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William H. Carson, M.D., president and CEO for Otsuka Pharmaceutical Development & Commercialization, Inc. **p. 20**

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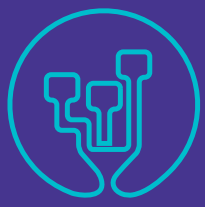

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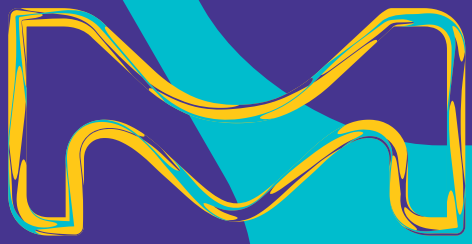

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Social Media Fans Flames Of Biopharma Blunders

ROB WRIGHT Chief Editor

What do Pokémon Go, Penn State, and Mylan CEO Heather Bresch have in common? All serve as recent examples of social media's (SM) ability to exponentially accelerate public awareness of various phenomena, while also revealing something else — bad judgment.

This past summer, the Pokémon Go mobile app took the world by storm. We quickly read reports of people crashing their cars while playing the game and other forms of bad judgment including folks (old enough to know better) playing in areas such as the Arlington National Cemetery, the 9/11 Memorial in lower Manhattan, and yes, even the Holocaust Memorial Museum in Washington, D.C.

But even the power of social media couldn't prevent Pokémon Go from fading out of the limelight faster than the ice bucket challenge.

Nonetheless, social media remains a powerful tool, especially for shining a spotlight on bad behavior. In August, members of the Penn State football team *allegedly* bought about $1,200 of food from sub shop Jimmy John's. Apparently, they neglected to tip for the delivery, and a disgruntled Jimmy John's employee took to Twitter to voice his dissatisfaction. In days gone by, such social faux pas would have had zero (if any) negative impact on a sports team or even a company. Today, however, social media affords *Jimmy* and Jane Q. Public a much larger opinion-sharing forum — essentially leveling the communications playing field between the masses and those typically afforded mass-media access (e.g., politicians, celebrities).

Last summer the media had a field day when Turing Pharmaceuticals CEO Martin Shkreli increased the price of Daraprim by 5,000 percent. So I was surprised that this year, with an impending U.S. presidential election that has drug pricing as one of its hottest issues, Mylan decided to raise the price of its EpiPen by 32 percent. Could that have waited? Considering Mylan recently announced that it would soon begin selling a generic EpiPen for $300, which is less than half the price of its $608.21 branded product, one would think — yes. Look, I don't begrudge any pharmaceutical company from pricing a product at the optimal point that a market will bear as long as it still provides good value to customers and a reasonable return for investors. And yes, Mylan CEO, Heather Bresch did make some good points about the true nature of drug pricing during a CNBC interview (e.g., a drug's price is the result of "four or five hands that the product touches and companies that it goes through before it ever gets to that patient at the counter"). But the reality is America won't listen to this type of rhetoric, no matter how legitimate it might be. Still, Americans certainly seem willing to rally behind the various forms of social media currently being used to bury the industry. For example, Bernie Sanders' August 28, 2016, tweet, "Heather Bresch's willingness to put profits before people is unforgivable and reckless: EpiPens save lives," (as of this writing) had been retweeted more than 1,500 times, with over 2,800 likes, meaning the message is reaching well beyond his 3.3 million followers. Only a few days later, Hillary Clinton unveiled her plan to stop price gouging on old drugs, calling the EpiPen price hikes "outrageous." Though social media has proven all too capable of fanning the flames of biopharma price-hiking blunders, one has to wonder how much fuel should biopharmaceutical executives continue to provide. For while rising prices and inflation are a part of life (much like death and taxes), biopharma leaders need to weigh carefully the short-term gains versus long-term impact on a company's overall reputation such product price hikes can have when placed under the powerful (and sometimes slanted) lens of the social media microscope. L

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Q What do you say to those who are looking at a job description/career that requires prior experience?

A IT CAN FEEL LIKE A CATCH-22 when a role requires specific experience to be considered a candidate, yet you can't get experience unless you are in that type of role! One solution to this dilemma is gaining the experience you need outside of your company. Associations offer the perfect opportunity to do just this. Consider what research and volunteer opportunities your industry's association has that are aligned to your target area.

At the Healthcare Businesswomen's Association, we design our volunteer roles to provide experiential learning across a highly diverse range of leadership opportunities. For instance, if you are looking for global experience, consider how participating in developing a globalization strategy or leading a global team – as a volunteer – could expand your knowledge of working in a global arena. I have seen firsthand how volunteers take their newly learned skills back to their company and successfully supplemented their justification of experience for their target role.

LAURIE COOKE, BS, RPH, PGDIP, CAE
is the CEO of the Healthcare Businesswomen's Association (HBA), a global nonprofit professional association.

Q What simple changes to biopharma manufacturing could be quickly implemented that would have almost an immediate impact on the lowering of drug prices?

A UNFORTUNATELY, NO CHANGE in the highly regulated bioprocess industry is "simple;" and it requires appropriate risk assessment. Still, if you could make changes with a lower post-approval change scrutiny, the first one I would make would be to go from stainless steel to single-use process technologies. The reasons for such range from reduced set-up times – and therefore higher manufacturing capacity utilization – to reduced cleaning/steaming needs which equal energy cost savings. Also, the footprint of these facilities is smaller, and fewer personnel are needed, which all contribute to a lower cost of goods. Pioneering sites like Amgen's Singapore site will accelerate a shift in the industry to more agile, multiproduct, and multipurpose processes.

MAIK JORNITZ
is COO of G-CON Manufacturing and founder of BioProcess Resources. He has more than 25 years of experience.

Q What big biopharma companies do you find most exciting and why?

A I AM IMPRESSED BY BRISTOL-MEYERS SQUIBB (BMS) AND J&J. Ten years ago you wouldn't have given BMS much of a chance after the channel-stuffing scandal. But today BMS finds itself as a very successful specialty biopharma company. And while they're not trying to compete with the big boys and are just focusing on coming up with good science, they remain big. As for J&J, Paul Stoffels was quite frustrated about the state of affairs in pharma and J&J. But to his credit, he did something to change it, and J&J is now producing a lot more sustainable innovation. The rest of Big Pharma rely on very large portfolios of branded generics. Because these products require a lot of marketing muscle and resources to keep them afloat, not only does it result in their taking their eyes off innovation resulting in mediocre performance, but it also messes up the culture.

BERNARD MUNOS
is the founder of the InnoThink Center for Research in Biomedical Innovation. Previously, he served as advisor in corporate strategy at Eli Lilly focused on disruptive innovation and the radical redesign of the R&D model.

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Congress' Abdication Of Authority Of Medicare To The Executive

JOHN McMANUS The McManus Group

Six years after the enactment of the Affordable Care Act (ACA), policymakers are just beginning to appreciate a little-known provision that essentially outsources Congress' authority over Medicare to the executive branch. While the Republican Congress launched fusillade after fusillade against unpopular aspects of Obamacare — the individual mandate, death panels (aka the Independent Payment Advisory Board), illegal funding schemes to prop up the exchanges, and new healthcare taxes — a much more sinister power center was emerging.

The ACA established the Center for Medicare and Medicaid Innovation (CMMI) to "test" new delivery models intended to better coordinate care, improve outcomes, and contain costs. That *prima facie* description sounds reasonable enough, but Congress is now learning that the new agency can preempt, ignore, and override long-standing statutory provisions through nationwide "demonstrations" that Congress has little ability to alter or halt.

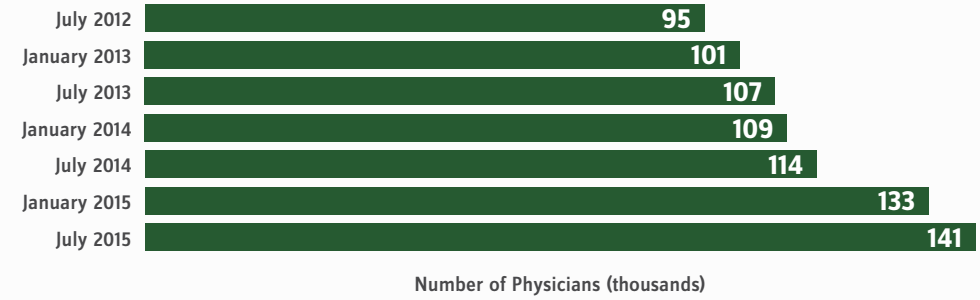
The ACA provided an astounding $10 billion a decade, forever, in automatic funding for the new agency. The administration acquired a building for the new agency a few miles down the road from the CMS suburban Baltimore headquarters. And for the first few years, the CMMI's rather academic staff toiled in relative obscurity, commissioning studies and RFPs to their ivory-tower colleagues, and initiated voluntary coordinated care demonstrations.

THE ACO FAILURE

Central to the Obama administration's CMMI efforts was creating and promoting accountable care organizations (ACOs) — mostly hospital-led providers tasked to better coordinate care and ostensibly control costs. By 2015, there were nearly 470 ACOs enrolled in either the Medicare Shared Savings Program or Pioneer ACO Program and serving nearly 8.9 million Medicare beneficiaries.

Establishment of these ACOs fueled provider consolidation by strengthening mega-hospital systems' leverage in negotiating buyouts of independent physician practices, ambulatory surgery centers, and other outpatient providers that served as alternative access points for patients and an important competitive counterbalance for the delivery of care. Physician practices

CHANGE IN EMPLOYMENT OF PHYSICIANS (Number of hospital-employed physicians)



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and other community providers were threatened with being frozen out of markets if they did not join up with dominant hospital systems embarking as an ACO. A September 2016 Avalere study found that between 2012 and 2015, hospitals acquired 31,000 physician practices, and the number of hospital-employed physicians increased by almost 50 percent.

But how did the ACOs fare in delivering higher quality and reducing costs? Poorly. In August, CMS released the 2015 financial and quality performance results and found that 48 percent of Medicare ACOs produced *no savings* and 69 percent did not produce enough savings, for bonuses in 2015. Moreover, the Medicare Shared Savings Program racked up a net loss of $216 million in 2015, after counting both bonuses and losses — not a huge number, but certainly nothing to make one think the CMMI will bend the cost curve in Medicare. A final dagger to the heart was the announced withdrawal of Dartmouth-Hitchcock from the ACO program, as Dartmouth researchers were key architects of the program.

REAL CMMI POWER REVEALED IN PART B DRUG DEMO

While this voluntary program appears to be a dud, the full scope of the CMMI's power came into view when it proposed a nationwide, compulsory five-year "demonstration project" regarding physician-administered drugs that would substantially cut reimbursement for expensive Part B drugs and later test "value-based purchasing" schemes, including reference pricing.

As stakeholders and Congress absorbed the implications of the proposal, it became crystal clear that this was unlike any Medicare demonstration project seen in the past — typically limited to several discrete geographical locations and populations and requiring explicit congressional approval before it could be implemented on a broader scale. The CMMI demonstration applied to *all* Part B products and *all* physicians and patients in three-quarters of the country. The ACA statute does not limit the scope of a CMMI demonstration in any way, and, in fact, it authorizes successful demonstrations to be expanded nationwide and made permanent without congressional assent. It also explicitly permits the CMMI to waive any statutory provision in Medicare, Medicaid, and associated fraud and abuse laws.

More than 300 patient and provider groups and a slew of bipartisan letters from hundreds of members of Congress objected to the far-reaching scope and substance of the demonstration. But we've now heard that the CMMI is determined to go forward with the proposal, though a final version has not yet been published. The CMMI statute denies stakeholders recourse in the administrative process or in the courts. Its proposals are protected from administrative and judicial review.

WHAT CAN CONGRESS DO?

Can't Congress legislatively alter or repeal a CMMI demonstration or the underlying authority provided to the CMMI? As it turns out, that will be most difficult.

In a seminal hearing in September, the House Budget Committee learned that the legislative branch's own budget analysts — the Congressional Budget Office (CBO) — were in the tank for the administration in regard to the CMMI's ability to save Medicare costs, notwithstanding the clear evidence of failure of ACOs, by far the largest demonstration undertaken by the agency. In fact, the CBO projects the CMMI will save a staggering $45 billion over the next 10 years, or a net $34-$35 billion over that time period. Based on what? The CBO witness could not explain to Chairman Price (R-GA), the methodology and formulas behind this gargantuan and baseless estimate.

But the CBO did make it clear that any provision that repeals, constrains, or otherwise hampers the CMMI's authority to test demonstrations would be assessed with a loss of savings. As Chairman Price stated, "This makes it virtually impossible for Congress to change policy and have it be seen as 'right' from a budgetary standpoint." If Congress blocked the Part B drug demonstration, that several-billion-dollar cost would have to be offset with a provision that cuts Medicare spending by an equal amount. However, nothing would prohibit the CMMI from issuing the identical or even more onerous demonstration with larger cuts applying to greater populations, immediately after Congress enacted the bill. As such, Congress has lost control over its own baseline and ability to oversee and manage the Medicare program.

The executive branch would be in full control because Congress would be required to cannibalize cherished programs and protections simply to preserve current policy that blocks the CMMI demonstrations, which override long-standing statutory law carefully negotiated by Congress — the people's representatives.

The end results of this are ominous indeed. The executive branch does not need congressional input and assent in making Medicare policy; the CMMI can do that on its own. Moreover, once issued by the CMMI, Congress has little ability to alter or halt that policy, no matter how pernicious.

Should we be more concerned with the constitutional abdication of power to the executive branch or the devious schemes being concocted on Medicare Part D and other sacred programs by leftists hoping to join a new Clinton administration? L

JOHN MCMANUS is president and founder of The McManus Group, a consulting firm specializing in strategic policy and political counsel and advocacy for healthcare clients with issues before Congress and the administration. Prior to founding his firm, McManus served Chairman Bill Thomas as the staff director of the Ways and Means Health Subcommittee, where he led the policy development, negotiations, and drafting of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Before working for Chairman Thomas, McManus worked for Eli Lilly & Company as a senior associate and for the Maryland House of Delegates as a research analyst. He earned his Master of Public Policy from Duke University and Bachelor of Arts from Washington and Lee University.

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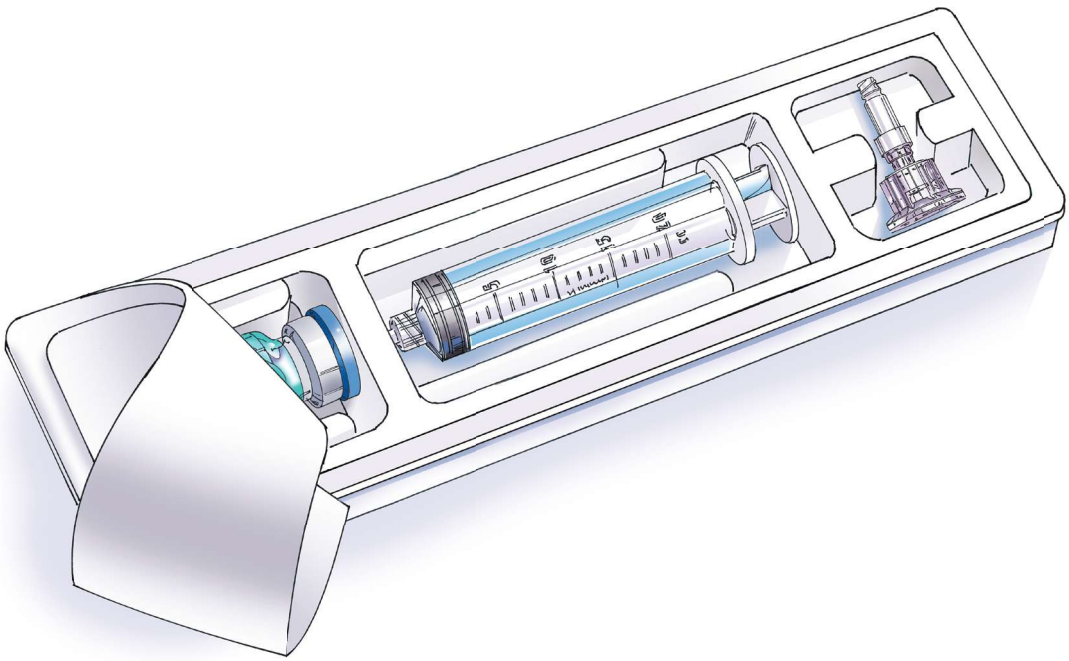

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WAYNE KOBERSTEIN Executive Editor
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SNAPSHOT

ViewPoint Therapeutics is an early-stage company in preclinical development with a small molecule, coded as VP1-001, for treating cataracts and presbyopia and investigating therapeutic applications for other conditions caused by protein misfolding, especially in the neurodegenerative disease area.

WHAT'S AT STAKE

Everything that folds can also misfold. Proteins present the best examples. The folded shape of a protein can unlock functions in living cells or give function to the protein itself. Thus, misfolding subverts the molecule's vital mission as a shape with meaning — often causing misfunction wherever it resides. Could a drug halt or reverse the error? That is the fundamental question that put ViewPoint in motion.

Dr. Leah Makley, president and CSO, founded ViewPoint based on five years of research she conducted in the lab of cofounder Dr. Jason Gestwicki, where all work is dedicated to protein misfolding, primarily in neurodegenerative diseases such as Alzheimer's. Makley wrote her graduate thesis on the neuro-associated protein alpha crystallin as a major component of the ocular lens.

"The lens of the eye contains a very high concentration of soluble proteins called crystallins, and the same protein molecules you're born with have to last for your entire lifetime," she says. "These proteins have to stay properly folded for the lens to be optically transparent. If they misfold, they aggregate, causing opacities that are clinically diagnosed as cataracts. Since these proteins are unusually long-lived, the lens is a really interesting system in which to study aging and protein folding."

It was also a project Makley always envisioned as having the potential for therapeutic applications. She had even discovered a possible small molecule drug candidate for cataracts. Finishing her thesis after transferring her work from the University of Michigan to UCSF, she and Dr. Gestwicki, who had also transferred his lab to UCSF, started up the company in 2014, and she still runs it, retaining the president and CSO titles but leaving the CEO slot unfilled for now.

As Makley observes, age-related cataracts are inevitable. "If we live long enough, we will all develop cataracts. Fifty percent of people over the age of 70 have cataracts, and these patients are currently only treatable by surgery. Cataract surgery is the most common surgery done in the United States, with a total cost to all payers of about $7 billion a year."

ViewPoint first developed a proprietary screening platform to identify small molecules that bind alpha crystallin and prevent and reverse its aggregation. It then formulated its lead compound as an eye drop and put it through preclinical tests on cataract mouse models, including age-related forms, successfully clearing the misfolded, aggregated protein and restoring transparency.

A scientist turned reluctant businessperson, Makley nevertheless exhibits plenty of confidence in her company and its future development. Yet she still cites scientific motivation for her business enthusiasm. "The science was compelling enough and the unmet need great enough that someone needed to translate this work out of the academic lab. It was important enough to me to make that happen, and the rest I have to figure out as I go along." Beyond the ocular area, she still has longer-term ambitions for the company's approach to stabilizing and restoring misfolded proteins in the neurodegenerative area.

No doubt about it — ViewPoint is early stage. It is so early stage, in fact, the likelihood of its success and the risk of failure are simply unknowable, and they will remain so for many years to come. But whatever the stage companies featured in this column have reached, they all share one thing in common — their fates still lie beyond the veil of the future. Their stories are unfinished. Their success is not assured. Therefore, representing the early development end of the continuum, ViewPoint is an ideal company to watch.

LEAH MAKLEY
President and CSO

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Biotechnology: The Hope For Rare Diseases

JOHN CROWLEY Chairman and CEO, Amicus Therapeutics

Nearly two years ago, the White House announced a major new precision medicine initiative, calling it a bold undertaking "to revolutionize how we improve health and treat disease." Earlier this year, during what was his last State of the Union address, President Barack Obama went one step further, announcing a "cancer moonshot," with the combined goals of accelerating research, getting more therapies to more patients, and improving the ability to detect and prevent various forms of the disease.

With both the precision medicine and the cancer moonshot initiatives in their relative infancy, I'm reminded that our industry – biotechnology – is itself relatively young. The first biotechs were founded in the '70s and '80s, born out of a need to find therapies and cures for diseases that had neither. Many of the great companies in biotech arose from the needs of a single family – a child, a parent, a loved one – saying, "We have a problem," followed by a scientist or physician responding, "I have an *idea*."

Nowadays, as biotechs grow through their early stages and begin to mature, partners arrive: venture capitalists, patient advocacy groups, or even other companies, helping not just to strengthen the foundations for a biotech company but also doing their part to advance research toward the development of a new therapy. Completing the cycle of drug development, from idea to molecule, through clinical studies to an approved medicine, is the rarest of feats that a biotech company can ever accomplish.

Indeed, the world of biotechnology is unique in that before we ever even get to common business issues like competition and pricing, we first have to have a technology that works. Translating a material, whether chemical or biological, into a medicine that is proven safe and effective in human beings has to occur before we can start the "blocking and tackling" common to the business world.

Biotechs in the rare disease space – which is the corner of biotechnology that I have lived and worked in for nearly two decades – face a particularly unique and fundamental challenge: Most of the 7,000+ known rare disorders sometimes affect no more than dozens to a few hundred or thousand people worldwide. The prevailing wisdom was once, and in some corners still is, "Why should I make a medicine that will benefit so few?"

Thankfully, this thinking is becoming more the exception than the rule. Perhaps it is the evolution of the internet and social media, where virtual support communities take root on Facebook, Twitter, and blogs, providing a community for those who once suffered from orphan diseases in isolation and raising public awareness along the way.

Or perhaps our recent advances in rare diseases reflect the growing role of parents like myself and my wife, Aileen. Our journey into the world of medicine began in 1998 with the diagnosis of our two youngest children, Megan and Patrick, with Pompe disease, a rare and then-fatal neuromuscular disorder. With that diagnosis, our family joined this battle against rare diseases. Our goal was to help to find a treatment and, hopefully someday, a cure for Pompe — making drug research very personal, indeed.

After the kids' diagnosis, we started a small biotech that played a role in the development of a first-generation enzyme replacement therapy for Pompe disease that saved our children's lives. Today, that journey continues at Amicus Therapeutics, where we focus on making new medicines in the fight against Pompe and other rare diseases.

The goal now is to end Pompe as we know it – and other rare diseases, as well.

That's why, to me and many of my contemporaries in biotech, the main question is no longer, "When will it be profitable?" Today, the question is, "What can I do to help improve someone's quality of life – or, perhaps, save it?" We believe that if we make great

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medicines that extend and enhance people's lives, that the creation of shareholder wealth will follow. Simply stated, make great medicines.

It helps when the leader of the free world supports initiatives like precision medicine. As it turns out, the treatment of rare diseases aligns perfectly with the goals of precision medicine, in that treating one rare disease may lead to treatments for any number of mutations for that disease. In our line of work, the words "precision medicine" are not just buzzworthy – they are a genuine approach to diagnosing and treating some of the world's deadliest diseases.

In my more than 18 years in this journey through rare disease drug development and biotechnology, I've met many doctors, scientists, and entrepreneurs whom I consider true pioneers and heroes. Their methods vary, but for the most part each person has subscribed to, and followed, these core beliefs and principles:

1. **THEY'VE SET A VISION.** Our industry is less than 40 years old, which means it doesn't have the centuries-long foundation that other business sectors have. This is where Big Biotech diverges greatly from Big Pharma. The ones that have succeeded have put aside concerns, like whether the prospective patient population might be an N=1 (a drastic example to be sure) and have set their sights instead on saving as many lives as possible by ensuring the greatest access possible.

2. **THEY TOOK RISKS – SMART RISKS.** Biotech, by its very nature, is all about risk taking – developing a therapy that would help a few dozen or a few hundred people at most was once seen as anathema. In the early days of biotech, very few companies paid attention to rare and orphan diseases. But without Genzyme, there wouldn't be a BioMarin. Or a Shire. Or an Amicus. As our industry's pioneers took the leap, and took smart risks, we showed others the way forward – for instance, the angel investors who have helped biotech grow and evolve.

3. **THEY PERSISTED ...** Many times within our industry, you'll hear of companies that are just one step away from insolvency. Some – or most – ride out years, even decades of not being profitable. In the past, I've told the story of a retired biotech pioneer who once candidly confided in me that his stock was "stuck at two bucks a share for more than a decade." I was struck by what he said at first – was that supposed to inspire me, or prepare me? – but then he added words I will never forget: "If you believe in the science," he said, "then push it as far as you can." That pioneer was Dr. Sol Barer, Celgene's founder.

4. **... AND THEY STAYED HONEST.** One day back in 2009, my colleagues and I had to present data from a failed early-stage clinical study to our investors. The market reaction was quite negative. But we were entirely transparent in what we shared. Later that day, one of our largest shareholders called, not to berate us for a failed study but to congratulate us for pushing the science and, most importantly, for being honest in the results. The words from that investor stayed with me and guide our business today: *Always be honest.* Don't whitewash the truth. Share the data, learn from your mistakes, and make improvements from there. Above everything, it's OK to say something doesn't work. In fact, almost everything we try in clinical studies, especially in early ones, does not work. That's OK. Learn, and move on.

5. **THEY TOOK ON THE PATIENT'S PERSPECTIVE.** I once had the privilege of hearing a man speak about the importance of medical research and developing therapies for conditions rare and common. He was a quadriplegic, having suffered a severe spinal injury that left him paralyzed. Regarding a cure for his condition, he was candid and blunt: "Maybe it won't come in time for me," he said. "But it gives me hope that it will eventually be in time for somebody." That man was Christopher Reeve, and his words gave me a new perspective on our collective roles in biotech. For me, the reason I got into this line of work was to help find a cure for my children. But at that moment, I thought of the cases that were yet to come. Yes, we develop technologies and drugs for those currently affected. But we are also doing it for those whom disease, rare or not, has not yet touched. We provide hope for those who don't even know that they need hope.

Biotech helped save my children's lives. It has given them time and quality of life. And it has given to us as biotech entrepreneurs time to come up with even better and more advanced technologies to treat diseases like Pompe. The treatments are important steps now in aiding us to move from early "treatments" to "cures."

While this journey began as the most personal of missions for two very special children, it continues with the hopes of millions who suffer from rare and orphan diseases. At its root, biotechnology is just a great big word that for so many people simply means "hope."

Even where the N=1. L

JOHN CROWLEY is the chairman and CEO of Amicus Therapeutics, a biotechnology company developing therapies for rare and orphan diseases. He also serves as the national chairman of the Make-A-Wish Foundation of America.

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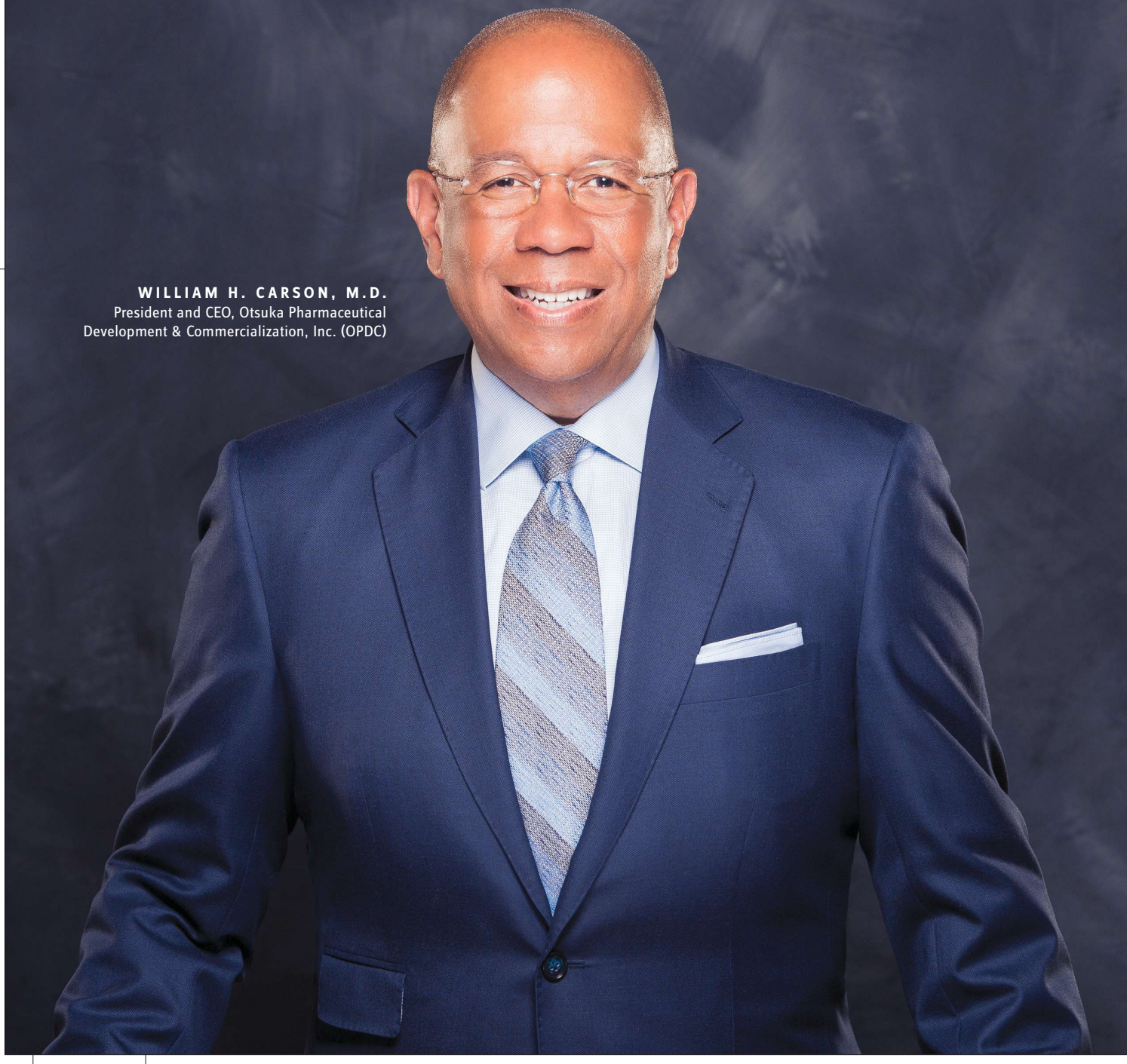
Why OTSUKA DIVERSIFIED Into Digital Health

ROB WRIGHT Chief Editor @RFWrightLSL



WILLIAM H. CARSON, M.D.
President and CEO, Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)

What does a Florida judge receiving the highest judicial honor given by the U.S. Supreme Court have to do with a Japanese pharmaceutical company? The correlation is there; you just need to understand the backstory, which is why we spoke with a top executive from that pharma company — William H. Carson, M.D., president and CEO of Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC).

Otsuka Pharmaceutical Co., Ltd. (Otsuka), the parent company of OPDC, made headlines this summer when it entered into a joint venture with IBM to create Otsuka Digital Health Co., Ltd. a stand-alone business (based in Japan) that develops and markets specialized software for analyzing psychiatric patient data. But, as Carson explains, a U.S.-based ODH, Inc. already had been founded in 2015 after three years of piloting the software solution. "ODH was the brainchild of Taro Iwamoto [who served as president of Otsuka from 2008 until his untimely passing in 2015]," Carson says. "Prior to the pilot, he was invited to IBM, where he was shown what would eventually become the question-answering computer system known as Watson. He then toured the New York City Police Department and saw how they were using IBM data analytics solutions to help make the city safer. After that, everything changed organizationally for us. The question became, 'How are we going to add data analytics into everything we do?'"

A WHOLE NEW MINDSET

Carson, who as the board chair for U.S.-based ODH, Inc., has responsibility for Otsuka's U.S. digital health initiatives, admits that one of the biggest challenges in building the original digital health system was answering the question that many employees were asking: "How does this relate to our pharmaceutical business?" Carson explains, "We had to consistently remind employees that the mission of Otsuka isn't to

A Judge And A Pharma Company Team Up

When Steven Leifman was appointed judge (1995) to the Eleventh Judicial Circuit, he became gatekeeper to Florida's largest de facto psychiatric facility — the Miami-Dade County Jail. But rather than continue business as usual, Judge Leifman decided to take a different approach toward how society (at least within his county) deals with people suffering from serious mental illness (SMI). In 2000, Leifman created the Eleventh Judicial Circuit Criminal Mental Health Project, a program that directs the mentally ill who committed low-level offenses away from incarceration and toward community-based care. For his efforts (which included the implementation of an advanced-care mental health technology developed collaboratively by Otsuka Pharmaceutical and IBM), in 2015, Judge Leifman became the recipient of the William H. Rehnquist Award for Judicial Excellence — one of the United States' highest judicial honors presented by the Chief Justice of the U.S.

But more impressive than his individual recognition are the Criminal Mental Health Project's results. As of July 2016, the recidivism rate for people who successfully complete the program after being charged with a felony was around 6 percent. Compare this statistic to national recidivism numbers that state that, within three years of being released from prison, nearly 68 percent of prisoners are rearrested. But perhaps the most telling statistic is that of those rearrested prisoners, more than 56 percent were arrested by the end of the first year. Leifman's prescription for helping the mentally ill is similar to one of his collaborative partners, Otsuka Pharmaceutical. According to William H. Carson, M.D., president and CEO of Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC), the mission of the company to improve human health expands beyond the making of pills.

be a pill company, but to create new products for better health worldwide. We had to build a new mindset that the digital health system we were developing had little or no relationship to our existing business."

When they were initially thinking about how to build the digital health system, Carson remembers having a conversation with Iwamoto that crystallized the paradigm shift of such an endeavor. "I was sharing with him a problem I was currently facing, and he said, 'I was just talking to Chairman Akihiko Otsuka, and we were discussing what the company might look like 300 years from now.'" Carson found this forward-looking notion to be somewhat analogous to the process of creating a new digital health system — figuring out how to turn Otsuka into something else without having 100 percent clarity on what that something else was, or even where it might fit into the overall business.

During another discussion early in the planning stages of developing the digital health system, the two men found themselves debating whether or not people needed titles. Iwamoto said that he didn't want an organization with titles because he was more interested in what a person knows, and if they were the right one for the task at hand. Carson says this became part of the model for building ODH. "Once we identified a person within Otsuka who was a good fit for a new job, we would go in and pluck them from what they were working on and give them a new opportunity," he states. "It is difficult to provide a road map for our approach because the process would require a company to first adopt this kind of diversity-of-thought culture."

To build a new digital health system, though, they needed external expertise — beyond that of IBM — for developing the new solution. That meant forging relationships with companies, groups, and individuals that had strong competencies in psychiatric treatment.

Enter Florida Judge Steven Leifman, who essentially was the gatekeeper to Florida's largest psychiatric facility — the Miami-Dade County Jail (see sidebar). "After establishing relationships with folks like Judge Leifman and with groups like the South Florida Behavioral Health Network, we better understood where we wanted to land and what it was we wanted a digital health system to do," Carson says. The first digital health system became operational in about 18 months.

THE POTENTIAL IMPACT OF A NON-PILL INITIATIVE

Today, ODH, Inc. is a business that is further developing the digital health system, with a five-member board and a leadership team. Headed up by Michael Jarjour, president and CEO, the company has grown to include 40 full-time employees and contractors and is focused on transforming the management of behavioral health by leveraging advanced technology and

Are Digital Medicines The Future Of Pharma?

In September 2015, Otsuka became the first pharma company to submit a digital medicine new drug application (NDA) to the FDA. A drug/device product, the digital medicine combined Otsuka's ABILIFY (aripiprazole) with a Proteus ingestible sensor. Taken as a single tablet, the product can digitally record ingestions and, with patient consent, share information (e.g., physiological responses) with healthcare professionals and caregivers. One of the problems often encountered with patients suffering from mental illness is adherence. Even in developed countries, about half of all chronic disease patients do not take their medications as prescribed. In the United States, poor compliance results in an estimated $100 to $300 billion avoidable healthcare expense. It is theorized that digital medicines (such as that developed by Otsuka and Proteus) might be able to improve medication adherence, help physicians make better-informed decisions, and tailor treatments to best meet patient needs. In April 2016, Otsuka and Proteus announced that the FDA had issued a complete response letter (CRL) requesting additional information. And while Otsuka might not have received the response for which it had been hoping, being the first company ever to submit a digital medicine for FDA consideration is (in and of itself) a milestone.

Editor's Note: *I would have been surprised if Otsuka had received approval from the FDA on its very first attempt. After all, Otsuka's digital medicine submission provided the regulatory body its first opportunity (ever) to review a digital medicine for regulatory approval. Since the FDA had never seen a digital medicine previously, it seems reasonable to expect a conservative approach when it comes to a first-time regulatory review.*

clinical expertise. ODH, Inc.'s first product, Mentrics, aggregates healthcare data from multiple sources and uses advanced analytics to assign a behavioral and physical health risk score for each member, thereby providing immediate actionable insights that alert care coordinators to treatment gaps or inconsistencies.

"One of ODH, Inc.'s first clients was the South Florida Behavioral Health Network, an organization for which Judge Leifman serves as board chair," Carson affirms. "That was where Otsuka first developed its digital health system."

Described as an ongoing community-based project, the pilot marked the first application of an Otsuka/IBM-developed solution. The technology platform, called Mentrics, combines IBM software and various data management tools with Otsuka's mental health expertise for risk stratification and predictive modeling, and is geared toward improving:

- Mental health system utilization management, including eligibility, enrollment, and consent
- Care coordination across clinical and social programs settings
- Insights into patient risk factors, crisis onset, crisis patterns, and costs
- Patient engagement in care management plans
- Organizational change management support

Since the initial pilot, the company has targeted additional opportunities. For example, this past June, ODH, Inc. joined forces with The White House Data-Driven-Justice (DDJ) initiative — a national effort to reduce the number of mentally ill persons in jail. A 67-member coalition of city, county, and state governments, the DDJ initiative represents a significant commitment to more broadly utilize the ODH, Inc.-Mentrics platform in an effort to keep low-level offenders with mental illnesses out of the criminal justice system.

What kind of impact could an initiative like ODH have? Consider this: It is estimated that more than 11 million American adults have debilitating mental illnesses, for which the U.S. spends about $150

billion annually for treatment. Unfortunately, that cost is just the tip of the SMI (serious mental illness) iceberg. Because the mentally ill are at a higher risk of poverty, they have greater need for other public safety-net services (e.g., food stamps, subsidized housing), which adds another $160 billion to the U.S. tax payer's annual bill. When you factor in other societal costs, such as annual lost earnings of this population (i.e., $200 billion), you suddenly realize how Otsuka's non-pill initiative has the potential to significantly improve upon a half-trillion-dollar problem. L

EDITOR'S NOTE: ODH, Inc. is a wholly owned subsidiary of the U.S. holding company, Otsuka America, Inc. (OAI). Further, the U.S.-based ODH, Inc. is a completely separate company and not affiliated with the announced Japanese joint venture between Otsuka Digital Health and IBM.

Otsuka Says No More RFPs For CROs

The fact that Otsuka Pharmaceutical's U.S. development group completely outsources its clinical development model doesn't make it unique. However, William H. Carson, M.D., president and CEO of Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC), believes the company's CRO (Contract Research Organization) selection process does differ from those of many other pharma companies.

"When we began refining how we wanted to partner with CROs, we first looked to get input from consultants that had experience working outside of the biopharmaceutical space, such as the aviation industry," Carson says. Why? Consider a 737, Boeing's smallest and most popular commercial jet. To build just one of these $50 million aircraft requires a complex web involving hundreds of suppliers. Now imagine if every time Boeing was interested in building a new 737, it required its suppliers to rebid for the work. While such a process might reduce costs, would it improve efficiency? "We were interested in adapting the aviation industry's outsourcing model for how we wanted to work with CROs as trusted partners," he shares. "This is why we selected Customized Improvement Strategies [CIS] as the consultancy to help us." In addition to a wealth of biopharmaceutical industry experience, CIS had team members who had worked with companies such as Boeing, Bell Helicopter, Lockheed Martin, and McDonnell Douglas. One of the first things CIS helped with was to get away from the typical RFP (Request for Proposal). "Doing RFPs for every project can be very time-consuming," Carson confirms. "We wanted to partner in a way that allowed us to be very nimble and agile so that we could get started much more quickly when projects came along."

To achieve that speed, Otsuka developed a CRO selection questionnaire. Because this wasn't the standard approach CROs were used to (i.e., come in and pitch what they're going to do), some didn't know how to respond. For example, one of the biggest CROs actually didn't answer the questions, so Otsuka didn't include them in the review process. According to Carson, people at the CRO were shocked not to have been included. "We were very specific in asking them to answer the questions, which we would then score," he states. "Based on the scores you either moved on to the next level or you didn't. Apparently they didn't believe this was the process and had planned on giving us the standard pitch."

Carson confesses that the CRO questionnaire process was very time-consuming initially. However, the Otsuka team felt that in the long run it would be much more efficient than the typical RFP process. "It was very satisfying to get to a place where we have special relationships with our CRO partners," he contends. The initial process began with 11 CRO candidates, which were eventually narrowed down to one. "Our first partner was Covance, which we worked closely with for years," he shares. "Over time, we expanded our business and needed to add other CRO partners, which today include Quintiles and INC."

The CRO selection process, which began at Otsuka in the United States, has since been globalized for the entire company. "The Japanese word we use to describe part of our culture is Jissho-Shugi, which basically means proof through execution," Carson concludes. "If you say what you are going to do, do it, and then you will be given more responsibility. It's a really strong principle as far as the Otsuka organization is concerned, and we expect similar accountability with our strategic partners."

THE NUTS AND BOLTS OF OTSUKA'S CRO QUESTIONNAIRE

The CRO questionnaire developed by Otsuka Pharmaceutical Development & Commercialization, Inc. consists of 18 pages. Obviously, given this length and the fact that it includes proprietary information, we aren't able to publish the document in its entirety. However, we would like to give you a feel for what is included should you, too, be interested in moving away from the revolving-door-CRO RFP process.

The Otsuka CRO questionnaire has the following eight sections with weights in parentheses for scoring and selection purposes:

Section 1: Contact Information

Section 2: Organizational Capabilities (10%)

Section 3: Leadership, Governance & Management (20%)

Section 4: Customer Focus & Strategic Planning (15%)

Section 5: Measurement, Analysis & IT (10%)

Section 6: Workforce Focus (15%)

Section 7: Process & Supplier Management (15%)

Section 8: Results (15%)

Below is a sampling of the types of questions included in the questionnaire.

1. Describe the key factors that your company has determined are drivers of competitive success.
2. How do your senior leaders communicate and promote values that encourage ethical, customer-focused behavior?
3. What would the ideal planning and feedback system look like?
4. How do you assess risk to projects and programs?
5. How do you assure the integrity, validity, and timeliness of your data?
6. How do you foster an organizational culture conducive to high performance and a motivated workforce?
7. Describe your project management process and approach.
8. Customer service outcomes: What are your organization's key customer satisfaction results? Please provide both current data and 3- to 5-year trends for such items as customer satisfaction, repeat business, etc.

Otsuka notes that the CRO questionnaire was distributed several years ago in paper format. In addition, the company says the questions were structured and scored in a variety of ways. Should your company be interested in taking a similar outsourced partner selection approach, Carson advises the following. "Be thorough in clearly stating what your purpose or reasons are for wanting to develop such relationships, think through what the qualities of a real partner would be in all facets of the operation (staffing, budgeting, planning, reporting, etc.), and involve all your internal stakeholders in designing questions that address each one of those facets."

ARE YOU READY TO FUND YOUR LIFE SCIENCES STARTUP?

ROB WRIGHT Chief Editor @RFWrightLSL

If you have an idea for a life sciences product geared toward meeting an unmet medical need, you have probably given a lot of thought as to what makes it special, as well as why insurance companies should be willing to pay for it. But no matter how differentiated or breakthrough your innovation might be, if you haven't considered how to finance your vision, it likely won't ever see the light of day.

Not long ago I attended an invitation-only event for CEOs of medtech and biopharmaceutical startups, which included a venture capital educational session. Conducted in a Q&A format, the panel consisted of four life science financial experts (i.e., Aftab Kherani, M.D., Aisling Capital; Axel Bolte, HBM Partners; Chau Khuong, OrbiMed; and Scott Weiner, Pappas Ventures). If you think your startup is ready to be funded but want to minimize the likelihood of making costly mistakes, be sure to take into account the following wisdom from these experienced venture capitalists.

What Kinds Of Biopharma Companies Interest Your Organization?

CHAU KHUONG, ORBIMED: For early-stage investing (i.e., working with scientific founders and academic entrepreneurs), one of our first screens is the quality of science and data. Our firm invests very early when the science and data make sense. While we will also invest in late-stage opportunities and pretty much everything in between, most of our companies are either in the clinic or about 18 months away from entering. If a company is more than 18 months away from clinical trials, we tend to look for a scientific area we find interesting (e.g., gene editing). For example, we have an early-stage investment with a company called Intellia Therapeutics. While we invested in Intellia because we believe its technology platform has potential, we also felt the company had a clear path for getting its therapeutic into man. Though there isn't a therapeutic area in which we haven't invested, because we are data-driven, the bar may be a little higher in some less-understood therapeutic areas. With medical devices, we tend to take a longer-term view and look to fund companies that can create the most value from approval to commercialization.

AXEL BOLTE, HBM PARTNERS: For us the management has to be fantastic, and the science has to be interesting. To find a good investment, we try to look for unique situations. For example, we worked with OrbiMed to bring an Austria-based company, Nabriva Therapeutics (NASDAQ: NBRV), to the King of Prussia (PA) area. We invested in a company that had no institutional shareholders but just Italian families. On the surface this might sound a little scary, but the result was Advanced Accelerator Applications moving to the states, being listed publicly (NASDAQ: AAAP), and becoming a billion-dollar company. We seek companies that look more like businesses.

Aisling Capital

"Our firm is basically the continuation of the Perseus-Soros Biopharmaceutical Fund," says Aftab Kherani, M.D., partner at Aisling Capital. "Since 2000, we have raised over $1.8 billion in committed capital across funds. While we are broad life science investors, we do more therapeutic investing than any other type. We still do devices, diagnostics, and some services (e.g., CROs and CMOs) and have a preference for late-stage companies."

Founded: 2000

Number Of Employees: 19

Location: New York

Website: www.aislingcapital.com

For general inquiries, contact Aisling at 212-651-6380.

AFTAB KHERANI, M.D.
Partner

Though early academic startups aren't the right group for us, we do enjoy giving them a look once their series A is through and we can join a syndicate.

AFTAB KHERANI, AISLING CAPITAL: Where we have the most conviction to actually write a check is with private companies and when we might have a shot at being the last private capital to enter. We understand we might be leaving some money on the table, but just given our risk-reward mandate, that's where we are most comfortable. While we do characterize ourselves as late-stage investors, it is important to note that late-stage for one therapeutic area could be completely different from late-stage for another. For example, we were involved in funding Loxo Oncology and were working with OrbiMed. We did a $33 million series A, and in a few months, we had inbound interest to basically do a crossover round. Nine months later Loxo went public. Late-stage in pain would probably be something much further along in clinical development or possibly even commercial. For devices, right now it'd probably be tough for us to do something that was pre-approved, similar to diagnostics. Our approach is to try to do all of our investing out of a fund, because we feel doing so helps us be nimble and capture the occasional inefficiency. For example, the one royalty investment [a category of private equity funding specializing in the purchase of consistent revenue streams derived from royalty payments] that we have done was with the compound ibrutinib. It was preapproved at the time, and we thought that led to a bit of inefficiency in the pricing, which was syndicated with two other groups. This is very similar to how we view some of the opportunities on the public markets as well. Suffice it to say, when it comes to private companies, we are nuanced in how we view late-stage, and this is dependent on therapeutic area.

SCOTT WEINER, PAPPAS VENTURES: Our firm invests in both preclinical and clinical stage biotech companies with a goal of funding through Phase 2 proof-of-concept (PoC) results. On the device and diagnostics side, we tend to lean toward later-stage opportunities. This is because on the device side we don't want to take engineering risk, and on the diagnostic side we prefer not taking precommercial risk. We know someone on the team at about 70 percent of the companies in which we invest. Perhaps we met them when they were just starting out, and it wasn't the right fit at the time. But as they've matured and hit some milestones, we've become more interested and ended up joining an investment syndicate. We really like to get to know the teams in which we are going to invest, as well as the other investors. As a company builds its investment syndicate, it is important to make sure the investors are as much aligned with each other as they are with the company's strategy. We also start two companies or so per fund cycle, and that is usually licensing IP and starting something from scratch or licensing an asset from pharma or academia.

Given The Recent Slowdown In The IPO Market, What Are Some Of The More Innovative Ways Companies Are Raising Money?

KHERANI: Right now, I could probably count on one hand the number of groups willing to write a check greater than $10 million for a preapproved medtech. For quality companies, there is still interest; it's just a little harder to go public right now. However, there will be opportunities in the follow-on environment [i.e., stock that is issued after a company has already IPO-ed]. That being said, some companies, even those that have had success, will have to get accustomed to the idea that the next follow-on financing might be done at a discount. There is a speculative nature to what we do, as our companies aren't typically valued on a multiple of cash flow. While it is great when Morgan Stanley, JP Morgan, and Goldman are fighting to take your company public, sometimes, given the investment environment, you have to play in a "less elegant" part of the finance swimming pool (e.g., Form 10s and reverse mergers), and these approaches work more often than not. (Editor's Note: For more on Form 10s and reverse mergers be sure to read my blog — *Beyond IPOs: Alternative Funding Options For Biotech*

Startups). In our view, these more-creative approaches can sometimes be a better path than doing the series F and getting the seventh VC on board.

KHUONG: It is hard to imagine the recent IPO market, the best in our industry's history, would have been sustainable without a blip. And while the market has come down, there are still IPOs happening. During times like these, strong clinical data is still appreciated by the market, as are certain technology platforms (e.g., gene editing) that open up newer ways to address diseases than traditional small molecules or other therapeutic modalities. In the public market where clinical data didn't work out and companies with cash end up being public shells, a reverse merger could be ideal. One of our companies, Pieris Pharmaceuticals, was in a situation where the venture investors in Europe were basically tapped out, and the company could no longer raise venture money. It went public through a reverse merger in December 2014, raising about $15 million. Though a very small market cap company, it got uplisted to the NASDAQ, raised another $30 million last year, and just recently closed on about $16 million as a public company. It is important to remain creative, as there are ways to access the public markets, even if the traditional IPO route is not there.

Where Do You See The Next Hot Therapeutic/Technology Platform Investment Opportunity?

BOLTE: Oncology will remain an extremely important area of investment, in particular for smaller companies such as the ones that we can finance as VCs and small-cap publics. While I cannot predict which specific areas will become hot, we currently have interest in immuno-oncology (IO) and cell therapies. As always though, these companies have to show that they can actually deliver. For the most part, the immuno-oncology market (i.e., checkpoint inhibitors) seems to be in the hands of large pharma. That being said, I could see more traditional oncology treatments (e.g., kinase inhibition) coming back into favor with investors. A good similar example could be drawn from antibiotics, which were a bit sleepy for a while. But with the rise of superbugs and government-supported initiatives such as the GAIN Act, we saw companies like Cempra really take off. Another thing to think about is the recent IPO market that saw about 200 companies go public during the past five years. Most of these companies will eventually run out of money and need to raise more. While that could be a good opportunity to invest, keep in mind that biotech attrition means that only 10 to 15 percent of these will end up being successful. The unfortunate reality is that a lot of these companies will have negative events, and you can actually see a wave of that starting to happen.

WEINER: The way we view opportunities as being either "hot or not" really is dependent upon the strength of the science. As science gets better, we have an improved understanding of mechanisms of action and more appropriate patient selection, which can de-risk clinical development. The spaces we currently view as being hot and where we are seeking risk-mitigated opportunities are those moving away from developing treatments and toward development of curative therapies. While cures may come with cell therapy, gene editing, or immuno-oncology, it is still very early days. When you consider that 40 percent

HBM Partners

"We are a healthcare-focused investor company with about $1.5 billion under management," states Axel Bolte, investment advisor at HBM Partners "We invest in biopharmaceuticals, devices, and diagnostics, and tend to be fairly agnostic when it comes to what therapeutic areas to invest in or what type of investment vehicle to use. However, we lean more toward later-stage and public-industry investing."

Founded: 2001

Number Of Employees: Approximately 21

Location: Zug, Switzerland

Most Recent Success Story: Advanced Accelerator Applications (NASDAQ: AAAP) is a $1.2 billion market cap company. HBM led the first institutional financing round for AAAP in 2013.

Website: www.hbmpartners.com

For general inquiries, contact HBM at +41-43-888-7171.

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"We are a global firm managing about $14 billion," says Chau Khuong, private equity partner at OrbiMed. "About two-thirds of our venture investments target biopharma companies, while the remaining one-third is focused on medical device, diagnostics, and digital health. We are active at every stage of investing – from startups that we can incubate inside our firm up through growth-equity – and in our public equity funds we invest all the way up to Big Pharma companies."

Founded: 1989

Number Of Employees: Over 100

Locations: New York, San Francisco, Shanghai (China), Mumbai (India), and Herzliya (Israel).

Most Recent Success Story: Acerta Pharma acquired by AstraZeneca in December 2015 for up-front and near-term payments of $4 billion and up to $3 billion in milestones.

Website: www.orbimed.com

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CHAU KHUONG
Private equity partner

of public biotechs are in the oncology space, one can presume that if going public is a goal, being in oncology can increase your chances. Although oncology has been a great space for us, we're still a little cautious unless we see a very specific indication and have a good sense of what the standard of care is. As early-stage investors, we have to be prudent with our approach. As such, we don't necessarily look for what is hot, but what we think will differentiate itself in the market and then return capital to the investors.

With Regard To Oncology Startups, Has The Investment Community Pivoted Too Far Toward Combination Therapies, And Is It Time To Scale Back?

WEINER: Depends on the opportunity. For us, it's more important to know that a company understands what the development path could be as opposed to whether or not you have a checkpoint inhibitor or need to run a combination trial. We want to have a good sense of what the path is, if that path makes sense, and how that path could change in the next few years based on evolving standards of care. If a company can articulate that, and we can validate it with oncologists in our network, then we're more open-minded and willing to invest in oncology companies. While we have always pursued investing in novel targets, it doesn't necessarily have to be the latest immuno-oncology mechanism. One of our biggest wins in oncology was a company called Plexxikon, which developed one of the first selective BRAF inhibitors.

KHUONG: Though we are very cautious right now about investing too much in oncology, the reality is that for this year four out of seven investments have been in oncology. What we are looking for are different mechanisms and targets beyond just immuno-oncology checkpoint inhibitors. While oncolytic viruses have been around for a long time, the current data is quite interesting, making this area ripe for revisiting.

KHERANI: It's easy to say oncology might be a fad, but I would disagree. In the past decade, treatments like ibrutinib, PD-1, PDL-1, CTLA-4, and even things like crizotinib should not be considered small advances. While there are regimens that have historically worked really well (e.g., the Stanford V for Hodgkin's), the reality is that for the most part, when treating cancer patients, we have been giving treatments that make them feel awful. As we better understand what drives cancer, we have improved our ability to target those drivers. As such, the challenge is shifting to finding patients who have those driver mutations or might be amenable to IO therapy. This shift is going to create interesting opportunities on the diagnostics side. The two areas in oncology where we've spent the most time are with companies working on therapeutics to treat those driver mutations and diagnostic companies developing technologies that can discern who has those driver mutations.

What Is Your Opinion On Going Public Via IPO Or Being Acquired As An Exit Strategy?

WEINER: You can't predict whether companies can go public or will become acquired. The benefit of having one our companies acquired is that we get the cash up front and don't have to worry about the challenges and fluctuations of the stock market. But companies are not sold, they are bought, and as such we are always careful to make sure companies never put up a "For Sale" sign. When the IPO window is open, if our companies can get out, great, but we tend to view these as financing events and not necessarily exits. It is important to note that public companies have a lot

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more flexibility in terms of capital raising and using their stock as collateral. That being said, we have had companies confidentially file for an IPO and get acquired right before they were ready to flip.

How Do You Pick Compounds That You Think Are Going To Make It, And How Do You Measure Your Level Of Success?

BOLTE: The ultimate test is your returns, and our investors measure these very carefully. There are companies that don't make the returns and are still successful; it just depends on the cycle of the markets. Despite a lot of due diligence, it is very difficult to achieve certainty when trying to pick which compounds might make it. As such, it is better to be able to look at a portfolio of compounds, because a single investment on a single compound can make or break even the largest of companies.

KHUONG: As investors we are judged by our returns, but that is just one metric. You can go back and see how many OrbiMed portfolio companies have developed drugs or devices that ultimately got to a point of approval. We recently did this for our portfolio of companies and found that our venture dollars supported FDA approval for over 40 drugs, and it was approximately half that number for devices.

KHERANI: Approvals are terrific, but all we are really judged on is a quarterly report card. In our experience, limited partners have gotten savvier and savvier in terms of really focusing in on performance and grading us four times a year.

WEINER: As we are earlier-stage investors, we know that things aren't always going to work, and that's OK. If nothing ever failed, then we probably haven't taken appropriate investment risks. When something fails, we try to understand why. If we got the science wrong, and that was something that couldn't be predicted, so be it. But if something failed because we didn't design the trial right, or we have a management team issue, then shame on us. There are certain risks in early-stage investing that sometimes can't be avoided. Risk mitigation combined with appropriate diversification has allowed us to achieve good returns.

KHUONG: Building on that — we try to avoid getting zeroes in our portfolio (i.e., a company fails, and there's nothing left). We mitigate that with other assets. So, if it's a company that has a platform technology, then you've got a couple of different ways to achieve success. In other cases where we've had clinical failures, we've pivoted the companies by bringing in other assets. For example, Receptos was a company where the initial technology failed, but we brought in a great management team with assets from another company, and it ended up becoming a big success. So, another way to measure success as an investor is to look at how we navigate through challenges.

WEINER: Agreed. There is a decent percent of our portfolio that have exited based on an indication that wasn't part of the original investment thesis. You do have to have flexibility and great management to recognize an opportunity to bring something in-house or elevate a secondary program to become a primary program. It is important to keep in mind that it is not always your lead program that will drive your ultimate success.

Pappas Ventures

"We are a North Carolina-based life science-focused venture capital firm that invests in therapeutics, devices, and diagnostics across the U.S. and Canada," states Scott Weiner, partner at Pappas Ventures. "We are therapeutic-agnostic, early- to mid-stage investors that evaluate more than 700 investment opportunities annually. We have raised more than $350 million in capital across multiple funds, with about a third of our companies having either completed IPOs or been successfully acquired."

Founded: 1994

Number Of Employees: 10

Location: Durham, NC

Most Recent Success Story: Pappas-founded Afferent Pharmaceuticals acquired by Merck in June 2016 for $500 million, plus up to $750 million in milestone payments.

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STAN ERCK
President and CEO of Novavax

THE ENTERPRISERS

Life Science Leadership In Action

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

NOVAVAX: Scouting Past the Long Trail to Market

PRESS-TIME THUNDER

Based on long-term discussions with Novavax, as well as close observations over several years, this article had been completed when, suddenly, a clinical lightning bolt struck the company. Novavax announced results of its Phase 3 RSV F vaccine trial for older adults that were far worse than the most pessimistic forecasts before the announcement. The trial failed to show efficacy in either the primary endpoint, prevention of moderate-severe RSV-associated lower respiratory tract disease, or the secondary endpoint, reducing the incidence of all symptomatic respiratory disease due to RSV. In perhaps the most dramatic demonstration of the trial failure, the company itself voiced surprise and disappointment at the results, possibly the worst for any vaccine in history. Obviously, the failure calls to question the basic focus and platform of the company and also the central premise of this article – that there is more to the company than this one trial. In fact, this single trial may be damaging enough to determine the fate of Novavax as a business entity – one I still believe has shown remarkable enterprise in a field even tougher than it imagined. The results will also make many of the hopeful plans and positions stated in this article ring hollow, or, at the least, poignant. It is humbling to admit that one day's event can indeed bring a different end (or turn?) to a long journey. Thus, we present the article here mostly as it was before the Phase 3 announcement, leaving its entrepreneurial narrative in the hard, but real, context of the press-time news.

PUBLIC COMPANY (NASDAQ, NVAX)

MARKET CAP: $2.11B (7Sep16); $352M (15Sep16)

STARTUP DATE: 1987

FOCUS: First new platforms, then new vaccines, with its lead candidate now in Phase 3 for RSV

Clinical challenges lurk all along the pathway for any company developing new vaccine candidates and technology — and that goes at least twice for Novavax. As we go to press with this, the company is dealing with an anxious investment community about the "failed" Phase 3 trial of its RSV F vaccine in older adults, for protection against respiratory syncytial virus (RSV). (See "Press-Time Thunder.") To outside observers, the trial's outcome may seem only binary, make or break. But for those who work inside Novavax or study it in greater depth, the picture is much larger and the story much richer. It is bound to be, for the company has taken an especially long and winding path, hopefully the path to innovative vaccines.

This is not the first time The Enterprisers has featured a vaccine developer (see the most recent, Codagenix, November 2015). The vaccine field is tough enough to require extraordinarily creative and tenacious enterprise by any company that enters it. Foresight — the ability to look all the way down the path and adjust development plans for the vagaries of the commercial environment — is particularly essential.

Novavax started up in Sweden almost 30 years ago, and since then it has gone through a series of corporate makeovers and temporary setbacks, punctuating general advancement in building new vaccine platforms and agents. In 2014, I met the president and CEO, Stan Erck, who covered the basics of the company, its technology, and its products in development. And when I spoke recently with John Trizzino, SVP of commercial operations, the conversation actually picked up where the previous one with Erck had left off — how Novavax has gone to exceptional lengths to study the potential commercial environment far in advance of launching its first product.

Significantly, Trizzino is not a marketing officer in the conventional sense, having no products to market yet. His title reflects an important, but too-often overlooked, function in entrepreneurial drug development — one that collects and imports knowledge about prospective practice settings, reimbursement factors, competitive forces, and other conditions its products are likely to face in the market and on the way to it. Such knowledge drives the company's decision making in multiple areas of R&D, from selecting target indications to designing trials. It also guides a progressive refinement of the company's entire business model in support of its development strategies.

LONG ROAD TOWARD LAUNCH

For its lead product, the RSV vaccine, Novavax is seeking indications covering the three most vulnerable

patient groups: over-60 adults, infants, and children six months to five years in age. Mothers receive the vaccine before birth to confer protection on infants. The vaccine is designed to block the fusion (F) protein on RSV, as does the only marketed treatment for RSV infection, the monoclonal antibody palivizumab (Synagis) from MedImmune. Novavax uses its own "recombinant protein nanoparticle" technology to produce a potentially higher-potency, more deliverable vaccine against the same target. No other RSV vaccine is approved, or likely to be soon.

Like other innovative vaccine developers, Novavax has created its own non-egg production technology to manufacture its products. It has engineered an insect cell line to make rDNA-produced nanoparticles and virus-like proteins (VLPs) that mimic the surface proteins on living human cells. "The particles we make are folded like natural viral proteins and are highly immunogenic," Erck told me. "Greater potency means greater shipping and storage efficiency," he added.

The distribution advantages and speed of production of the Novavax technology especially appealed to BARDA (Biomedical Advanced Research and Development Authority) back in 2011, when it awarded the company a contract worth up to $179 million for development of recombinant seasonal and pandemic flu vaccines. Moreover, prevention always beats treatment, of course — medically, logistically, and financially.

In recent years, the company shifted its primary focus from flu to RSV, and it replaced its VLP-based flu vaccine with a nanoparticle candidate. "The RSV program has accelerated quickly, and our new nanoparticle flu vaccine candidate is the result of many lessons learned over the years about the benefits of this nanoparticle technology, as well as what we've learned from our RSV program development," says Trizzino. Based on such knowledge, Novavax will ultimately fold the reformulated flu vaccine into a combination flu/RSV candidate slated for the start of a Phase 1 trial this fall.

Trizzino explains that the pairing of RSV and flu vaccines is hardly random; both viruses produce lower respiratory tract infections that are often confused and misdiagnosed because they have similar symptoms and occur in the same fall-to-spring time frame. Reformulating the flu component ensured both parts of the combo vaccine conform to the nanoparticle modality. "The formulation is naturally a better fit than if we took two completely different technologies and tried to co-formulate," he says.

The RSV F vaccine will launch first, however, according to current company plans — and hopes. Data from the Phase 3 "Resolve" trial in over-60 adults is due soon. RSV infection can cause a wide range of symptoms, in some cases mild, but in others severe to fatal. It is particularly dangerous to children under two years old, for whom it is the biggest cause of hospitalization. Trizzino says it kills 200,000 children globally every year, mainly in low-resource countries, and the Gates Foundation, a Novavax funder, is determined to help develop an RSV vaccine to protect those populations.

In 2015, the foundation awarded the company a grant worth up to $89 million to support the Phase 3 trial and regulatory filings for the vaccine in pregnant

AWARENESS TO ACCESS: THE VACCINE PATHWAY

John Trizzino, SVP of commercial operations at Novavax, shares some of the details of how the company is laying the groundwork for commercialization of its lead product, the RSV F vaccine for prevention of complications of respiratory syncytial virus (RSV) infection, in one of its target patient populations: adults over 60 years of age:

TRIZZINO: We have to demonstrate the significance of the burden of disease in its frequency and its economic burden – why are we trying to vaccinate this population? Is it cost-effective? Here are some of the statistics: Our RSV vaccine's target population of 60 years and older is now about 65 million people in the United States. By 2020, it will be 80 million. Every year, more than 5 percent of them will be infected with RSV. Of that 5 percent, about two-and-a-half million people today, by today's statistics, 900,000 will have some kind of a medical intervention: an unscheduled visit to the doctor, an emergency room visit, or a hospitalization, all amounting to a direct cost burden to the system of some $3.5 billion. Also, more than 16,000 of them will die from RSV complications on an annual basis. The direct and indirect cost burden in the older adult population – from loss of life and exacerbation of underlying conditions, such as COPD, chronic heart or lung disease, and increase in frailty due to hospitalization – will likely exceed $30 billion in the United States alone. We factor all of those costs and implications to the healthcare system into the strategy. We also know we have the advantage of a relatively receptive target population of people who want to avoid conditions that could erode their quality of life as they age.

JOHN TRIZZINO
SVP of commercial operations

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women. Under the grant terms, in exchange for World Health Organization (WHO) prequalification, Novavax agreed to make the vaccine "affordable and accessible to people in the developing world." It has a development agreement with the global health group PATH, (formerly the Program for Appropriate Technology in Health), from which it will receive about $7 million for RSV vaccine trials in low-income countries.

Novavax is also preparing for future business outside North America and Europe through CPL Biologics (CPLB), which is its joint venture with Cadila Pharmaceuticals of India, and a licensing deal with LG Life Sciences of South Korea. In Europe, the company still has its facility in Uppsala, Sweden. It also has candidates in development for Ebola and Middle East Respiratory Syndrome (MERS).

The company is not alone in pursuing RSV, of course; almost every vaccine developer of every size has an RSV program, though just a handful are in human trials. The Novavax candidate has been the leader in the field, and it is the only vaccine to block the same domain on the fusion protein as does Synagis, which may be the strongest possible validation of its target at this point. The nearest competitor candidate is GSK's recombinant vaccine, now in Phase 2.

Erck told me more about why the correspondence of the RSV vaccine with Synagis is important: "Our vaccine effectively turns people into living Synagis factories, invoking the same antibodies. MedImmune did us a great service over the past decade or so by discovering the minimum level of antibodies required on a dose-per-weight basis. We found that, when we vaccinate healthy adults, we stimulate a level of antibodies tenfold greater than the minimum level — a very powerful antibody response."

Some journalists and analysts have applied the word "disappointing" to results from the Novavax RSV Phase 2 trial in pregnant women, announced in September 2015, which has clouded the picture somewhat. The trial data showed the vaccine induces antibodies to RSV in the mothers but did not demonstrate the pre-birth, maternal inoculation passing the antibodies to the infants. Still, in the company's and its partners' view, the results were positive enough to support proof of principle and inform the Phase 3 trial design.

The Novavax strategy drives a stake in the ground — applying a novel platform it has taken decades to develop in formerly unexplored ways. "No one has ever put an RSV vaccine and a flu vaccine together in a combination," Trizzino says. "Some companies have taken a run at RSV vaccines and failed, but no other company has been able to demonstrate efficacy for an RSV vaccine as we have in our Phase 2 trial, and now we will take another novel step in moving into a combination flu/RSV vaccine."

MARKET VISION

Few precommercial companies have a "commercial readiness" program anywhere near the scale of the one at Novavax. Trizzino speaks about the meaning of the term and purpose of the program: "Stan Erck had a vision and knew that introducing a new vaccine would be quite different than launching a small molecule. Vaccines require a lot of foundation-laying work in the marketplace. For starters, here we have RSV disease, which is unfamiliar to most people, so we knew we needed to do disease-state awareness." Trizzino applies his own "four Ps" concept to vaccine commercial readiness: *product, policy, payer, and physician/patient.*

"By product, I mean the target product profile that every marketing person talks about, but in this particular case, we collaboratively designed the target product profile with the R&D folks. I have a great relationship with Dr. Greg Glenn, the president of R&D, and from early on we were collaborating about what the product should look like, what the target populations should be, and what we are trying to accomplish for them. Are we simply preventing an infection, or are we preventing disease?"

He notes the answer in one case was the latter: The primary endpoint of the Phase 3 clinical trial in older adults is prevention of moderate to severe RSV disease, rather than total prevention of infection. "Why is that important? Because the older adult immune system, as a result of immunosenescence, is a hard immune system to stimulate. Therefore, we may not be able to prevent the infection entirely, but we want to prevent the more severe complications of that infection."

Regulatory and public health *policy* also plays a special role in vaccines, says Trizzino, giving a key example. "You will not sell your vaccine unless you have supportive policy, most importantly coming from ACIP, the CDC's Advisory Committee on Immunization Practices, but also from advocates for the vaccine in the healthcare practitioner community. A vaccine is not a treatment. It's a prevention. So you communicate to people that they should want to be vaccinated to prevent something bad from happening." ACIP evaluates and recommends vaccines, even issuing the pediatric and adult vaccination schedules. "An ACIP recommendation is critically important, so we had to begin early forming a working group to advise ACIP on RSV in advance of its formal review of our candidate."

The third essential "P" is a *payer* strategy, says Trizzino. "Many times, no matter how many product marketing people get their hands on a great product,

the last thing that they think about is a payer strategy. And when the product comes to market, the door is slammed shut. So we're already considering what needs to be done there. We're already in conversations with the CMS. We already understand the private pay implication, because it's not a "65 and above" target product profile. It's "60 and above," which includes both Medicare and private pay. Anyone over 65 years will be covered by Medicare, but there's still work to be done helping the CMS understand exactly what that coverage means." For private insurance companies, Trizzino notes, the Affordable Care Act mandates that any ACIP-recommended vaccine must be covered at zero cost-share.

"We design a payer strategy that supports the target product profile that supports a policy recommendation, ensuring the product will be reimbursed. Marketing folks often refer to an access strategy — an access strategy is really nothing more than the coordination of policy and payer strategy. We want to set it up so people can easily find a healthcare provider that will vaccinate them, and their insurance will cover the vaccination. That means you go to the pharmacy or to the doc, pull out your insurance card and say, 'I want to be vaccinated.' You get vaccinated, and you walk out the door. That's an access strategy."

He is careful to clarify that the early conversations with payers do *not* include discussion of potential product price points. "We tell payers we will come to them with an economic model that makes sense. We start with a health-economics analysis, which we are already doing — cost-benefit models, quality-adjusted life years, pricing analogs, and other contextual data. All those things triangulate into a nice, reasonably tight range of pricing, which gives us the comfort of knowing we'll be somewhere within this reasonable, palatable range compared to successful products already on the market."

Trizzino says the last "P" is twofold — combining the *physician* and the *patient*. "This is about disease-state awareness," he says. "We want the doc to be aware enough of the significance of RSV to make the recommendation, but we also want the target population to be aware enough of this disease that, if the doc isn't recommending the vaccine, they're asking the doc whether they can be vaccinated for RSV."

He cites a "great example" of a successful awareness campaign that Pfizer conducted for the launch of Prevnar (diphtheria CRM197 protein) in older adults, called "Get this one done," in combining disease-state awareness information delivered to healthcare providers with direct-to-consumer advertising. "Thanks to the Prevnar campaign, the importance of adult vaccinations is now more top of mind. More people are aware of the need for adult vaccinations."

Does this sound like marketing now? Perhaps so, and conventional wisdom would say it has no place in precommercial development. But can a company afford to wait until regulatory approval before it begins to plan such a campaign? "Build it and they will come" may sometimes apply to an outright cure for terrible diseases or epidemics, but Trizzino's point is merely logical: People do not seek out prevention so readily without adequate awareness of the disease and the preventative agent. The seeds of a marketing campaign must be sown early and mature through clinical insights as development proceeds to the end goal, and the product enters the commercial realm. By necessity and invention, Novavax is one company scouting down that path and, it hopes, all the way to the market.

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What GSK Learned From Using Mobile And Wearable Technologies

ED MISETA Chief Editor, ClinicalLeader.com @EdClinical

Regulatory concerns are still a factor for companies considering the adoption of mobile and wearable technologies in clinical trials. In fact, industry group ACRO (Association of Clinical Research Organizations) recently released a report that showed this to be the No. 1 concern of companies looking to implement mHealth technologies.

But for every company hesitant to move forward because of regulatory concerns, there is another that is willing to forge ahead and show others how it can be done. GlaxoSmithKline is one of the companies making that move.

"As a company that is moving forward with mobile technology adoption, I can tell you that regulators are probably the least of our concerns," says Rob DiCicco, VP, clinical innovation and digital platforms at GSK. "I think the bigger challenge for many sponsors is they aren't sure how to invest in new technologies and how to properly incorporate them into a trial design from end to end (i.e., from protocol to report)."

According to DiCicco, the FDA and other regulatory agencies have been very clear about their expectations regarding the use of mHealth technologies and the data and information obtained from them. He believes regulators have been at the table with the industry, both in individual conversations with companies and at conferences sharing their direction and views. Several industry working groups, including the Clinical Trial Transformation Initiative (CTTI), have also been active at conferences discussing regulatory issues.

Glen de Vries, president of Medidata Solutions, a provider of cloud-based solutions for clinical research that has worked with GSK, agrees. While there are companies that do not want to be the guinea pigs, de Vries has found the FDA is always available to sit down with sponsors to discuss studies and specific concerns. "The FDA is willing to set up meetings long before the study starts to address potential issues," he says. "They are also asking for input from sponsors as to how they should be managing and reviewing this process. We all agree we will get better efficacy and safety data using mobile health devices, and the FDA is asking companies to work with them to devise the right approach to regulating this data."

Still, incorporating mobile and wearable technologies into a clinical trial can be a daunting task. Every company has clinical standards to uphold, and that makes executives dependent on new devices performing as promised, which is not always easy to verify. "In a hospital environment, machines are maintained and calibrated on a regular schedule," says DiCicco. "It is much more difficult to do that in an environment where the patient is at home and doing things like sweating, showering, swimming, and other activities that can impact the performance of the device."

To overcome this problem, GSK is developing platforms that allow the company to test new devices in different settings. One example is Gadget Trial, a GSK program that studied healthy volunteers in a clinical pharmacology unit. Gadget Trial allowed the company to monitor participants and evaluate the performance of sensors. In addition to sensor performance and data acquisition, user acceptance/preference was also assessed. "We asked them to assess which one they liked better, which ones worked better, and which ones were more or less convenient to use," says DiCicco. "We also tested if the information came out of the

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device correctly, if there was missing data, how long the battery lasted, and if it provided good connectivity. It's an important test, because we would want to know all of those things before placing a new sensor into a study requiring significant investment."

INCORPORATE THE RIGHT DEVICES

According to DiCicco, selecting the right device is an important consideration when incorporating mHealth into a study. GSK currently has a study underway for patients with amyotrophic lateral sclerosis (ALS). For this study, the company selected a medical-grade activity device. With the technology, GSK is able to glean a lot of information from the device, including how many steps patients have taken and their positions over the course of the day.

While DiCicco would not rule out using a consumer-grade wearable device (such as a FitBit) in a trial, he does believe companies use them at their own risk. "The appeal is the commonality of it, along with the cost and availability," he says. "For important decision-making studies or studies that could affect our label, the main focus should not be on cost. Trials will still be expensive, regardless of which devices you use. Medical-grade devices require an additional investment, but that is necessary to get a device that will safely and securely move patient information to the cloud and make proper use of password access. We need that rigor around the data-collection process."

Although a medical-grade device might impact the cost of a trial, DiCicco is more concerned about risk and believes that is what will make or break the adoption of a device into a trial. However, if you insist on looking at the higher cost of incorporating medical-grade devices, he recommends you also consider the costs involved in not incorporating these devices. Without a device, some trials will require home visits for participants who are not able to make it to a clinic. That is also expensive. Those patients who do make the trip might have to drive an hour, pay $30 for parking, sit in the waiting room for a couple of hours, and then do it all over again the following week. That does not help patient retention.

"If we could gather information from them during the course of their normal daily life, study visits could be reduced substantially," says DiCicco. "In that situation, we dramatically change the cost basis for conducting a trial. Continuous monitoring would improve the outcome of the trial and the quality of the data collected. It would also enable us to learn things from data that we might otherwise not have access to. By making the trial easier on the patient, we could also improve patient retention rates, which save a lot of money in the long run."

"Mobile health gives us a chance to measure what is happening in real life, but in a clinical trial context," adds de Vries. "By allowing us to measure the efficacy of a therapy in the real world, these technologies will drive better outcomes for patients. For sponsors, mHealth devices also provide a higher quality hypothesis of whether or not a drug is worth bringing to market. That is a very valuable proposition."

"I think the bigger challenge for many sponsors is they aren't sure how to invest in new technologies and how to properly incorporate them into a trial design."

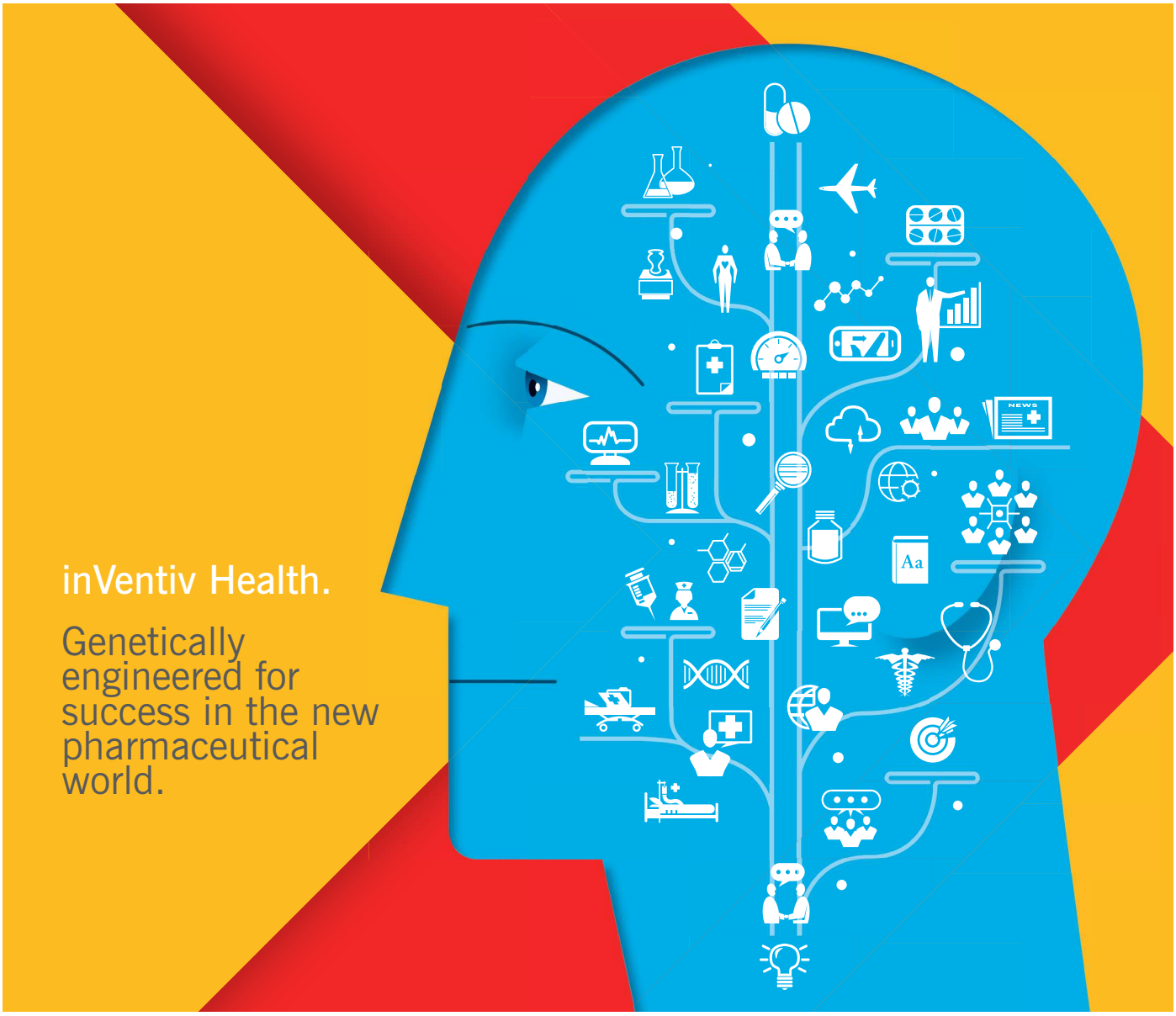
ROB DiCICCO
VP, clinical innovation and digital platforms, GSK

OVERCOME INTERNAL BARRIERS

Despite the advancements being made in mobile and wearable technologies, pharma remains a conservative industry. Trials can cost millions, if not billions, of dollars. Therefore, anything that introduces new risks to a trial will be evaluated carefully. In fact, in a large pharma firm like GSK, any technology change can have a huge impact on many departments and face many detractors. For that reason, DiCicco put together a cross-functional team to help with the effort.

The team included individuals from departments across the company, and each participant had an interest in advancing the use of mobile technologies within GSK. "I think the main thing we did was establish a case for making future investment," says DiCicco. "A year ago, the group had no formal full-time employees and no budget. Today, it has both."

There were barriers the team had to overcome, and one of them was certainly cost. Incorporating a wearable device into a trial might cause costs to increase by, say, 20 percent. That can cause some pushback



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to the project. DiCicco notes this is where the budget can come into play. "If our team believes a piece of technology can help the study or the patient and produce better data, then we use our budget to cover the cost and make that obstacle go away," he says.

In just the first year, DiCicco has also seen the cross-functional team evolve. Initially, it was very exploratory. The team would seek out academics in the algorithm space and companies that were advancing solutions to handle data generated by mHealth devices. The goal was to learn what products were out there and how they worked. The team was also looking for places where the technologies could be used.

Since receiving an operating budget, the team has flipped things around. Today, it tries to identify problems and pain points within the company, and then looks for digital and mobile technology solutions that might solve them.

ONE TEAM TO ASSESS PRODUCTS

Within GSK are therapy area units (the portfolio owners) and platform groups (charged with implementing clinical trials). Those groups include clinical development specialists, clinical operations, and preclinical regulatory therapists. DiCicco notes that across the clinical trials enterprise, any number of individuals within various departments might have service agreements with the same companies, but no awareness of what the others were doing. Eventually, senior managers recognized that it would be inefficient for every therapy area unit and every platform group to continue to work with companies in this manner.

"Vendors can be very ambitious and persistent when it comes to convincing sponsors that their product will transform clinical development," says DiCicco. "Sometimes the technology is interesting, and sometimes it's not. But if one group tells them no, that doesn't stop them from making their pitch to another group. So in that respect, the group was born out of a necessity to provide information-sharing within the company. Initially, it led to greater coordination across groups, but a year into it we realized that if we really wanted to get traction, we needed to make formal investments in this space."

Today, a vendor with a sensor would make its presentation to the cross-functional team, which would then evaluate whether it was effective and where it could best be utilized. DiCicco notes the entire evaluation process is done with complete transparency and awareness. The clinical operations group may have no use for a device today, but the value-evidence generation group might. By having one group evaluate how a technology can be used, there is a multidisciplinary assessment of the opportunity and how it can address problems within GSK.

OVERCOMING DATA CHALLENGES

One thing the team did not have to struggle with was getting data from a device to the cloud. "It is not an issue today," says DiCicco. "We are doing that reliably and are confident the data is secure and has an acceptable level of integrity. The challenge we now face relates to integrating data from multiple and different devices. In other words, how many different interfaces do we need to put in front of the patients and how many different interfaces does a study team, data scientist, clinician, or statistician need to deal with?"

If patients have to run five apps on their smartphones, that can quickly drain the batteries and require them to be near a power source all day. DiCicco also does not want a patient to have to carry multiple devices, one to perform a clinical outcomes assessment, another to track activity, and still another to measure breathing. The preferred model would be one where patients could use their own devices. On the back end, a study team could work with one vendor or one integrator to pull all of the information together.

"Today there are different data formats and platforms," says DiCicco. "We also have to deal with different configurations, hardware, and software. That is where we are going to need some help. We have data coming in from electronic health records (EHRs), labs, phones, and sensors. Getting everything in the same standard format will require a concentrated effort by sponsors, vendors, and industry groups."

Here again, DiCicco believes guidance from the FDA has been clear. He notes the requirements to get a medical device 510(k) approved are straightforward. The FDA has also issued guidance for the industry on electronic source (eSource) data in clinical investigations. The guidance explains the FDA's expectations in terms of the level of validation needed for the data to be acceptable.

DiCicco believes the bigger problem will be things like device upgrades. "Anyone who has ever had an iPhone or Android device knows the experience of having to download a software update," he says. "Then you realize you can't find your pictures. Or the phone has a different look and a different layout. When that software changes, it can also affect an algorithm that was calculating someone's heart rate. We don't always know what will be impacted by an upgrade. I suspect we will be able to deal with it, but it's something we will have to better understand so that we can explain to regulators how we will handle it. With many of these sensors, algorithms, and apps, we are in uncharted water."

Along with the increases in data volume come improved methods of analyzing it. Statisticians have devised new statistical methods to deal with the

volumes of clinical data now coming in, and machine learning is being used to identify outliers and understand what is going on in underlying data that a human might not be able to see. De Vries notes that by grouping similar patients together, statisticians can better identify patterns in the groups.

NEW EXPERTISE MAY BE REQUIRED

As companies move into these uncharted waters, they will also need new skillsets. Some of those skills will likely come from outside the pharma industry. DiCicco thinks that in a few years, project teams within pharma companies will be organized and populated differently. New capabilities will exist, especially in the sensor space.

"I might need someone with a bioengineering background to tell me if a sensor is going to overheat and burn the patient," says DiCicco. "I might also want to know if the sensor is going to drain the battery, what the battery life will be under varying conditions, if the sensor will transmit when I want it to, and more. If a company is not currently employing wearable devices, those skillsets might not exist. You will also need people to validate the technology and someone with experience in math to help vet the algorithm."

DiCicco believes new hires in the areas of data science and statistics soon will evolve and become more valuable to the pharma industry. He also believes many individuals with those skills may already be in pharma companies, but the companies don't know it. Therefore, companies may need to make an effort to discover if needed skillsets may already exist within the company.

"We will absolutely need people to think about the mathematics, statistics, and techniques necessary to create reliable endpoints that regulatory authorities will know are worthy of their attention," adds de Vries. "We need to get mobile health data that will be substantial evidence to the regulatory agencies."

But being in uncharted waters also brings more complicated challenges, which DiCicco refers to as preparing for the unknown unknowns. Companies are not able to predict every eventuality when launching a new technology. But DiCicco also believes that is not a reason to hold back on the adoption of mobile technologies. Too many other factors necessitate the implementation of new methods.

"The rising cost of drug development is in the news every day," he says. "We need new tools to help bring down the costs and get needed medicines to patients faster. We may not always get it right the first time, but we need to do what we can to jump-start that process of evaluation and implementation." L

Big Pharma Goes Small With Moves Into Incubator Space

SCOTT WESTCOTT Contributing Writer

From the limited view in his cramped cubicle at a Big Pharma company a few years back, Joseph Payne envisioned launching a startup to develop innovative ribonucleic acid (RNA) pharmaceuticals and technologies. Payne was confident he and a coworker had promising ideas, the necessary entrepreneurial mindset, and solid science to lead their own successful biotech company. Yet it was the need for money, resources, and infrastructure to fund and provide ongoing support for such a venture that posed the most daunting barriers.

Still, the partners made the leap, quitting their jobs and pooling savings to launch Arcturus Therapeutics, of which Payne serves as president and CEO. "At the beginning, we were completely focused on how we were going to get funding and how we were going to get lab space," Payne recalled. "It is just so difficult. It requires a lot of money – a lot of money fast."

The partners were deep in the process of trying to secure funding in early 2013 when they heard about Johnson & Johnson Innovation's JLABS in San Diego. Then in the pilot stage, JLABS offered a think-tank style lab environment aimed at attracting startups that typically gravitate toward an incubator funded by an academic or public institution, or strike out on their own to get funding, space, and equipment.

"At first I was concerned that getting involved with a Big Pharma company might not be the right idea," Payne said. "Yet JLABS made it clear from the start there were no strings attached. We ended up with multiple other companies in one space, and found a lot of synergies, free learnings, and consultation. It was a collaborative and innovative culture."

Indeed, the opportunity proved tailor-made for Arcturus, which in the three years since has enjoyed mercurial success. In Payne's view, the game-changing factor of JLABS was the credibility that came with the state-of-the-art building and equipment, which he believes significantly boosted the comfort level and interest of would-be investors. Despite starting with no assets or pipeline, Arcturus raised $1.3 million in seed funding from high-net-worth investors shortly after joining JLABS. Four months later, the company tapped most of those investors again and added interests from Canada, Japan, and the United States in a $5 million series A round.

"The reality is if potential investors are coming to your living room or your garage, it's just not going to give them that warm, fuzzy feeling," Payne said. "Once they saw JLABS, which is a class-A external R&D engine at a class-A company, they just went, 'Wow!' It immediately sent a message that we were serious."

BIG PHARMA RETHINKS THE OLD R&D MODEL

JLABS is one of several examples of Big Pharma's move into smaller, incubator-type arrangements and partnerships as a more cost-effective complement to traditional R&D. The incubator path provides a Big Pharma the opportunity to connect with startups it might otherwise not be exposed to, as well as the potential to get on the inside track of the most innovative and promising pharmaceuticals and technologies.

The trend comes at a time when traditional R&D spending is on the decline, amid increasing

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consolidations within Big Pharma and ongoing shakeups within existing R&D departments. The reordering is driven in large part by simple economics: R&D, particularly in biotech, is risky and speculative with a high percentage of failures at many stages. Even promising biopharma drugs cost approximately $2.6 billion to bring to market, and 92 percent of those drugs will fail, according to the Tufts Center for the Study of Drug Development.

Meanwhile, incubators are where successful innovation is increasingly occurring. The majority of drugs approved in the past several years originated at smaller startups and labs. In fact, last year 64 percent of the drugs approved were initially hatched in startups, according to HBM Partners, a healthcare investing firm. Meanwhile, small biotech companies received $5.6 billion in up-front licensing payments in 2014 — that's double the prior year, according to BIO.

Such trends have driven many of the biggest players in Big Pharma to assess their internal R&D strategies while seeking pathways into the incubator and startup space. Bayer, for instance, opened CoLaborator, "a unique incubator space" for startup companies next door to its U.S. Innovation Center in the Mission Bay neighborhood of San Francisco.

CoLaborator is located in the city's life sciences cluster and features a flexible, open floor plan with 6,000 square feet of shared, rented lab space designed to house startup life sciences companies whose technology platforms, drug targets, or drug candidates may align with Bayer's interests. Bayer support includes, among other things, access to nearby University of California, San Francisco (UCSF) core services such as imaging, bioinformatics, and proteomics.

THE OPPORTUNITY TO DO THE RIGHT EXPERIMENTS

Meanwhile, Bristol-Myers Squibb (BMS) engages with the startup community through a couple of different initiatives. "Incubators fit into our broader strategy of R&D and extend our model beyond traditional business development," said Paul Biondi, head of business development at BMS. "We are looking at ways we can interact directly with people developing interesting intellectual properties and ideas coming out of academia and smaller incubators."

Specifically, BMS developed a joint venture with Allied Minds, a diversified holding company focused on venture creation within the life sciences and technology sectors.

Called Allied-Bristol Life Sciences, the partnership aims to seek out university partners with deep biology expertise who are interested in applying their scientific knowledge to the development of therapeutic candidates. Allied-Bristol provides access to a fully integrated drug discovery center, expertise in drug development, and the necessary financial backing and experienced management to drive early-stage therapeutic projects to success. Promising ideas are then transferred to a BMS facility in Bangalore, India, which has the resources, talent, and equipment necessary to fast-track further research and drug development, Biondi said.

"The reality is if potential investors are coming to your living room or your garage, it's just not going to give them that warm, fuzzy feeling."

JOSEPH PAYNE
President and CEO, Arcturus Therapeutics

In addition, BMS recently became a sponsor of LabCentral, a 28,000-square-foot facility in the heart of the Kendall Square, Cambridge, MA, biotech innovation hub. LabCentral promotes itself as a "first-of-its-kind shared laboratory space designed as a launchpad for high-potential life sciences and biotech startups."

LabCentral offers fully permitted laboratory and office space for as many as 25 startups comprising approximately 100 scientists and entrepreneurs. LabCentral provides facility and administrative support, skilled laboratory personnel, a domain-relevant expert speaker series, and other critical services and support early-stage companies need to begin laboratory operations on day one.

BMS's platinum sponsorship at LabCentral provides the company the opportunity to sponsor two lab benches for promising entrepreneurs focused on research that aligns with BMS's interests. In addition, BMS announced plans to open a research facility in Cambridge in 2018, and the LabCentral sponsorship "is part of our entrance into the Cambridge community," said Biondi.

"The primary value is the space itself," Biondi said. "LabCentral offers premium lab space and state-of-

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the-art instrumentation. Providing this high-quality lab space allows more time to focus on the science and research. These small companies face a lot of pressures, and we hope this gives them the opportunity to do the right experiments and do them in a way in which they are not wasting time and money on overhead."

JLABS: J&J AIMS TO REMOVE THE HURDLES

Arguably, the most ambitious player in the Big Pharma-goes-small movement has been J&J, which has aggressively created a network of JLABS sites throughout North America in life sciences clusters. JLABS flagship is in San Diego, and there are also sites in San Francisco, South San Francisco, Boston, and Houston. Most recently, in May J&J opened JLABS @ Toronto.

All told, the facilities are home to more than 140 early-stage companies advancing bio/pharmaceutical, medical device, consumer, and digital health programs. The six JLABS facilities have a total capacity for 225 resident companies.

JLABS head Melinda Richter said JLABS was launched as a way to tap into and support science and technology innovation occurring outside of J&J's traditional R&D. The JLABS model was designed to address the biggest challenges facing entrepreneurs and would-be startups: gaining access to infrastructure and necessary resources and technology.

The startups pay rent and "there are no strings beyond that" Richter said.

"It's a straightforward transaction which allows the company the freedom, flexibility, and power to grow their own equity," Richter said. "Yet along the way, as we provide support, if they wish to engage in discussions around something in particular, we have our early-stage deal team, Johnson & Johnson Innovation Centers, and our venture arm, Johnson & Johnson Innovation, that entrepreneurs can tap into."

The result can be a wide range of arrangements from a traditional license agreement to a collaboration or equity investment arrangement. "We can do creative, smaller deals that are about helping scientists take the next step, and then onto the next step," she said. "The approach we have for innovation is meant to be comprehensive, flexible, and end-to-end."

Beyond space, equipment, and resources, JLABS provides education and encourages collaboration among participants. Meanwhile, it aims to avoid the creep of bureaucracy or corporate policies that might slow the innovation process.

"It can be tough to move quickly when you have a big organization; all these processes and procedures are in place to keep everything running as consistently and predictably as possible," Richter said. "That being said, it is amazing how fast J&J has changed and how fast they can make decisions now because of this new structure. All types of deals can be done very, very quickly."

ARCTURUS: A JLABS ALUM HITS IT BIG

One such deal occurred with Arcturus Therapeutics. In June 2015, the JLABS alumnus inked a global research collaboration and license agreement with J&J unit Janssen Pharmaceuticals Inc. to develop and commercialize messenger ribonucleic acid (mRNA)-based drug candidates to treat undisclosed disease targets, also using the unlocked nucleomonomer agent (UNA) and a proprietary RNA technology platform called LUNAR. In return, Janssen agreed to make an undisclosed up-front payment along with preclinical, development, and sales-based milestone and royalty payments on product sales. Janssen agreed to provide R&D support and assumed responsibility for development and commercialization costs.

"It was great and critical for us at the time, but from the J&J perspective, they also got a barnburner of a deal on the technology," said Payne. "It's a win-win. We got our first deal and validation, and J&J wins by having the opportunity to get in on the ground floor at a good price."

Indeed, the deal paved the way for more opportunity. A few months after the Janssen deal, Arcturus and Ultragenyx Pharmaceutical Inc. agreed to a rare disease research collaboration and license deal to discover and develop mRNA therapeutics using its unlocked UNA oligomer chemistry and lipid-enabled and LUNAR nanoparticle delivery platform.

The deal provided Arcturus with $10 million up front. During the initial phase, Arcturus will design and optimize mRNA therapeutics for two undisclosed rare disease targets, and Ultragenyx has the option to add up to eight additional rare disease targets during the collaborative research period. Ultragenyx will oversee development and commercialization of any products emerging from the collaboration in return for preclinical, clinical, regulatory, and sales milestone payments of up to $156 million for each target, plus reimbursement of research expenses as well as royalties on product sales. All told, Arcturus stands to collect up to $1.56 billion from the deal.

No doubt, the blockbuster deal provides Payne with a much better view than he had just a few years back in that Big Pharma cubicle.

"I think a lot of incubators are modifying their whole process to match more closely what J&J has done," Payne said. "I think many of them will be trying to duplicate the J&J model, which should create some good competition. Ultimately, that is good for entrepreneurs and startups, and good for the entire industry." L

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9 Biotech Valuation Enhancers: Preparing For Big Pharma Due Diligence

BRIAN DANIELS, M.D., AND DON THERASSE, M.D.

Mergers and acquisitions are an important growth strategy for many life sciences companies looking for new agents to strengthen or complement an existing portfolio, enter a new market, or replenish an expiring patent, among other reasons. According to a global study conducted in Q2 2015 by Mergermarket and Reed Smith, 94 percent of senior life science executives planned to make an acquisition in 2016, so biotech firms need to do everything possible to make sure they are properly positioned to get the most value for their asset.

In our former roles at Bristol-Myers Squibb and Eli Lilly & Company, we evaluated hundreds of potential assets to add to our portfolios. Now that we've graduated from Big Pharma and are consulting or doing venture investing, we are frequently asked by biotech companies for advice on what Big Pharma is looking for in potential partners or acquisitions, and how biotechs can put their best foot forward.

If you want to attract more suitors and maximize the valuation of your asset or company, the first rule is to do good science. This is a given. After that, follow these nine rules:

1. **KNOW THE BUYER LANDSCAPE.** In addition to understanding your product and data, you should also understand how your asset fits into your potential partner's portfolio and strategy. Are buyers looking to build on a strength or fill a gap? Are they looking to add or mitigate risk in their portfolio? The stronger the fit, the higher the valuation will likely be.

2. **PRESSURE TEST THE DATA.** Blind spots are a big issue for any size organization, so it's important to critically examine your data and get an external perspective before you get it from your potential buyers. Having an external expert perform a detailed, objective assessment and ask the tough questions will help you identify blind spots and develop a road map to address issues before you engage with potential suitors.

3. **ADDRESS SHORTCOMINGS HEAD-ON.** Pharmaceutical development is incredibly challenging, and every asset or development program has its flaws. So don't try to hide or minimize those deficiencies; instead, acknowledge and address them head-on. Any attempt to hide or mask deficiencies will eventually be uncovered, and will result in damaged credibility, loss of trust, and suspicion that there are more surprises yet to be found.

4. **IDENTIFY A SPEEDY AND EFFICIENT PATH TO PROOF OF CONCEPT.** As with all drug development activity, the greater the certainty, the higher the value. For early-phase assets, a biotech that is well on its way to demonstrating clinical proof of concept is a much more attractive partner than one that still has a way to go.

5. **ASSESS HOW DATASETS ARE STRUCTURED.** Keep in mind that ultimately all safety data related to your asset will have to be integrated for submission to regulatory authorities, and in most cases that

WHICH OF THE FOLLOWING ARE YOU CONSIDERING TO INITIATE IN THE NEXT 12 MONTHS? (Question asked in Q2 2015. Answers include all that apply.)

Source: Mergermarket and Reed Smith

will require electronic transfer of the data to the acquiring company's safety database. Especially for later-stage assets with large and fragmented datasets, this assimilation of safety data can present a significant (and expensive) challenge to your partner. Just as poorly organized data can have a negative impact on negotiations and valuation, well-structured datasets can be a significant positive.

6 **MANAGE THE NUMBER OF DEVELOPMENT PARTNERS.** It may be tempting to hire a host of CROs to speed up the development process; however, more partners means more data sources to assimilate. For late-phase assets this will mean a complex network of datasets and a nightmare for acquiring life sciences companies. As you go through development, keep the end in mind and carefully manage the number of development partners you use.

7 **HAVE YOUR INTELLECTUAL PROPERTY HOUSE IN ORDER.** One of the biggest and most time-consuming challenges for your pharma partner during the due diligence process is often sorting out the IP and freedom-to-operate status of your asset. Before getting into discussions with a potential partner, engage with an IP attorney to ensure everything is in order.

8 **THINK BIGGER.** Once you have interest from a potential partner and understand its portfolio and strategy, think carefully about additional ways your asset can add value. Are there additional indications or combinations that could be pursued? Look at immediate and future applications, and paint scenarios for them. The more a biotech can think about how they can bring value to the acquiring company, the more the partner will understand how it can fit the asset into its longer-term portfolio/enterprise strategy.

9 **BE TRANSPARENT DURING VALUATION.** When valuing your company, it's extremely important to be transparent about your assumptions. Show exactly how you arrived at your valuation so both sides can sit down and reconcile their term sheets. Remember, there will always be dialog and negotiation. Knowing exactly what the starting point is for each party will create greater understanding and a much more cordial environment and efficient process. L

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Hiring Millennials

A Balancing Act

WENDY MANTEL

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www.mantelcoaching.com

The millennial generation (Generation Y, ages 19-39) has been stereotyped as narcissistic, selfie-obsessed, self-promoters. But they are the largest, most diverse demographic cohort in American history, and their potential to make myriad unimagined strides in our country's progress can't be understated.

There are those who argue that millennials aren't narcissistic at all; they're *individualistic*. They want to make their mark at work and view work as a key part of life, not something to be "balanced with life." They want to be recognized for a job well done. They're in a hurry for success, but not to the exclusion of feedback and guidance.

How, then, does a company mentor these hungry, driven, young leaders?

The business literature suggests that millennials need opportunities to balance self-discovery and personal fulfillment with a sense of higher purpose. They want close, meaningful relationships with mentors — in and outside of work. But they need to feel empowered to use their individualism — to be authentic, to discover, and to become their own brands. Engagement, learning, growth, visibility, relevance, integrity, and opportunity are watchwords for this generation.

Charismatic executives who lead a cult-like following won't cut it with millennials. Neither will cultures where power is misaligned, and there is manipulation, misuse, or no use of talent — a recipe for employee disillusionment in any case. And traditional one-on-one mentoring programs won't do it either.

Social impact and communications strategist Erica Williams Simon puts it this way:

> *"The reality is, when you look at young people, all the data shows that young people are civic-minded in a very different way ... They are not as interested in politics, but are interested in social change and finding creative, innovative ways to make a difference that are in a way more effective than the systems of the past."*

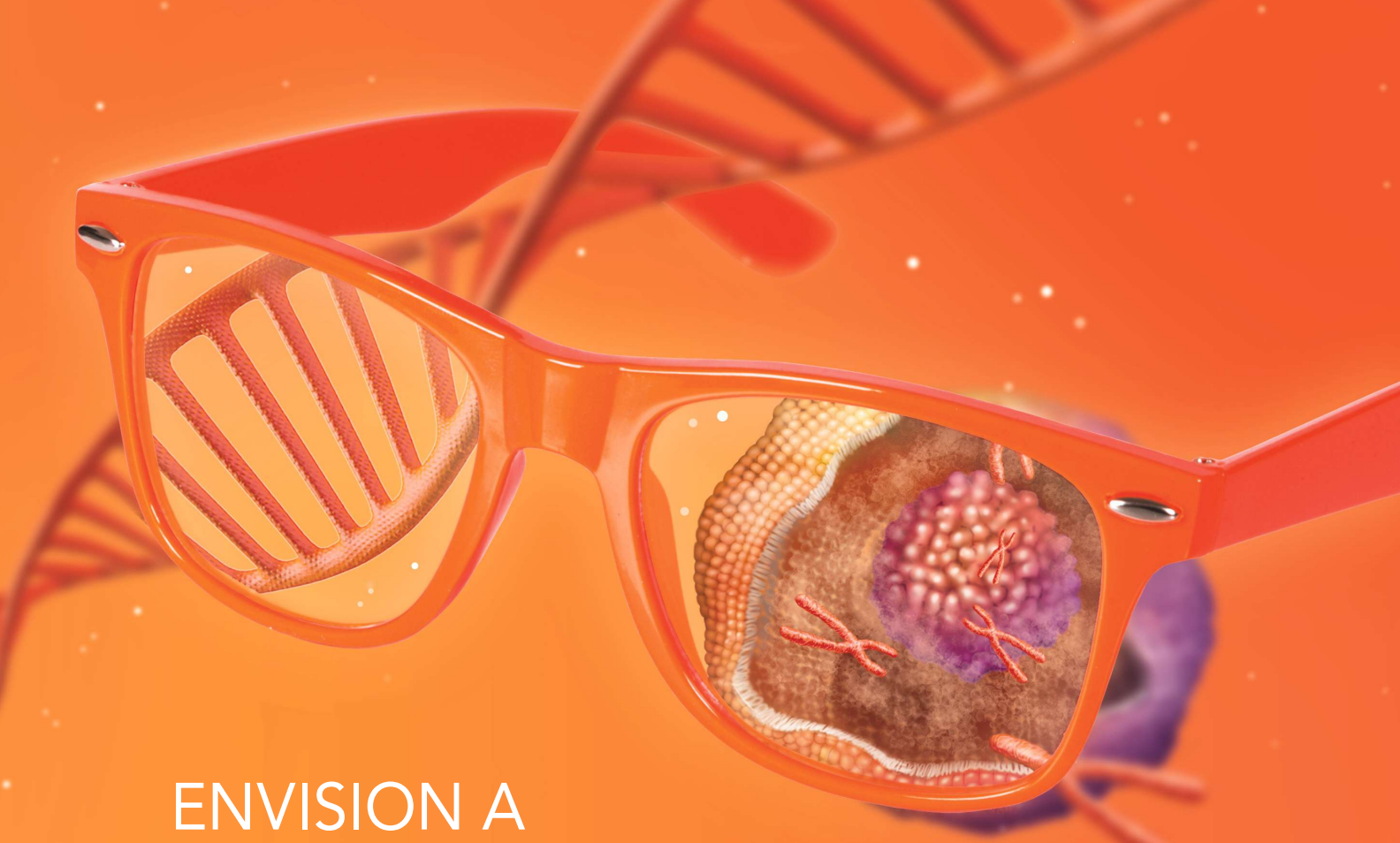
According to a survey by Virtuali in November 2014, millennials see mentoring as the most effective and desirable form of career development training. That's the good news.

However, unlike earlier generations, millennials want faster, more effective mentoring. Faster and more effective means fulfilling the millennial's high goals by preparing him or her to rise and reach the executive ranks more quickly. This requires, in some companies, thoroughly rethinking the established mentoring approach.

In some cases, rotational programs are being created to enable employees to circulate through pivotal departments over a year or longer. The mentee works with a series of executive mentors, creating, in effect, a personal board of advisors. This benefits the company too, establishing a panel of seasoned managers who can observe these employees firsthand and spot high-potentials early on.

In other cases, mentees tap into internal and external mentoring resources, such as the Healthcare Businesswomen's Association group mentoring program.

What's really different about the millennial generation is that it isn't waiting around for the dream to come true. If the dream doesn't materialize at one company, they'll find it at another, and they won't wait long for the signals. Progressive companies that recognize the fine balance between drive and development will create mentoring programs that support individual development and advancement, while positioning the company to reap the benefits of its future leadership.



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