advance its platform. In exchange, Takeda gets an option to license ex-US commercialization right

BIONTECH AG
PFIZER INC.

In a multi-year collaboration, **BioNTech AG** and **Pfizer Inc.** are teaming up in the development of mRNA-based vaccines for influenza. (Aug.)

Both firms will jointly perform R&D activities. Once a first-in-human study is complete by BioNTech, Pfizer will take over and solely handle further clinical development and gets worldwide commercialization rights to any resulting flu vaccines. Pfizer will pay BioNTech $120mm in up-front, equity, and near-term research payments, plus up to $305mm in development, regulatory, and commercial milestones. BioNTech is also eligible for tiered sales royalties up to double-digits. Pfizer says that mRNA vaccines have potential as a new method for protein or multi-protein coding. They can be manufactured more rapidly and cost effectively and at higher potency levels than currently available flu vaccines. The agreement represents a step into the human infectious disease space for BioNTech; prior to this it has been focused on immunotherapies for cancer.

bluebird bio Inc.

GRITSTONE ONCOLOGY

Gritstone Oncology agreed to use its *EDGE* personalized neoantigen platform to provide ten tumor-specific targets (and T-cell receptors (TCRs) directed to those targets) for cell therapy and gene editing firm **bluebird bio Inc.** (Aug.)

EDGE is an artificial intelligence platform that uses sequence data from a patient's tumor biopsy to predict mutations that will generate tumor-specific neoantigens most likely to be present on the tumor cell surface. These targets that are unique to certain tumor cells will be presented to bluebird for use in its cell therapy program, specifically for the development of new solid tumor treatments. In exchange for Gritstone's work, bluebird pays $20mm up front and made a $10mm equity investment in Gritstone's Series C round, which closed concurrent with the alliance. Gritstone is also eligible to receive up to $1.2bn in development, regulatory, and commercialization mile-

stones, plus tiered single-digit royalties. The research term of the collaboration is initially five years, extendable by one additional year. The deal was announced on the same day that Gritstone filed for its initial public offering. The company, which was formed in 2015, seeks a listing on the Nasdaq Global Market.

BLUEBIRD BIO INC.
REGENERON PHARMACEUTICALS INC.

Regeneron Pharmaceuticals Inc. and **bluebird bio Inc.** will lean on each other's platform discoveries to together discover and develop antibodies and T-cell receptors directed against tumor-specific proteins and peptides. (Aug.)

Bluebird brings to the deal its lentiviral vector-based T-cell modification technology, gene transfer capabilities, and cell therapy development expertise, which will be utilized in tandem with Regeneron's *VelociSuite* antibody and T-cell receptor discovery and characterization platform. The parties jointly chose six initial targets, and plan to share all R&D costs up to IND filing. Regeneron can opt in to a co-development and co-commercialization agreement for certain targets under a 50/50 cost- and profit-sharing arrangement. (If it doesn't opt in, it will instead receive milestones and royalties on resulting candidates.) Regeneron will make a $100mm investment in bluebird (420k shares at $238.10, a 59% premium to bluebird's August 3 closing price.) The premium equals about $37mm, which will be credited against Regeneron's 50% funding obligation. The partners believe that the collaboration (which has a five-year term) will result in the development of modified T-cell therapies that can access both extracellular and intracellular tumor antigens and address safety and efficacy concerns associated with other chimeric antigen receptor T-cell (CART) therapies.

BOEHRINGER INGELHEIM GMBH
GLENMARK PHARMACEUTICALS LTD.

Glenmark Pharmaceuticals Ltd. exclusively licensed Western European rights to a generic version of **Boehringer Ingelheim GMBH**'s *Spiriva HandiHaler* (tiotropium bromide dry powder inhaler) for chronic obstructive pulmonary disease. (Aug.)

The *HandiHaler* reported sales of $724mm in the EU in the twelve months ended March 2018. This is the second inhalation product that Glenmark has in-licensed in Europe, reaffirming its commitment to respiratory as a key area of focus. Back in 2015, the company licensed semi-exclusive rights to develop and market a generic version of **GlaxoSmithKline**'s *Seretide Accuhaler* (fluticasone/salmeterol) dry powder Inhaler from **Celon Pharma S.A.**

Boehringer Ingelheim GMBH

IMPERIAL COLLEGE LONDON
Imperial Innovations Group PLC
OXFORD BIOMEDICA PLC
UK CYSTIC FIBROSIS GENE THERAPY CONSORTIUM

Boehringer Ingelheim GMBH is expanding its reach into gene therapy via an option agreement with **Oxford BioMedica PLC** and **Imperial Innovations Group PLC** (tech transfer office of **Imperial College of London**). (Aug.)

Per the terms of the agreement, BI will collaborate with the **UK Cystic Fibrosis Gene Therapy Consortium** (GTC; made up of Imperial College of London, the **University of Oxford**, and the **University of Edinburgh**) on research and development of a long-term therapy for cystic fibrosis. The consortium began its work in the space nearly 17 years ago and now the parties are on the final frontier of the lentiviral vector gene therapy. While the GTC will continue to lead development to move into clinical trials, BI will provide its R&D expertise and capital. Oxford BioMedica will provide non-financial support and will manufacture the lentiviral-based viral vector. The approach is novel in that it uses a replication-deficient lentiviral vector in an inhaled formulation, to introduce a healthy copy of the CFTR gene into lung cells. Oxford currently manufactures the lentiviral vector in **Novartis'** CART *Kymriah*. While financial terms of the deal remain private, BI does have the right to exercise an option for exclusive global rights to manufacture and commercialize Oxford's lentiviral vector-based cystic fibrosis gene therapy.

D. WESTERN THERAPEUTICS INSTITUTE INC.
GLAUKOS CORP.

Glaukos Corp. and Japanese biotech **D. Western Therapeutics Institute Inc.** (DWTI) are teaming up to create new glaucoma therapies. (Aug.)

DWTI is granting Glaukos access to its Rho kinase (ROCK) inhibitor compound library and an undisclosed technology for use in designing and synthesizing intraocular candidates for glaucoma. Glaukos is responsible for compound evaluation and development. Glaukos will provide DWTI with an up-front fee and funding for research. Glaukos gets exclusive rights to any resulting compounds and will develop intracameral and topical therapies that can be delivered via its own *iDose* drug delivery system.

DEUTERX LLC
POXEL SA

DeuteRx LLC granted **Poxel SA** exclusive global rights to DRX065, a Phase I candidate that Poxel intends to develop for non-alcoholic steatohepatitis (NASH). (Aug.)

DRX065 is a deuterium-stabilized R-stereoisomer of the Type II diabetes drug pioglitazone that has shown promising results in studies for NASH. While the negative side effects of standard pioglitazone (including fluid retention, weight gain, and bone fracture) make it an unattractive option for NASH, DeuteRx's DRX065 has exhibited improved efficacy and fewer side effects. Poxel pays €6.8mm ($8mm) up front and will issue 1.29mm of its ordinary shares (a 4.99% stake) at €6.91 per share, a slight premium. DeuteRx could also receive development, regulatory, and sales milestones, plus low single-digit royalties (*Strategic Transactions* estimates 1-3%). In addition to the DRX065 rights, Poxel also gets exclusive global rights to additional undisclosed programs for rare and metabolic diseases. DRX065 is complementary to Poxel's PXL770, a AMPK activator entering Phase II for NASH. Investment Banks/Advisors: MTS Health Partners (Poxel SA)

EVOTEC AG
NOVO NORDISK AS

Evotec AG and **Novo Nordisk AS** are partnering to discover and develop small molecule therapeutics aimed at diabetes and obesity as well as associated comorbidities such as nonalcoholic steatohepatitis (NASH), cardiovascular diseases, and diabetic kidney disease. (Aug.)

Evotec will initially use its ligand-based drug discovery technology to select safe and efficacious candidates. Once preclinical compounds are identified, Novo Nordisk will use Evotec's *INDiGo* platform to move them into the clinic. *INDiGo* can accelerate early-stage candidates into clinic trials by reducing time from nomination to regulatory submission in 52 weeks or less. Evotec chose Novo Nordisk as a partner because of the firm's expertise in the diabetes and obesity space, however Novo is not particularly familiar with the development of small molecules. Financial terms of the agreement were not disclosed.

GENOMICS PLC
VERTEX PHARMACEUTICALS INC.

Vertex Pharmaceuticals Inc. and **Genomics PLC** agreed to collaborate in a three-year deal (possible extension to five) in which the latter will use its machine learning platform to assist Vertex in its discovery of selected targets for precision medicine. (Aug.)

While specific financial terms of the alliance were not disclosed, Vertex is concurrently making a £10.5mm investment in Genomics PLC as lead investor in the company's Series B round. Vertex will fund resources committed by Genomics to the collaboration along with milestone and royalty payments for targets taken through the clinic. Chief Scientific Officer of Vertex Dr. David Altshuler will also join Genomics' board of directors. Founded in 2014 by scientists at the **University of**

Oxford, Genomics PLC has developed a unique analysis engine with over 100bn data points that uses genetics to understand human biology. The database utilizes proprietary machine learning and statistical algorithms to link human genetic variation at over 14mm positions in the human genome to thousands of measurements and disease outcomes.

GILEAD SCIENCES INC.
SIERRA ONCOLOGY INC.

Gilead Sciences Inc. granted **Sierra Oncology Inc.** all rights to its JAK1/JAK2 inhibitor momelotinib, which completed Phase III trials in myelofibrosis-related anemia. (Aug.)

Gilead originally gained rights to the candidate through its 2012 acquisition of **YM Biosciences**, but discontinued development in 2016 following the completion of two Phase III trials. The biotech had hoped the candidate could improve anemia symptoms in patients with the bone marrow cancer myelofibrosis while also reducing enlarged spleen size, a common occurrence in the disease that causes pain. Gilead's trials reported mixed results--reduction of spleen size but not a sufficient reduction in anemia--leading the company to cease development. Sierra pays $3mm up front for the chance to bring the candidate to market, and also committed to up to $195mm in milestones, plus royalties ranging from the mid-teens to high-twenties. (*Strategic Transactions* estimates 14-29%.) Sierra adds momelotinib to its pipeline of oncology compounds, including SRA141, a selective CDC7 inhibitor, and SRA737, a checkpoint kinase 1 inhibitor. The company concurrently announced a new $15mm debt facility agreement with Silicon Valley Bank, available in $5mm tranches. The first tranche was drawn down immediately and will go towards the momelotinib deal. Investment Banks/Advisors: Mizuho Bank Ltd. (Gilead Sciences Inc.)

GLENMARK PHARMACEUTICALS LTD.
Glenmark Pharmaceuticals SA
HARBOUR BIOMED

Glenmark Pharmaceuticals SA granted **Harbour BioMed** exclusive rights to develop and sell its bispecific antibody GBR1302 for solid tumors in Greater China. Harbour BioMed also retains a manufacturing option. (Aug.)

The deal is potentially valued at over $120mm, including an up-front payment and milestones for development, regulatory, and sales achievements, plus tiered royalties. GBR1302 is the first cancer project that Glenmark discovered using its *BEAT* (*Bispecific Engagement by Antibodies based on the T cell receptor*) bispecific antibody production technology. The candidate stimulates a patient's immune system against HER2-overexpressing tumor cells and is in Phase I trials for HER2+ cancers, including breast and gastric tumors. Harbour notes that GBR1302 is complementary to the research pipeline it is building through the use of its H2L2 and HCAb transgenic mouse platforms.

GLOBAL BLOOD THERAPEUTICS INC.
ROCHE

Global Blood Therapeutics Inc. (GBT) received exclusive worldwide rights, and sublicensing rights, to develop, manufacture, and commercialize **Roche**'s preclinical fully human monoclonal antibody inclacumab against P-selectin, a target in sickle cell disease. The deal also includes patent rights and know-how, as well as modified compounds derived from inclacumab and interacting with P-selectin. Concurrent with the present agreement, GBT licensed Roche nonexclusive global and royalty-free rights to inclacumab for diagnostics uses. (Aug.)

Roche gets $2mm up front and up to $125.5mm in total milestones ($40.5mm for development and regulatory, and $85mm in sales) related to the sickle cell disease indication. For other indications, Roche could receive up to $19.25mm in development and regulatory milestones. Further, Roche may achieve another $5.5mm in development and regulatory milestones tied to inclacumab that are owed to a third party. In addition, GBT will pay tiered royalties for the first annual net sales totaling over $1bn from the low double-digits to mid double-digits (*Strategic Transactions* estimates 10-29%). Regarding GBT's sublicensing rights, should the company partner inclacumab, Roche would have a right of first negotiation to negotiate with GBT the terms of that transaction. Tiered percentages of net proceeds that GBT receives from such a deal, or a change-in-control agreement over a certain period following inclacumab's launch will go to Roche. The Big Pharma had been developing the candidate for acute coronary syndrome and saphenous vein graft disease, but suspended work in early 2015 for an unknown reason, possibly because it was not prepared to conduct the larger-scale trials that would have been required. At one point, inclacumab was the only cardiovascular project in its pipeline. Instead, GBT will now pursue the antibody in vaso-occlusive crises associated with sickle cell disease, and aims to file an IND application in 2021. There are already other selectin-targeting compounds in development by competitors, led by **Pfizer**'s rivipansel in Phase III. GBT plans to use Roche's existing safety data generated on inclacumab, and is working on technology transfer to a contract manufacturer. GBT already has voxelotor (GBT440) in Phase III for sickle cell disease, where it has a 62% likelihood of approval, 2% above average.

GTREEBNT CO. LTD.
Lenus Therapeutics LLC
YUYANG DNU CO. LTD.

GtreeBNT Co. Ltd. and fellow diversified Korean company **YuYang DNU Co. Ltd.** created a joint venture called **Lenus Therapeutics LLC** around the former's Phase II epidermolysis bullosa (EB) candidate RGN137, a topical gel formulation of therapeutic peptide thymosin beta 4 (TB4), which will be known by GtreeBNT as GBT101. (Aug.)

EB is a rare genetic dermatological condition. If RGN137/GBT101 receives marketing approval, it will obtain exclusivity in the US and Europe as an orphan drug. GtreeBNT originally in-licensed the candidate (also known as RGN259/GBT201 in a solution form for ophthalmic indications) and related intellectual property from **RegeneRx Biopharmaceuticals** under a 2014 deal and the partners went on the following year to create a JV, **ReGenTree**, to develop RGN259 for dry eye and the degenerative corneal epithelium orphan disease neurotrophic keratitis. RegeneRx initially gained rights and IP to TB4--a naturally-occurring regenerative peptide with multiple mechanisms, including promotion of cell protection and collagen maintenance, and decreased apoptosis and inflammation--from the **NIH** in 1999. Through the current deal, Lenus will hold exclusive worldwide development and IP rights to RGN137/GBT101 (within EB) from GtreeBNT. YuYang, already the largest shareholder of GtreeBNT (a position it secured last year), is making an investment of about $17.8mm in cash into the JV, which will operate as a GtreeBNT US subsidiary. Lenus plans to first conduct an open study of RGN137/GBT101 to lure potential Big Pharma partners, followed by a worldwide Phase III trial.

HARBOUR BIOMED

Sichuan Kelun Pharmaceutical Co. Ltd.

Harbour BioMed licensed exclusive global rights (excluding the Greater China region) to develop, manufacture, and sell **Sichuan Kelun Pharmaceutical Co. Ltd.**'s (Kelun Biotech) anti-PD-L1 antibody A167. (Aug.)

Kelun is eligible for over $350mm, including an up-front payment and milestones for development, regulatory, and sales achievements, plus royalties. A167 is in Phase I and II trials in China for lymphoma and solid tumors. The partners will also work together to develop combination therapies with A167 and other treatments, and agreed to share data generated from independent research. The deal is the second this year for the companies; they also cite a partnership involving co-discovery, co-development, and co-commercialization of antibodies for cancer and immune diseases based on Harbour's discovery platforms. For Harbour, the collaboration

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is the second it signed just this month. It also licensed exclusive Chinese rights to one of **Glenmark Pharmaceuticals'** bispecific antibodies for solid tumors.

ION CHANNEL INNOVATIONS LLC
ROIVANT SCIENCES GMBH
Urovant Sciences Ltd.

Roivant Sciences GMBH's **Urovant Sciences Ltd.** licensed exclusive worldwide development, manufacturing, and commercialization rights to **Ion Channel Innovations LLC**'s naked DNA gene therapy hMaxi-K, for overactive bladder (OAB). (Aug.)

Urovant paid $250k up front and could also provide up to $35mm in development and regulatory milestones, up to $60mm in sales milestones, plus tiered net sales royalties in the mid-to-high single digits (*Strategic Transactions* estimates 4-9%). ICI's hMaxi-K uses human gene transfer, which places genetic material (DNA or RNA) directly into a person. A potassium channel promoter, hMaxi-K is administered locally through an injection into the bladder wall and has a six-month duration of action intended to reduce or prevent bladder smooth muscle overactivity and thus correct OAB symptoms of urinary urgency, frequency, and incontinence. Prior studies by ICI in rodent and primate animal models of aging, diabetes, and atherosclerosis have shown that hMaxi-K improves urogenital pathophysiology. ICI has funded prior OAB clinical trials through several SBIR grants (totaling over $2.7mm) from the US government's **Department of Health & Human Services**. Urovant plans to initiate a Phase II study in 2019 to investigate hMaxi-K in OAB patients who have not responded to other pharmacological therapies. The compound started Phase II trials (in 2015) for erectile dysfunction, but it's not clear if Urovant will pursue further development in that indication. The addition of hMaxi-K is complementary to Urovant's other OAB candidate vibegron, a Phase III oral beta-3 adrenergic agonist, to which--concurrent with its launch last year--Urovant licensed global rights (excluding Japan and certain Asian territories) from **Merck & Co.** Earlier this month, just prior to signing the current deal, Urovant filed for a Nasdaq IPO.

IONIS PHARMACEUTICALS INC.
Akcea Therapeutics Inc.
PTC THERAPEUTICS INC.

Ionis Pharmaceuticals Inc.'s **Akcea Therapeutics Inc.** licensed **PTC Therapeutics Inc.** exclusive rights to develop, manufacture, and commercialize its rare disease drugs *Tegsedi* (inotersen) and *Waylivra* (volanesorsen) in Latin America and certain Caribbean countries. Akcea has also granted PTC a right of first negotiation to commercialize AKCEA-TTR-LRx, a follow-on candidate to inotersen, on an exclusive basis in the territories. (Aug.)

Akcea receives $12mm up front, $6mm on the earlier of FDA or EMA approval of *Waylivra*, and up to $8mm in regulatory approvals in the licensed territories. PTC will also pay sales royalties in the mid-twenty percent beginning the earlier of 12 months after the first commercial sale of a product in Brazil or when PTC recognizes revenue of at least $10mm in Latin America. The parties will create a joint steering committee to oversee the collaboration. Akcea got exclusive rights to the drugs from Ionis earlier this year. That deal could potentially be worth up to $1.9bn in the form of up-front and milestone payments. Any milestone and royalty payments paid by PTC for *Tegsedi* will be split on a 60% Ionis/40% Akcea basis, and 50/50 for *Waylivra*. *Tegsedi* is an antisense therapy in pre-registration in the US for hereditary transthyretin amyloidosis (ATTR), a disease characterized by a buildup of abnormal protein deposits in organs and tissues. It has a PDUFA date of October 6, 2018. From the EU, the drug received marketing authorization approval for the treatment of Stage 1 or 2 polyneuropathy in adults with hereditary ATTR. *Waylivra* is currently under regulatory review in the US, Europe, and Canada for familial chylomicronemia syndrome. Its PDUFA date is August 30, 2018. The therapy is also in clinical trials for familial partial lipodystrophy.

LACERTA THERAPEUTICS INC.
SAREPTA THERAPEUTICS INC.

Sarepta Therapeutics Inc. licensed exclusive worldwide rights to **Lacerta Therapeutics Inc.**'s gene therapy candidate for Pompe disease (an autosomal recessive metabolic disorder which damages muscle and nerve cells) and has options to license two additional neuro-focused candidates from Lacerta's pipeline. (Aug.)

Sarepta will make a $38mm up-front payment ($8mm in cash and a $30mm equity investment), pay development and sales milestones, and provide single-digit royalties on net sales of resulting products. Lacerta will manage most of the preclinical work with Sarepta taking over clinical development and commercialization. A stealthy start-up founded last year, Lacerta has multiple adeno-associated virus (AAV) vector technologies licensed from the **University of Florida**, where they were invented by company co-founders Joseph Reddy, PhD (CEO), and Kenneth Warrington, PhD (CTO). The platforms are incorporated into the company's AAV gene therapy pipeline, which is focused on central nervous system and lysosomal storage diseases. Under the deal Sarepta also has use of these technologies, including a screening method that combines rational and combinatorial methodologies to identify capsid variants possessing selective vector characteristics, and the insect cell-based *OneBac* scalable AAV manufacturing platform. Although the specific therapeutic areas of the two optioned programs were not yet disclosed, Lacerta has potential gene therapies in development for Sanfilippo syndrome type B, aromatic L-amino acid decarboxylase deficiency, neurodegenerative proteinopathies, spinocerebellar ataxias, and glioblastoma. The deal boosts Sarepta's existing eight-program gene therapy pipeline (currently solely for Duchenne muscular dystrophies (DMD)) to 11 candidates, and into potential therapeutic areas beyond DMD.

MERCK & CO. INC.
PERRIGO CO. PLC

Perrigo Co. PLC licensed exclusive rights to market and distribute a non-prescription version of **Merck & Co. Inc.**'s nasal spray *Nasonex* (mometasone) in the US. The treatment is on the market for seasonal/perennial rhinitis, sinusitis, and nasal polyps. (Aug.)

Perrigo announced the OTC switch license on the same day that the company declared plans to divest its prescription pharmaceuticals business to focus on expanding its consumer/OTC offerings. (Specific details on the separation have not yet been disclosed.) Perrigo is a leading global manufacturer of OTC and store-brand consumer products, with products for cough, cold, allergy, pain, gastrointestinal ailments, smoking cessation, infant formula and foods, and animal health. The *Nasonex* deal is the first OTC switch licensing for Perrigo, and the product will be the first national brand marketed by the company.

MERCK & CO. INC.
REXAHN PHARMACEUTICALS INC.

Merck & Co. Inc. and **Rexahn Pharmaceuticals Inc.** penned an agreement to study the combination of Rexahn's RX5902 (supinoxin) with Merck's *Keytruda* (pembrolizumab) as a potential therapy for metastatic triple negative breast cancer (TNBC). (Aug.)

RX5902, an inhibitor of phosphorylated-p68, is in Phase II breast cancer trials and has been studied in earlier trials for other solid tumors including renal, ovarian, pancreatic, colorectal, and stomach cancers, as well as melanoma. *Keytruda*, a PD-1 antagonist, is marketed for melanoma, non-small cell lung cancer, and Hodgkin's lymphoma, as well as bladder, stomach, esophageal, colorectal, and cervical cancers. Trials are ongoing for a variety of other solid and blood tumors including breast, renal, liver, small cell lung, pancreatic, and others. The partners will evaluate the combination in a Phase II trial with metastatic TNBC patients who have progressed after undergoing at least one prior treatment.

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SHANDONG LUOXIN PHARMACEUTICAL GROUP CO. LTD.
SYNERGY PHARMACEUTICALS INC.

Synergy Pharmaceuticals Inc. granted **Shandong Luoxin Pharmaceutical Group Co. Ltd.** (Luoxin) exclusive rights to develop and sell *Trulance* (plecanatide) for chronic idiopathic constipation and constipation-predominant irritable bowel syndrome in China, Hong Kong, and Macau. (Aug.)

Luoxin is responsible for costs and activities surrounding the development, approval, and commercialization of *Trulance* in its territories. Synergy gets $12mm up front, up to $56mm in regulatory and sales milestones, and tiered royalties. The deal is the second out-licensing for *Trulance* this year; **Cipher Pharmaceuticals** paid $5mm up front for Canadian rights in February. Luoxin's portfolio includes treatments for oncology and allergy, as well as infectious, viral, respiratory, CNS, endocrine, cardiovascular, and inflammatory conditions. It also has a wide offering of gastrointestinal therapies, including the ulcer/GERD products lansoprazole, pantoprazole, esomeprazole, and others. In development, the company is working on LXI15028, a proton pump inhibitor in Phase III trials that it in-licensed from **CJ Healthcare**.

UNITED THERAPEUTICS CORP.
ALLERGAN PLC
Watson Laboratories Inc.

As part of a patent settlement, **United Therapeutics Corp.** licensed **Watson Laboratories Inc.** rights to market a generic version of *Tyvaso* inhalation solution (treprostinil; marketed for the treatment of pulmonary arterial hypertension) beginning on January 1, 2026. Watson's generics business is part of **Teva** as **Allergan PLC** divested the business in July 2015. (Aug.)

Financings

ACER THERAPEUTICS INC.

Acer Therapeutics Inc. (treatments for rare and ultra-rare diseases) netted $43mm through a public offering of 2.55mm common shares (including the overallotment) at $18. Proceeds will support continued development, regulatory activities, and future commercialization of lead candidate *Edsivo* (celiprolol) for vascular Ehlers-Danlos syndrome (vEDS), ongoing trials with ACER001 for urea cycle disorders and maple syrup urine disease (MSUD), and additional corporate and development needs. (Aug.)

Investment Banks/Advisors: CIM Securities; HC Wainwright & Co.; Raymond James & Associates Inc.; Roth Capital Partners; William Blair & Co.

ADAMIS PHARMACEUTICALS CORP.

Respiratory disease-focused **Adamis Pharmaceuticals Corp.** netted $37.8mm through a follow-on offering of 13.4mm common shares (including full exercise of the overallotment) at $3 each. (Aug.)

Investment Banks/Advisors: B. Riley FBR Inc.; HC Wainwright & Co.; Maxim Group LLC; Raymond James & Associates Inc.

AMPIO PHARMACEUTICALS INC.

Ampio Pharmaceuticals Inc. (inflammatory-focused therapeutics) netted $7.4mm in a follow-on public offering of 20mm common shares at $0.40. Each share comes with a warrant entitling the holder to purchase an additional common share for a period of five years at a strike price of $0.40. The company intends to use the proceeds for preclinical and clinical product development and for working capital. (Aug.)

Investment Banks/Advisors: Canaccord Genuity Inc.

ARIDIS PHARMACEUTICALS LLC

Infectious disease-focused **Aridis Pharmaceuticals Inc.** netted $24.2mm in an oversubscribed initial public offering of 2mm common shares at $13 each, the low end of its anticipated range. (Aug.)

Investment Banks/Advisors: Cantor Fitzgerald & Co.; Laidlaw & Co.; Maxim Group LLC; Northland Securities; Seaport Global Securities

AVEO PHARMACEUTICALS INC.

Aveo Pharmaceuticals Inc. (mainly oncology) netted $5.4mm through a public offering of 2.5mm common shares at $2.26. Proceeds will support development and pre-commercial expenses related to lead candidate tivozanib, which is in Phase III trials as a third-line treatment for advanced renal cell carcinoma (aRCC) and Phase I/II in combination with *Opdivo* (nivolumab) for RCC. (Tivozanib is already approved for aRCC in the EU, Norway, and Iceland as *Fotivda*.) (Aug.)

Investment Banks/Advisors: Piper Jaffray & Co.

BEIGENE LTD.

BeiGene Ltd. (immuno-oncology) netted $875.5mm through its initial public offering on the Main Board of the Stock Exchange of Hong Kong Ltd. (SEHK). The company sold 65.6mm ordinary shares at $13.76 (the mid-point of its $12.03-14.22 range). Of the total, 5.9mm shares were offered to the public in Hong Kong and 59.7mm shares were offered globally. BeiGene completed its US initial public offering on the Nasdaq Global Select Market in February 2016, through which it netted $170mm with the sale of 7.6mm American Depositary Shares (representing 98.7mm ordinary). Current proceeds will go towards development, regulatory activities, and future commercialization of zanubrutinib (mantle cell lymphoma), tislelizumab (classical Hodgkin's lymphoma), and pamiparib (solid tumors including ovarian, gastric, and brain tumors), and will also support pipeline expansion in cancer and possibly other indications. (Aug.)

Investment Banks/Advisors: CLSA; China International Capital Corp. Ltd.; China Renaissance; Credit Suisse Group; Deutsche Bank AG; Goldman Sachs & Co.; Morgan Stanley & Co.; UBS Investment Bank

BIOCRYST PHARMACEUTICALS INC.

BioCryst Pharmaceuticals Inc. netted $54mm through the follow-on public offering of 10.45mm common shares (including full exercise of the overallotment) at $5.50 each. The company will use some of the proceeds for activities (mostly in the US, EU, and Japan) for its prophylactic (Phase III) and acute (Phase II) BCX7353 for hereditary angioedema, development of its fibrodysplasia ossificans progressiva and other preclinical rare disease programs, and post-approval activities for *Rapivab*/*Alpivab* for influenza. (Aug.)

Investment Banks/Advisors: JMP Securities LLC; JP Morgan & Co.; Jefferies & Co. Inc.

CITIUS PHARMACEUTICALS INC.

Citius Pharmaceuticals Inc. (anti-infective and cancer-focused critical care drugs) netted $9.2mm in a follow-on public offering of 5.5mm units at $1.275 (each unit consists of one common share and one five-year warrant to purchase an additional common share at a strike price of $1.15) and 2.3mm pre-funded units (each pre-funded unit offers the right to purchase one common share and one warrant) at $1.265. The company plans to use the proceeds from the offering toward R&D for its products including its Phase III *Mino-Lok* trial for the treatment of catheter related bloodstream infections and its Phase IIb trial of *Hydro-Lido* cream for hemorrhoids; for working capital; and capital expenditures. (Aug.)

Investment Banks/Advisors: HC Wainwright & Co.

EMERGENT BIOSOLUTIONS INC.

Emergent BioSolutions Inc. (medical countermeasure and emergency preparedness solution products to address public health threats) secured a commitment from Wells Fargo for a new five-year term loan in the principal amount of $450mm (available to be drawn in a single advance). The proceeds will support Emergent's potential $735mm concurrent buy of specialty pharmaceutical company **Adapt Pharma**. The financing is contingent upon the closing of the M&A transaction. To further fund the acquisition of Adapt, Emergent also added $150mm onto its separate, existing October 2017 $200mm credit facility with Wells Fargo. Adapt is focused on overdose and addiction and sells *Narcan* (naloxone HCl) nasal spray for the immediate emergency treatment of opioid overdose. (Aug.)

ENTASIS THERAPEUTICS HOLDINGS INC.

Antibiotics developer **Entasis Therapeutics Holdings Inc.** filed for its initial public offering. (Aug.)

Investment Banks/Advisors: BMO Financial Group; Credit Suisse Group; SunTrust Banks Inc.; Wedbush PacGrow Life Sciences

EXICURE INC.

Exicure Inc. (gene regulatory and immunotherapeutic drugs) grossed $22mm through the private placement of 4.9mm shares (a 10% discount) at $4.50 each to investors including Sphera Global Healthcare, Knoll Capital Management, Broadfin Capital, and Sio Capital Management. Exicure will use the funds for ongoing development of its pipeline candidates, including Phase I ASTo08 for solid tumors and Phase I XCUR17 for psoriasis. Ladenburg Thalmann, Castle Hill Capital Partners, and Katalyst Securities were the placement agents. (Aug.)

Investment Banks/Advisors: Katalyst Securities LLC; Ladenburg Thalmann & Co. Inc.

GRITSTONE ONCOLOGY

Personalized neoantigen therapeutics company **Gritstone Oncology** has filed for its initial public offering. (Aug.)

Investment Banks/Advisors: BTIG LLC; Barclays Bank PLC; Cowen & Co. LLC; Goldman Sachs & Co.

KIADIS PHARMA NETHERLANDS BV

Kiadis Pharma Netherlands BV (T-cell immunotherapies) entered a €20mm ($23.4mm) debt facility with Kreos Capital. (The agreement is new and separate from a €15mm debt financing with Kreos completed in 2017.) Under the current transaction, Kiadis drew down an initial €5mm tranche immediately (9% interest, with a term of 45 months), and can draw down the remaining €15mm (9% interest, 48-month term) once it receives a positive opinion from the EMA for its ATIR101, in Phase III for prevention of graft-vs-host disease in blood cancer patients who undergo allogeneic hematopoietic stem cell transplantation). Funds will support ATIR101 development and help the firm plan for a European commercial launch. (Aug.)

KRYSTAL BIOTECH INC.

Gene therapy company **Krystal Biotech Inc.** (rare dermatological diseases) grossed $10mm through the private sale of 625k shares at $16 (a slight premium) to Frazier. Chardan acted as the placement agent. The company will use the proceeds to fund ongoing pipeline R&D. Earlier this month, the FDA granted orphan drug status to KB105, Krystal's preclinical candidate for transglutaminase 1 (TGM-1) deficient autosomal recessive congenital ichthyosis, a rare disease that causes skin scaling due to impaired epidermal barrier function. Lead candidate KB103, its Phase II topical gene therapy for dystrophic epidermolysis bullosa (blistering caused by lack of collagen in the skin), received both FDA fast track and orphan drug designations earlier this year. (Aug.)

Investment Banks/Advisors: Chardan Capital Markets

PRINCIPIA BIOPHARMA INC.

Principia Biopharma Inc. (oncology and immunology drug discovery) filed for its initial public offering. (Aug.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Leerink Partners LLC; Robert W. Baird & Co. Inc.; Wells Fargo Securities LLC

PROGENICS PHARMACEUTICALS INC.

Progenics Pharmaceuticals Inc. netted $70.5mm through public offering of 9.1mm common shares at $8.25. The company develops and sells targeted cancer therapies and treatments for GI and infectious diseases. Marketed products include *Relistor* (methylnaltrexone bromide) for opioid-induced constipation, and *Azedra* (iobenguane I 131) for unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma (rare neuroendocrine tumors of neural crest origin). (Aug.)

Investment Banks/Advisors: BTIG LLC; CIM Securities; Cantor Fitzgerald & Co.; Credit Suisse Group; Jefferies & Co. Inc.; Needham & Co. Inc.

PROTAGONIST THERAPEUTICS INC.

Peptide therapies developer **Protagonist Therapeutics Inc.** netted $21.8mm through the sale of 2.75mm common shares at $8 each (a 12% premium) to investors including BVF Partners. The company also issued five-year warrants to purchase 1.38mm common shares at $10 and 1.38mm shares at $15. Protagonist will use the funds for ongoing development of Phase II PTG100 for ulcerative colitis. (Aug.)

REDHILL BIOPHARMA LTD.

RedHill Biopharma Ltd. netted $23.7mm in a public offering of 4.2mm American Depositary Shares (ADSs) at $6 per ADS. (Each ADS represents 10 ordinary shares). The company expects to use the proceeds to fund clinical development programs, including preparations for a second Phase III trial for RHB104 in Crohn's disease and initiation of a pivotal Phase III study with RHB204 for nontuberculous mycobacteria (NTM) infections (which was granted qualified infectious disease product (QIDP) designation by the FDA in May 2018 for an expedited review process). Some money will also go toward funding commercial operations--including activities related to the potential launch of Phase III *Talicia* (RHB105; amoxicillin/omeprazole/rifabutin) for H. pylori infection, which also has the QIDP designation, with an NDA filing anticipated in early 2019--and future acquisitions. (Aug.)

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

REGENXBIO INC.

REGENXBIO Inc. (gene therapies for retinal, metabolic, and neurodegenerative diseases) netted $189.7mm through the public sale of 3.1mm common shares (including the overallotment) at $65. Proceeds will support continued pipeline development, including work on RGX314 for wet age-related macular degeneration, RGX501 for homozygous familial hypercholesterolemia, RGX111 for mucopolysaccharidosis Type I, and RGX121 for mucopolysaccharidosis Type II (Hunter syndrome). (Aug.)

Investment Banks/Advisors: Bank of America Merrill Lynch; Barclays Bank PLC; Morgan Stanley & Co.; Raymond James & Associates Inc.

RESVERLOGIX CORP.

Resverlogix Corp. (epigenetic therapeutics) grossed $Cdn26mm ($20mm) in a private placement of 10.4mm equity units at $Cdn2.50 ($1.93; an 18% discount). Each unit consists of one common share and one-half of a three-year common share purchase warrant (strike price of $Cdn3.00). The company plans to use the proceeds to support R&D, including funding of its Phase III BETonMACE (apabetalone/RVX208 for high-risk CVD patients with Type II diabetes and low high-density lipoprotein) trial; to repay debt; and for working capital. (Aug.)

SIERRA ONCOLOGY INC.

Sierra Oncology Inc. (developing cancer therapies that target the DNA Damage Response (DDR) network) entered a $15mm debt facility with Silicon Valley Bank. The company can borrow funds in $5mm tranches, the first of which was made available immediately and will support Sierra's acquisition of all rights to **Gilead**'s myelofibrosis-related anemia candidate momelotinib. An additional uncommitted $25mm facility could be made available at a later date. (Aug.)

SPRING BANK PHARMACEUTICALS INC.

Spring Bank Pharmaceuticals Inc. (drug development using its small molecule nucleic acid hybrid (SMNH) chemistry platform) netted $35mm through a public offering of 3mm common shares at $12.50. Funds will support ongoing preclinical and clinical work on candidates for HBV and other viral diseases and cancer. (Aug.)

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

VACCINEX INC.

Vaccinex Inc. (biotherapeutic mAbs for cancer, neurodegenerative diseases, and autoimmune disorders) netted $37.2mm in an initial public offering of 3.3mm shares at $12, the low end of its anticipated $12-15 range. (Aug.)

Investment Banks/Advisors: BTIG LLC; Ladenburg Thalmann & Co. Inc.; Oppenheimer & Co. Inc.

Y-MABS THERAPEUTICS INC.

Cancer immunotherapies developer **Y-mAbs Therapeutics Inc.** filed for its initial public offering. (Aug.)

Investment Banks/Advisors: BTIG LLC; Bank of America Merrill Lynch; Canaccord Genuity Inc.; Cowen & Co. LLC

ZOGENIX INC.

CNS-focused orphan drug developer **Zogenix Inc.** netted $293.3mm in a public offering of 6mm shares at $52. The company will use the proceeds to fund regulatory submissions and commercialization activities for ZX008 (fenfluramine) for Dravet syndrome, a childhood epilepsy, for which it has fast track and breakthrough therapy designations in the US, as well as orphan status in both the US and the EU. Following positive Phase III results in this indication last month, an NDA filing is expected soon. Zogenix will also use some of the money to support additional R&D of ZX008, including an ongoing Phase III trial in Lennox-Gastaut syndrome, another rare form of pediatric epilepsy. (Aug.)

Investment Banks/Advisors: Bank of America Merrill Lynch; JMP Securities LLC; Leerink Partners LLC; LifeSci Capital LLC; Mizuho Bank Ltd.; Stifel Nicolaus & Co. Inc.

RESEARCH, ANALYTICAL EQUIPMENT & SUPPLIES

Financings

BIONANO GENOMICS INC.

Life sciences instrumentation company **BioNano Genomics Inc.** (genome mapping systems) netted $19mm in its initial public offering of 3.36mm units at $6.125. Each unit consists of one share of common stock and one warrant to purchase one common share at an exercise price of $6.125. Last month, the company announced it first planned to offer 3.35mm shares between $8-10, but later revised that range to $5-6 for 5.5mm shares, and again updated the offering to a proposed 2.45mm units at a $6-7 price. (Aug.)

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

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