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THREE OF THE IRONWOOD PHARMACEUTICALS FOUNDERS (from left):
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The Story Behind The Building Of Ironwood Pharmaceuticals

p. 16

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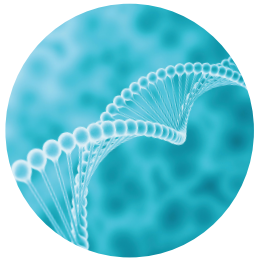

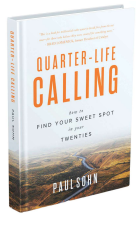

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The U.S. Tax Man Cometh; The U.S. Corporations Leaveth

ROB WRIGHT Chief Editor

Getting organized to file our annual household tax return, I ponder how we as a society have allowed the U.S. federal tax code to grow so complex that it requires 13 miles of paper to contain it. For an employee it can be easy to forget the number of hurdles entrepreneurs overcome to found the businesses that pay the wages we use to provide for our families. Do you think that when Peter Hecht, the CEO of Ironwood Pharmaceuticals and subject of this month's cover feature, first set out to build a sustainable pharmaceutical company back in 1998, he and his cofounders *truly* understood the challenges that lay before them? We're not just talking about spending a million dollars to file an NDA (new drug aspplication) plus a few hundred million more in R&D. What about taxes (e.g., federal and state unemployment, social security, Medicare, and net investment income taxes)? If ever profitable, the company faces paying either an alternative minimum tax (AMT) or the third highest corporate tax rate in the world (i.e., 39 percent). Oh, let's not forget that once your company reaches a certain size you'll also need to provide health insurance. Early clinical trial success for a lifesaving drug may result in folks demanding inclusion on grounds of compassionate use. Finally, if fortunate enough to get a drug developed and approved, however it's priced, it is likely to face significant political and public scrutiny.

Starting a business anywhere is hard. But doesn't it seem, in the land of opportunity, that starting a biotech is just a little bit harder, especially today? And for those that have succeeded, shouldn't we be trying to provide more incentives for them to stay rather than creating further disincentives that push them to leave? Since 1982, 51 U.S. companies have reincorporated in low-tax countries. But even more telling is the fact that 20 of these have happened in just the past three years — this despite 2004 legislation intended to abolish the practice! We have moved from an average of losing one company a year for 30 years, to more than six a year the past three years. In response, the Obama administration opted for a further tightening of tax-inversion rules. The result of this "Katie bar the door" mentality is the tragic loss of yet another American institution — Pfizer, a company older than 3M, Ford, GE, Coke, and Major League Baseball.

While U.S. legislators continue to enact more stringent guidelines (and penalties) for U.S. corporations seeking tax relief, Ireland has been welcoming them with a corporate tax rate of 12.5 percent — a rate less than *all* of the BRICs (Brazil - 34, Russia - 20, India - 34.6, and China - 25) and high-tech hubs such as Singapore (17) and Hong Kong (16.5). Heck, it's less than Lebanon (15)! Of Ireland's 20 biggest incorporated companies, 12 were founded in the U.S.; six are life science companies (Alkermes, Allergan, Endo, Jazz, Medtronic, and Perrigo). Ireland understands that the key to its continued GDP growth is policy making that encourages continued foreign direct investment (FDI). Though it was a European that first stated you can catch more flies with honey than vinegar, it was our own FDA that proved this to be true (e.g., incentive programs spur the drug development you want). To stop the current U.S. corporate exodus requires similar forward thinking, as well as your action. If you haven't written your senator or congressman, now would be a good time to do so. After all, Pfizer was as American as apple pie, and if it can leave, what other U.S. corporate giants might soon follow? L

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LIFE SCIENCE LEADER
5340 Fryling Rd., Suite 300 / Erie, PA 16510-4672
Telephone: 814 897 7700 / Fax: 814 899 4648
WWW.LIFESCIENCELEADER.COM

SVP OF PUBLISHING/PRODUCT DEVELOPMENT
Jon Howland / Ext. 203
jon.howland@lifescienceconnect.com

VP OF CONTENT
Ed Hess
ed.hess@lifescienceconnect.com

EDITORIAL DIRECTOR
Dan Schell / Ext. 284
dan.schell@lifescienceleader.com

CHIEF EDITOR
Rob Wright / Ext. 140
rob.wright@lifescienceconnect.com

EXECUTIVE EDITORS
Wayne Koberstein
wayne.koberstein@lifescienceleader.com

Louis Garguilo
louis.garguilo@lifescienceconnect.com

Ed Miseta
ed.miseta@lifescienceconnect.com

Trisha Gladd
trisha.gladd@lifescienceconnect.com

SENIOR DIRECTOR OF PUBLISHING
Perry Rearick
perry.rearick@lifescienceconnect.com

VP OF AUDIENCE DEVELOPMENT
Michael Bennett
michael.bennett@lifescienceconnect.com

PRODUCT DIRECTOR
Jenell Skemp
jenell.skemp@lifescienceconnect.com

PROJECT MANAGER
Megan Rainbow
megan.rainbow@lifescienceconnect.com

DIRECTOR, LIFE SCIENCE TRAINING INSTITUTE
Bill Beyer
bill.beyer@lifescienceconnect.com

PUBLISHER, CLINICAL & CONTRACT RESEARCH
Sean Hoffman / 724 940 7557 / Ext. 165
sean.hoffman@lifescienceconnect.com

PUBLISHER/BIOPHARM & LAB
Shannon Primavere / Ext. 279
shannon.primavere@lifescienceconnect.com

PUBLISHER/OUTSOURCING
Cory Coleman / Ext. 108
cory.coleman@lifescienceconnect.com

ENGAGEMENT MANAGER
Kevin Morey
kevin.morey@lifescienceconnect.com

GROUP PUBLISHER/OUTSOURCING
Ray Sherman / Ext. 335
ray.sherman@lifescienceconnect.com

BUSINESS DEVELOPMENT MANAGER
Mike Barbalaci / Ext. 218
mike.barbalaci@lifescienceconnect.com

SR. ACCOUNT EXECUTIVE
Scott Moren / Ext. 118
scott.moren@lifescienceconnect.com

PRODUCTION DIRECTOR
Lynn Netkowicz / Ext. 205
lynn.netkowicz@jamesonpublishing.com

MANAGE SUBSCRIPTIONS
814 897 9000 / Ext. 315
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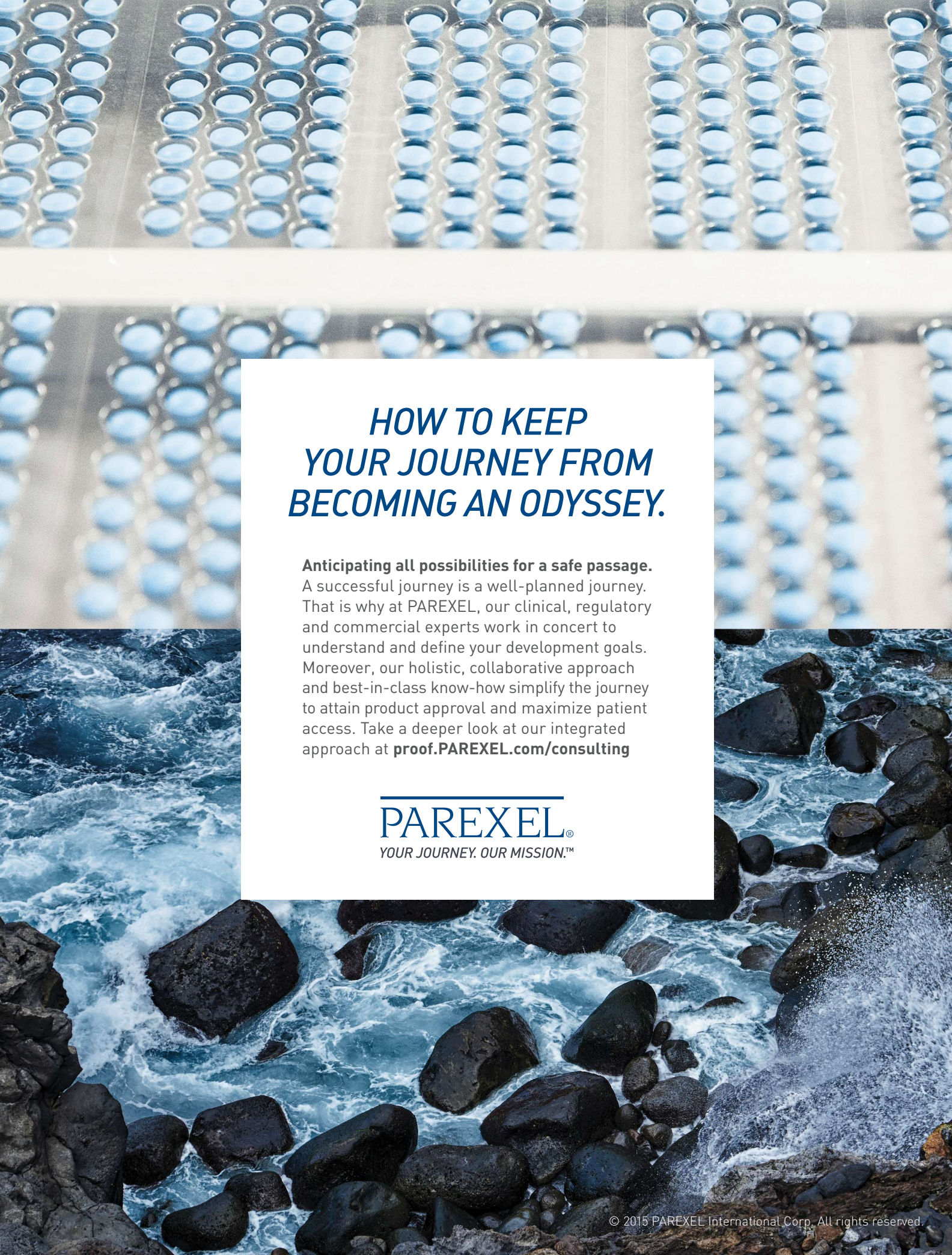

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Q Will CRISPR deliver on the promise to transform the field of biology?

A CRISPR QUESTIONS SHOULD NOT BE WILL OR WHY, but rather, should we or should we not? CRISPR technology promises to elicit genome-wide edits in living organisms. In a short time – partially due to the ease of reducing to practice the technology and results – there have been discussions in scientific circles on germline editing. We are forgetting something in that debate. When scientists discuss the ability to cure genetic diseases through germline manipulation, they would also be assuming that we had the ability to recognize the disease firsthand. My sense is that scientists wish to forge ahead using altruistic message statements, hiding ulterior motives. In the wrong hands, when combined with a targeting moiety and delivery technology, we have a perfect genetic weapon. With time and controlled experimentation, though, CRISPR can deliver on promises.

ALEX CHANG, PH.D.
began as research scientist with Roche and ImClone before transitioning into business development. He is the head of business development and alliance management at KLOX Technologies.

Q What are some of your favorite leadership books?

A

- *Good to Great* by Collins – a goldmine of nonobvious factors for success in companies that stand the test of time. My favorite – the level five leader!
- *Leading Change* by Kotter – an absolute must for a leader managing any change initiative large or small
- *The First 90 Days* by Watkins – whether in a new company, department, or role, an invaluable guidance for success at any level of leadership
- *Thinking Fast and Slow* by Kahneman – the definitive guide to understanding cognitive biases writ small on the daily scale and writ large in corporate strategy
- *Profiting from Uncertainty* by Shoemaker – a very compelling framework for understanding how to plan and chart strategy through uncertainty and ambiguity
- *The Strategy-Focused Organization* by Kaplan and Norton – a must-have reference to the balanced scorecard, a foundational approach to operationalizing strategy
- *Getting Things Done* by Allen – just about the most valuable reference for personal productivity I have come across

JOHN REYNDERS, PH.D.
is the CIO for Moderna Therapeutics. He has held senior R&D and technology leadership positions at AZ, J&J, Lilly, Celera Genomics, and the Los Alamos National Laboratory.

Q How does single-use technology (SUT) impact sustainability goals in the industry?

A IT DOES SO BY REDUCING WATER AND ENERGY CONSUMPTION for cleaning and sterilization processes. However, SUT brings an increase in solid waste compared with traditional process equipment, and it requires additional warehouse space and material handling efforts. Before use, SUT needs to be unpackaged and maneuvered into production areas. After use, the SUT and its packaging need to be removed and managed as waste or recyclable material. These new tasks, workflows, and the additional material for disposal detract from sustainability scores and add costs to operations. To get the most benefit from SUT companies need to look for synergies between sustainability and financial goals. By applying a Lean operations perspective to SUT design, delivery, and use, engineers can reduce the impact of new workflows on operations and also reduce the volume of solid waste to manage. Done properly, SUT will yield improvements in both sustainability and financial performance.

MARK PETRICH, PH.D., PE
is director, component engineering, at Merck. He serves as second vice chair of the Bio-Process Systems Alliance.

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Egalet

Developing Safer Opioids In A Market Under Siege

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

In some ways, Egalet exemplifies the pain-medication space for smaller companies; in others, it appears exceptional. Public for two years, it has two products on the market: Sprix (ketorolac tromethamine) nasal spray, a nonopioid alternative limited to acute or short-term use; and Oxaydo, an oral formulation suited to either acute or chronic pain. The company has two abuse-deterrent formulations of opioids for chronic pain in Phase 3, another in Phase 1, plus a Phase 1 candidate in ADHD.

WHAT'S AT STAKE

What is pain? Why can't we measure it objectively, as we do other physiological phenomena? Why does any treatment for the worst pain also cause pleasure so rich for some people it becomes addictive? Perhaps even more mysteriously, why are the only reliable medications for severe pain still the same type that humans have used for thousands of years — opioids?

Such questions define what's at stake for any company such as Egalet, developing new forms of opioids designed to mitigate their inherent disadvantages. Moreover, the current movement to control a prescription-opioid epidemic makes drug development in the pain area more daunting than ever. Although companies large and small have worked diligently to create abuse-deterrent delivery forms, now policymakers have begun to urge an almost total crackdown on opioid prescribing, including a virtual cut-off for chronic-pain patients — even those with intractable conditions that condemn them to a lifetime of debilitating pain. In response, companies in the pain space are putting more focus on acute-pain formulations. Yet, not all are abandoning chronic pain. Egalet, for one, appears to take the long-term view that a pendulum swing in one direction promises another in return.

"Companies have spent many millions of dollars looking for effective non-opioid pain treatment, and to date, they really haven't found anything," says Robert Radie, president and CEO. "For many people, opioids are the only answer that can get patients with severe, chronic pain to a point where they can be comfortable and function normally. That has been true for years, and I don't see anything on the horizon telling me otherwise."

The company's nonopioid alternative, Sprix, is a self-administered nasal spray formulation of the potent nonsteroidal ketorolac, otherwise available only in an intramuscular injection or pill form. Limited to maximum use of five consecutive days, the product may address single-incident pain or occasional breakthrough pain in patients on chronic-opioid regimens. The abuse-deterrent measures built into Egalet's opioid candidates address the most common practices of the rotten apples who spoil the barrel for patients with pain: crushing, snorting, "shooting" through needles, and so on. Oxaydo, licensed from Accura, employs the Aversion platform, which adds a nasal irritant to the compound. For its other products, the company uses its own injection-molding technology, Guardian, to produce pills no household tools can break apart.

This column normally watches companies developing original or novel compounds rather than developers of reformulated versions of existing drugs. But the unique history of the severe-pain space — and, let's face it, the stunning lack of progress since its earliest times — forces this exception. Innovation in the form of new modalities has not stalled for lack of trying. Despite the many former casualties, some companies have novel agents in the late stages, but no actual alternatives to opiates will likely emerge for years. Until then, to see real innovation in severe-pain medication, keep your eye on Egalet and others creating new forms that bring an ancient and reliable, but risk-filled remedy into the current era.

ROBERT RADIE
President and CEO

Vital Statistics

79
Employees

Headquarters
Wayne, PA

Finances

In 2015:

NASDAQ listing
$15M
venture debt

Hercules Technology
$61M
offering, convertible senior notes

$86.3M
equity follow-on offering

Latest Updates

February 2016:
Agreement with Septodont to promote SPRIX Nasal Spray to U.S. dentists

December 2015:
Submitted NDA to the FDA for Arymo ER (morphine sulfate)

December 2015:
Agreement with Teva Pharmaceutical Industries to commercialize SPRIX (ketorolac tromethamine) nasal spray in select geographies outside the United States

November 2015:
Granted U.S. Patent for Guardian Technology, abuse-deterrent product candidates

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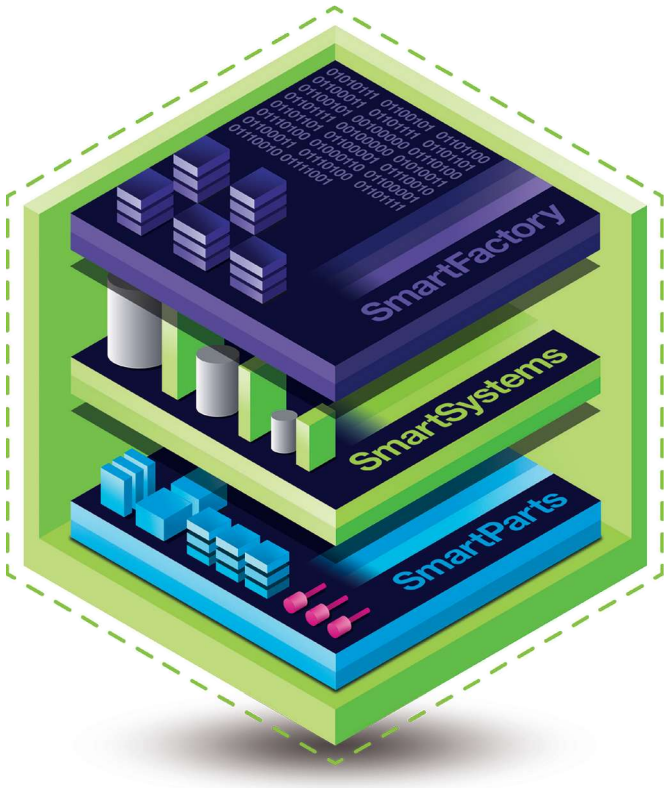

Negotiation Of Medicare Drug Prices

JOHN McMANUS The McManus Group

Already anxious about the intense scrutiny of aggressive pricing strategies by several companies, the pharmaceutical industry went into DEFCON 1 when Republican presidential frontrunner Donald Trump expressed his interest in negotiating drug prices for Medicare.

Who could blame the populist, best-selling author of *The Art of the Deal,* who had also asserted that he would negotiate much tougher trade deals with China, Japan and Mexico, for claiming that he could get pricing down on prescription drugs? After all, Trump seems untethered to Republican and conservative free-market dogma when it comes to healthcare and a number of other economic matters.

But his actual claim was quite curious. At a rally in New Hampshire he said, "These guys that run for office, that are on my left and right and plenty of others, they're all taken care of by the drug companies. And they're never going to put out competitive bidding. So I said to myself, wow, let me do some numbers. If we competitively bid drugs in the United States we can save as much as $300 billion a year."

Really? That's a lot of money, particularly when National Health Expenditures data shows all of American spending on prescription drugs — which includes all government programs, all commercial plans and all out-of-pocket of every individual in the country – totaled just $305 billion in 2014 (the most recent year data was available)! Medicare's portion of that spending was $143 billion.

So, "The Donald" is prone to hyperbole. Shocker! But what about his underlying contention that the Medicare program could benefit from competitive bidding?

Mr. Trump should be heartened to learn that competitive bidding is precisely how the Medicare drug program has operated since its inception about 10 years ago. Medicare contracts with numerous private health plans that, in turn, negotiate drug prices with pharmaceutical manufacturers and pharmacies. The more effective the drug plan is at keeping down costs, the lower its premium will be to attract beneficiaries. Beneficiaries are attracted to the most efficient plans, and enrolling in those plans restrains Medicare expenditures.

That competitive bidding design has worked better than anyone dreamed. The Medicare Part D drug benefit is a rare government success story. Actual costs have come in about 45 percent below initial projections, and patient satisfaction is consistently sky high.

Notwithstanding the impressive results, for more than a decade liberals and the Democratic establishment have tried to empower the Secretary of Health and Human Services to directly negotiate prices with pharmaceutical manufacturers. They have urged repeal of the so-called "non-interference" clause in the statute which prohibits the Secretary from interfering in the negotiations between the plans and pharmacies.

§1860-D(11)(i) of the Social Security Act: "In order to promote competition under this part and in carrying out this part, the Secretary –

- *May not interfere with the negotiations between drug manufacturers and pharmacies and prescription drug plan sponsors; and*
- *May not require a particular formulary or institute a price structure for reimbursement of a covered Part D drug."*

The theory is that the Secretary would have more leverage negotiating drugs on behalf of all 37 million beneficiaries than the competitive, pluralistic market has achieved. But that contention fails to recognize several important dynamics:

1. **The plan sponsors that contract with Medicare also contract with employers and therefore have much more market power than Medicare alone.** For example, Express Scripts, a major player in Medicare Part D, provides drug coverage for 85 million Americans. CVS Caremark and Optum Rx also have substantial national market share and are highly sophisticated negotiators and managers of drug costs.

2. **A single drug plan undermines the government's negotiating power.** A single drug plan means the patient has no choice. Therefore, the seniors, patient advocates and, yes, drug company lobbies would effectively compel coverage of virtually all drugs. If the Secretary could not limit access to particular products, on what basis could she truly negotiate?

3. **How would the Secretary negotiate?** Would the Secretary personally negotiate with over 150 manufacturers for more than 2,000 products in nearly 200 therapeutic classes? Secretarial negotiation for one drug undermines private plan negotiations for all other competing drugs. Whom does the Secretary represent in negotiations — plans, patients, or providers?

The ultimate impact of Secretarial negotiation is to centralize decision making within the Center for Medicare

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and Medicaid Services (CMS). CMS would become the locus for lobbying campaigns where decisions would be made through a political prism.

This is precisely what the Left desires. It would gain the control over the pharmaceutical industry that it now foists upon the hospital industry, physicians, and a slew of other groups that are directly paid by Medicare. CMS does not negotiate with these groups to determine the terms and conditions of their payment. Rather, it administers a raft of detailed fee schedules and reimbursement formulas that are dictated in statute and interpreted by the agency through complex rules, regulations, and program memoranda.

Indeed, the Medicare Part D drug benefit is an island of negotiation in a sea of administered prices.

In February, the Obama Administration's FY 2017 Budget proposed empowering the Secretary to negotiate with pharmaceutical manufacturers for high cost drugs and biologics. However, the Administration's own actuary assessed this policy proposal as providing ZERO savings. The Congressional Budget Office has similarly stated that "Risk-bearing private plans have strong incentives to negotiate price discounts for such drugs and that the Secretary would not be able to negotiate prices that further reduce federal spending to a significant degree."

The real risk to the pharmaceutical industry is not a legitimate negotiation per se — Medicare has already hired powerful and able contractors to fulfill that function effectively. Rather, the risk is establishing an arbitrary price control that does not reflect market value.

Most troubling, CMS does not require new statutory authority from Congress to establish such a pernicious pricing system. It could use its authority under Obamacare's Center for Medicare and Medicaid Innovation (CMMI). Unlike most demonstration projects, which waive discrete sections of the statute and are time-limited (e.g., 3 years) and limited by population and geography (e.g., 5 sites or no more than 200,000 beneficiaries), CMMI may waive the entire Medicare and Medicaid statute for any "Phase 1" demonstration project.

This means the project could essentially be national (exempting Delaware, for example) and last for years. Thus, nothing would prohibit the Secretary from testing the Canadian or Veterans Affairs price of Sovaldi, all cancer products, and a host of other high cost drugs for Medicare beneficiaries residing in the 20 largest statistical areas for five years.

WHAT CAN BE DONE TO PROMOTE GREATER EFFICIENCY IN MEDICARE PART D?

Policy makers are searching for solutions to the rising political invective on pharmaceutical prices. A good place to start would be to examine the distortionary policies Congress enacted to address drug pricing in the first place.

One example is "Medicaid Best Price." As a condition of participating in the Medicaid program, manufacturers must pay rebates to states. This rebate equals the greater of 1) 23 percent or 2) the "best price" negotiated in the private market, plus any price increase exceeding inflation from date of launch. In a series of scathing government reports dating back into the early 1990s, the Congressional Budget Office and the Government Accountability Office documented that imposition of "Medicaid Best Price" resulted in smaller discounts in the private sector and may have contributed to higher launch prices of new products.

Manufacturers negotiate discounts to the customers in order to gain something of value in return — better access to their patients, improved market share, etc. But if they have to provide that same low price to a government program that can deliver no such value, they will have little incentive to provide substantial discounts.

The massive expansion of the Medicaid program by Obamacare — adding 14 million beneficiaries, increasing the program by 25 percent — compounded the distortionary aspects of this policy. Secondly, 340B hospitals that now account for one out of every three hospitals, also utilize the "Medicaid Best Price" scheme to determine their mandated discounts. And that program has grown geometrically in the last five years.

"Mr. Trump should be heartened to learn that competitive bidding is precisely how the Medicare drug program has operated since its inception."

Not everyone can get the lowest price in the market. Requiring huge swaths of the population to be provided the lowest price when they can provide no market benefit in return has undoubtedly resulted in higher prices to other individuals and groups.

Congress made the right decision in 2003 when it enacted a provision added by Ways and Means Chairman Bill Thomas (R-CA) to exempt Medicare Part D plan price negotiations from the "Medicaid Best Price" formula. The Congressional Budget Office scored that provision as saving Medicare $18 billion over 10 years because it encourages manufacturers to negotiate substantial discounts without penalties.

Congress should similarly repeal best price in its entirety so that more consumers may benefit from aggressive negotiations that would surely follow in a more market-based dynamic. This is a much better solution than enabling government bureaucrats to determine prices in an arbitrary matter that would only empower Washington but not hold down costs in the long run. 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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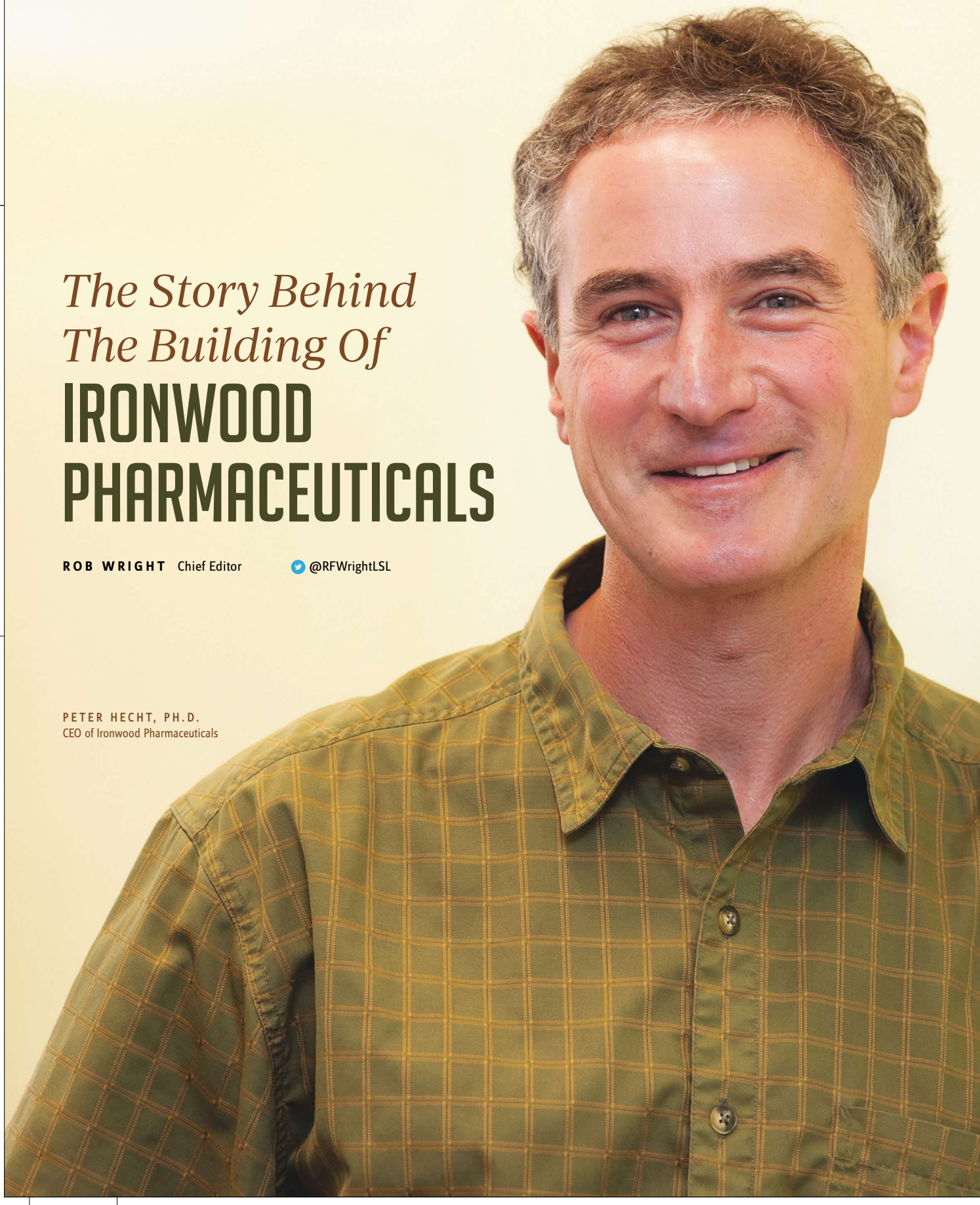
The Story Behind The Building Of IRONWOOD PHARMACEUTICALS

ROB WRIGHT Chief Editor @RFWrightLSL



PETER HECHT, PH.D.
CEO of Ironwood Pharmaceuticals

DO YOU REMEMBER YOUR FIRST JOB? HOW ABOUT YOUR FIRST BOSS?

Peter Hecht, Ph.D., sure does. "I worked at a grocery store in high school," recalls the cofounder of Ironwood Pharmaceuticals. From this early formative experience he learned something very valuable about himself. "I'm a pretty bad employee," he laughingly attests. "I'm always challenging the status quo, asking questions, wanting to see if we can figure out how to do things better."

Though this might be fine in his current role as Ironwood's CEO, what the would-be entrepreneur learned back then was that most bosses (i.e., those who have been running a supermarket the same way for 30 years) really don't want the guy bagging groceries to tell them how to run their businesses more efficiently. Some 15 or so jobs and similar experiences later, Hecht figured he needed a job where he could either work with a bunch of partners or for himself. In the mid-1990s, while working as a research fellow at the Whitehead Institute for Biomedical Research, an MIT affiliate, Hecht decided he was finally ready to scratch his entrepreneurial itch, and he began formulating the notion of building a sustainable pharmaceutical company from scratch.

BUILDING A BIOPHARMA IN GREATER BOSTON

There's no doubt that being in Cambridge, MA, and at MIT were two factors that significantly helped Hecht launch Ironwood. For example, the first three people he

HOW IRONWOOD EMBEDS A LONG-TERM FOCUS

Since the pharmaceutical product life cycle is lengthy and unpredictable, Ironwood believes it is critical to have a long-term strategic horizon. To that end, the company strives to embed a long-term focus through certain policies and practices, which include:

- A dual-class equity voting structure (which provides for super-voting rights of pre-IPO stockholders only in the event of a change of control vote). This is designed to concentrate change-of-control decisions in the hands of long-term focused owners who have a history of experience with Ironwood.
- Weighting compensation to equity over salary for all of Ironwood employees. For example, many employees have a significant portion of their incentive compensation in milestone-based equity grants that reward achievement of major value-creating events.
- A change-of-control severance plan for all employees. This is to encourage employees to share their best ideas, giving them the peace of mind that in the event of a change of control and employment termination, they still have an opportunity to share in the economic value they helped to create.
- All board of director members are substantial Ironwood investors and are required to hold all shares of stock acquired as payment for their service throughout their term.
- Partnerships with Allergan, Astellas, and AstraZeneca all include standstill agreements. These serve to protect Ironwood from an unwelcome acquisition attempt by a business partner. The company also had change-of-control provisions in its partnership agreements to protect the economic value of linaclotide.

approached for advice about his idea were Charlie Cooney, Ph.D., Chris Walsh, Ph.D., and David Baltimore, Ph.D. Cooney, who cofounded Genzyme, and Baltimore, a Nobel Prize winner who started half a dozen companies, were both at MIT, within walking distance of Hecht's office. Walsh, who had been a scientific advisor to dozens of pharmaceutical companies, was just across the river at Harvard Medical School. "Even though I didn't know anything, very quickly I was able to tap into the people who did, ask a lot of questions, and learn very fast," recalls Hecht.

In contrast to his boss at the supermarket who didn't want to hear his suggestions, Hecht says all three of these academic leaders and biopharma heavy hitters were very supportive, connecting him to investors and other scientists. But when Cooney and Walsh told him that they liked his idea and that they wanted to invest, he thought, "Now what do I do?"

As Hecht and his six cofounders (Brian Cali, Joseph Cook, Gerald Fink, Gina Miller, Todd Milne, and Eric Summers) continued to bounce ideas off their ever-expanding network, Ironwood continued to take shape. Twelve years after being legally founded, the company executed its IPO. Though selling 19.2 million shares at $11.25 each was well below its target of $14 to $16, considering the timing (on the heels of the Great Recession) and being the first biopharma IPO in about three years, the successful raising of $203 million via the IPO in 2010 was a significant milestone.

But even more significant was the discovery of their first molecule, LINZESS (linaclotide). "It's an oral peptide that survives through the harsh environment of the stomach and gets into the gut and works on a receptor there to relieve abdominal pain," Hecht shares. "It also brings fluid into the gut, so it helps with constipation." But it is the drug's pain relief that got the folks at Ironwood really excited. "As soon as we saw, even in early and preclinical studies, that the drug had a direct pain mechanism in the gut, we knew we had a big opportunity to help millions of people suffering from GI-related discomfort," he says. In August 2012, Ironwood received FDA approval for LINZESS, indicated for irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adults. LINZESS, like Ironwood, is enjoying consistent growth, approaching use in nearly 1 million patients thus far.

EVER HEARD OF THE WARREN BUFFETT SCHOOL OF BUSINESS?

Warren Buffett is one of the most successful investors the world has ever seen, a fact not lost on Peter Hecht, even at the age of 12. "I've been a Warren Buffett groupie since I was a little kid," Ironwood Pharmaceuticals' CEO admits. "For various reasons, I started getting Buffett's annual reports when I was young." Hecht admits to always being very inquisitive about the business world, which may have been because he saw his father start his own business. Hecht's older brother convinced him that he should read Buffett's reports, if for nothing else, that they were funny. "The first couple years I read them just for the Mae West jokes," he laughs. "But Buffett is a clear thinker and a good writer, and I started finding that I really liked business, and I actually understood what he was talking about. For example, he'd have sections in the annual report where he'd do accounting explanations." Hecht even remembers reading a Buffett accounting treatment for acquisitions back in high school. "At that time, there were two ways you could legally account for an acquisition, and he [Buffett] discussed each and the consequences of each for your financials. And it made a lot of sense to me." Though Hecht went on to earn a B.S. in mathematics, an M.S. in biology, and a Ph.D. in molecular biology, he believes he got his MBA long beforehand. "I have the Warren Buffett version," he insists, "Because I read all of his Berkshire Hathaway annual reports and was able to get ahold of the old Buffett partnership documents, which I have read a bunch of times. I'm a pretty serious Buffett groupie," he reiterates.

BECOME A TALENT MAGNET

When speaking with Hecht, he's quick to note that, although he's a cofounder of the company, "The story is really not about me." Others — and history — may disagree, though. For instance, Hecht, who was called "a talent magnet" by one of Ironwood's investors, is the guy who managed to woo his fellow cofounders to invest in the company. He did that despite the fact that three of them, Cali, Milne, and Summers, had all received offers to work at premier academic institutions — and in spite of himself having zero formal business, entrepreneurial, or leadership training.

Still, during our conversation Hecht continued to deflect any attribution of company success to himself (a true leadership quality, by the way), instead crediting Ironwood's core mission as the true talent magnet. "We're here to create new medicines that can really change people's lives, as hard as that might be," he says, adding that if you're going to have grandiose goals, by default, you need incredible talent to reach those goals. He claims it's those big goals — the desire to build a great pharmaceutical company from scratch and to have it last a couple hundred years — that have helped

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IS DEATH THE BEST EXIT STRATEGY?

Listening to Peter Hecht tell the story of Ironwood Pharmaceuticals, you initially get the impression that everything went smoothly in those early years. The cofounder and current CEO of the company makes it sound easy when he tells the story of getting $10 million in series-A financing from Venrock, Polaris Partners, Aberdare Ventures, and several angel investors in 1998. But then he tells what happened leading up to that initial investment. As he puts it, "It's a funny story."

"Very early on, even before we raised our first round, we met with a bunch of different VC funds," Hecht begins. "Remember, although this was at the height of the dot-com bubble, it was still a very hard time for biotechs to try to raise money. One of the firms asked us what our exit strategy was, and I simply said 'Death.' Well, he almost got up from the table and walked out of the door!"

Though Hecht realized that death as an exit strategy was probably not the best way to describe his and his cofounders' commitment to seeing Ironwood succeed, not every investor would share this level of devotion. Nevertheless, he believes, especially in those early days, stating this death strategy worked well when selecting investors. "Those investors who were looking for success in a shorter amount of time than us were discouraged from investing when they heard our death as an exit strategy," he explains. "In addition, it helped us connect with the best venture capitalists in the healthcare industry that were very long-term oriented and focused on building great businesses." Over time, Hecht refined his response. "I learned to say something a little more politically correct, like, 'That's a very good question. We're working to build a great company and to earn the right to create returns for our investors. We'll create on- and off-ramps so that you can get an exit at the right time, but we intend to keep building the business.'"

Ironwood attract top talent. "We wanted to collect likeminded, crazy people who were very mission-driven," he explains. "They had to accept the company's very long-term focus. They had to understand that drug development is all about managing your way to success through failure. After all, the products we're talking about discovering, developing, and bringing to market have 10- or 15-year development cycles, and then they have 15- or 20-year franchise lives. That long business cycle is the reality of biotech."

THREE OF THE IRONWOOD PHARMACEUTICALS FOUNDERS (from left): TODD MILNE, VP OF SGC R&D; PETER HECHT, CEO; BRIAN CALI, SENIOR VP OF PRECLINICAL R&D

THE IMPORTANCE OF COLLABORATIVE SCIENCE

When talking about Ironwood's allure to employees, Hecht frequently mentions the term "collaborative science." It's a concept that he stresses is part of the very fabric of the company. It's basically team-based science, as compared to working solo in a lab. But it's more than that. He explains that the latter has the goal of simply uncovering new knowledge for the sake of doing so, while collaborative science actually translates that knowledge and insight into something that can be incredibly meaningful to a patient. "It's a faster, more exciting, and productive approach that offers the opportunity to make a difference in the world in an applied way," he says. It's also why his cofounders turned down their academic offers.

At Ironwood, collaborative science is a very iterative process, starting with a molecule that has some activity against a target of interest. What follows is a labor-intensive effort to keep improving the attributes of the molecule, a process that requires close collaboration among biologists, chemists, pharmacokinetic and pharmacodynamics people (i.e., the DMPK group), and pharmacologists.

"The process is not driven by one group but a collective," Hecht elaborates. "We form project teams that can consist of three to six people." The goal is to involve at least one person from each of the groups listed previously. The groups start improving on what they call a "pharmacophore," which is the core molecule that has some of the desired attributes. "The group members tend to learn from each other, so that over time our chemists start to think more like pharmacologists, and our pharmacologists tend to think like chemists,"

Hecht explains. "Once we get a molecule that looks like something being targeted, we bring in preclinical and early clinical folks. Whether it is safety toxicology studies or preparing the molecule for chemistry scale-up, we want to continue this close collaborative process throughout the organization, all the way through to development."

Although Hecht believes there are many successful approaches to the drug development process, at Ironwood there is a concerted effort to avoid the development of silos. To explain why, he recounts a story he heard from the head of chemistry at a pretty big pharmaceutical company. The chemistry group had about 100 chemists in the EU and another 100 in the U.S., all working toward the same target for about a year and a half. They ended up making some very potent molecules against the target. But when the molecules were finally shipped off to the biology group, it was discovered that they didn't get across the target membrane at all. Though they had devoted around 200 people to conduct 18 months of exquisite chemistry, it was far away from making a drug. "At Ironwood, we love the idea of cross-disciplinary learning and being able to draw on those resources," Hecht says. "After all, humans are learning machines."

Hecht and his colleagues have certainly been emulators of this principle. Since the early days of founding the company, the Ironwood team has applied the iterative process of scientific drug development to the business of building a biopharmaceutical company — learning, growing, evolving. Today, Ironwood (NASDAQ: IRWD) has a market cap of $1.37 billion, a commercial engine to capture and maximize value, and a pipeline Hecht believes is robust enough to keep things going for a long time to come. "Exclusivity with LINZESS should get us to at least 2031, and our second generation, if successful, takes us to 2036," he shares. Combine this with Ironwood's efforts in refractory GERD (Gastroesophageal Reflux Disease) and vascular and fibrotic diseases — both programs that are expected to be blockbusters with IP protection well into the 2030s — and it appears Hecht and team are well on their way to building a pharmaceutical company that can generate rapid, sustainable, high-margin growth, just as they set out to do back in 1998. It's easy to imagine that the only thing this one-time grocery store employee will soon be bagging is accolades from patients, providers, and yes, even shareholders. L

Abbey Meyers:
Did the Pioneer of Orphan Drugs
Spark Biopharma?

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

I was just a baby editor then. In my first months of being the *editor of an industry trade journal, a momentous letter arrived. It was from a woman I had just mentioned in my monthly column, where I praised her organization and the legislation she had helped create, coaxing companies onto the path of orphan-drug development and making new treatments available for patients with rare diseases. Surprisingly, her letter took issue with my editorial, saying something like, "You know, Wayne, unless a drug is affordable, it is not truly available."*

At the time, before most U.S. insurers began to pay the premium for orphan drugs, patients and their families would bear the cost. Companies could and did take advantage of a key incentive built into the Orphan Drug Act (ODA) of 1983 — *exclusivity* — to fund new drug development for rare diseases but also to push the premium price levels upward. The ODA granted seven years of additional market exclusivity for the first product to gain approval for a rare disease, defined as any condition with 200,000 or fewer patients in the United States.

By the time Abbey Meyers, founder of the National Organization for Rare Disorders (NORD) and chief architect of the ODA, wrote her letter to me a few years later, the paradoxical conflict of orphan-drug availability versus price had become obvious. Almost from the beginning, Meyers was perplexed by the discord. For patients, the Act worked spectacularly well in stimulating development of rare-disease therapies. But for the industry, or at least for some companies, a spotlight on the financial incentives often cast a shadow on the patient benefits.

Of course, a lot of new elements have come into the picture since the Act's passing. Entering the scene are huge health-management, payer, and prescription benefit management groups. On one hand, patient-assistance programs for expensive orphan drugs have multiplied; on the other, the industry has shifted away from developing primary care medicines to greater reliance on narrowly focused drugs with premium prices. As often cited, more than half of the 45 NMEs (new molecular entities) the FDA approved in 2015 were for orphan indications.

Spiking co-pays, deductibles and other "cost-sharing" measures have once again placed an increasing burden on U.S. patients just as orphan-drug development reaches new heights. Payers initially adopted the cost-sharing measures for general circumstances, not only for orphan drugs, but the measures have fallen especially hard on patients with rare diseases for which drug prices are traditionally high.

In recent years, however, list prices for

new orphan drugs have reached a new order of magnitude, up to the mid-six figures. So payers and PBMs (pharmacy benefit managers) are exercising even greater "management" of orphan-drug spending, such as switching from co-pays to co-insurance and blocking some drugs with purchasing bans. If a large PBM refuses to pay the asking price, a particular orphan drug may even become unavailable for many patients, at least until a new, lower-cost supplier steps forward.

So it is now upon a new stage, a new world, that I once again connect with Abbey Meyers for this "Industry Explorers Blaze On" article. From the time of our first exchange, Meyers continued to lead NORD and help pass several amendments to "fine-tune" the ODA over several decades. All the while, she was observing and mixing with industry leaders, legislators, policymakers, and many other stakeholders in orphan drugs — above all, patients. It is the patient community that still concerns her the most, though long ago she learned how to speak with the industry and others in the halls of power.

Industry Awakening

The key facts in the story of how Meyers became an orphan-drug advocate have been well reported — her son had a rare disease but lost access to a helpful investigational drug when its clinical trial was canceled. She then rallied parents of rare-disease patients and others to establish NORD and push for the ODA, and she worked directly with Congress members to write and pass the bill. But all of those dry facts fail to convey the dramatic change and adversity that journey brought to her life. One of the problems was learning where new medicines originated: an industry made of profit-making companies that developed, produced, and sold them.

"It was a shock. I approached this all, truly, as a housewife," says Meyers. "People can recall what a housewife was in the 1970s. You stayed home and raised the children — and don't even think about a career! I had no thought about the pharmaceutical industry or where drugs came from or why they were developed until my son was diagnosed with Tourette's syndrome."

The word "orphan" is not synonymous with the word "rare," though the two terms are often conflated. Even now, 33 years since the passing of the ODA, an estimated 95 percent of rare diseases still lack an effective drug treatment. A drug to treat a rare disease often already exists, at least on the bench, but it has no "parent," no company sponsor to take it through development. Meyers' story illustrates how drugs with the potential to treat rare diseases can become orphans.

"We worked with the drugs available on the market at that time, mostly sedatives, but they were not satisfactory," she recalls. "My son would fall asleep in the classroom. Our doctor in New York, the guru of Tourette's syndrome (TS) at that time, was using an experimental drug for the condition. The drug had initially come from Europe but wasn't approved in the United States, and the company was reluctantly including a small number of TS patients in a clinical trial of the drug for a more common disease. But the doctor said if I was willing to put my son into the trial, he could go on this experimental drug. At that time, I didn't even understand what a clinical trial was."

Thus Meyers began her climb up a steep learning curve, with the clinical trial as her introduction to the pharmaceutical industry. She had many worries about the trial, but a major one was whether could she afford to pay for the monthly blood tests the trial required. "It was $45 per test in the 1970s and not covered by insurance," she says. "It was a really tough struggle for us, so instead of going every month, we did the tests every six weeks. I found out years later the investigators were slapped by the FDA for allowing the longer test period. Of course, the FDA doesn't think about who's paying for the tests, either."

When the company suddenly canceled the trial, Meyers went from reaction at a distance to close interaction with the industry. Rather than accept the loss of treatment as fate, she decided to seek continued supply of the drug that had obviously helped her son. She secured a meeting with company executives, who ultimately agreed to continue producing the drug for the patients it had benefitted. Meanwhile, however, Meyers began to learn about other rare disorders poorly served by the industry. In several cases she mentions, small labs in individual institutions, such as New York's Mt. Sinai Hospital, would compound a drug for its own patients.

"These compounded drugs were all over the country. It was typically academic doctors who had discovered them but could not find any company willing to make them because the potential market for each drug was too small for the big manufacturers." And thus Meyers extended her education in the ways of the industry and soon came to some practical conclusions.

"Our economy runs on profit and loss, and it's OK to run a business entirely on that basis if you make tires or bicycles, but when you apply it to a medical field like drug manufacturing, it can step over the line of human need. Is there an ethical point where a company cannot just say no to developing a needed drug because it will not make enough profit? Back then, if someone had a great idea for a drug that would treat a rare disease, drug companies routinely rejected it based on a low profit projection and walked away. It was obvious we had to find a way to let decent, ethical people know what the situation was, so they would put pressure on the government and the industry to do the right thing."

Pressure Pointing

Meyers and NORD subsequently sought and found many ways to exert such pressure, but one in particular helped open the floodgates and turn on the power: *Quincy*, the 1980s TV series starring Jack Klugman as a coroner-detective. After reading about orphan drugs, Klugman's brother convinced the actor to focus on the problem as the theme for two *Quincy* episodes.

"The *Quincy* programs really pushed the law through the House and actually got President Reagan to sign it," Meyers says. "He wanted to veto it, so we had to do a lot of work in the last few days."

Later, at a key Congressional hearing to write an amendment that would put a specific number on the Act's vague use of "rare," Meyers and the only other woman in the room, the FDA's head of orphan drugs, Dr. Marion Finkel, found the otherwise empty women's restroom the

Friends In All Places

Abbey Meyers says two of her key industry mentors "in the formative years" were Max Link, chairman, and Craig Burrell, executive VP, of the pre-Novartis Sandoz. "Max and Craig were extremely supportive and went out of their way to introduce me to people in the industry so I could fully understand the corporate structure and how companies made decisions about drug development." But Sandoz also created one of the first challenges to the Orphan Drug Act's practical application, introducing the first drug to make kidney transplants possible for patients, Sandimmune (cyclosporine) — at $8,000 per year. It was a tremendous breakthrough, says Meyers, but its unprecedented price caused a shock wave. "It might as well have been $1 million a year, because $8,000 per year was way more than anybody could afford in the late 70's, early 80's."

At the time, insurance companies generally had no special provisions for orphan drugs, but they had limits to drug coverage, and they would likely have precluded payment for a four-figure yearly price tag. But then as now, U.S. kidney-disease patients had a special insurance status — Medicare paid for all kidney dialysis — though the new drug presented them with a conundrum. Medicare at first refused to pay at all for Sandimmune, then later changed its policy to pay only for the first year of its use.

"What good would that do?" says Meyers. "People who had transplants no longer had to do dialysis three times a week; they were feeling a lot better, and they were independent so they didn't have to live close to a dialysis clinic. But if Medicare would pay for the drug for only one year, after one year, what could they do? They couldn't get private insurance because they had kidney disease. They would stop taking the drug and they would reject their transplanted kidneys."

Meyers' phone rang. It was Craig Burrell. Sandoz was in a quandary over Sandimmune's payment problem in the United States and could not decide how to deal with it. Would NORD help?

"Craig said the company was eager to find a methodology for ensuring all patients would have perpetual access to the drug and thus avoid rejection of precious kidney transplants. He said the marketing people at Sandoz shouldn't be making the decision about which patients will receive or not receive the medicine. So, we went to work and created the first medication assistance program, which included cyclosporine and eventually more than a half-dozen other Sandoz drugs."

NORD actually ran the program; patients applied to the organization and, if eligible, were required to reapply and requalify annually in exchange for a free supply of the medicine. Medicare had assumed transplant patients would become healthy enough after a year on Sandimmune to go back to work and support themselves enough to pay for the drug. But NORD found the folly in that belief; even though patients felt much better, the rigors of transplant and drug side effects kept them far from normal health, physical or financial.

most private place to discuss the issue. Finkel's preferred figure was 100,000. Meyers wanted twice that number, and after she cited several unserved conditions with patient counts hovering just above that number, they agreed to argue together for 200,000 as the defining figure for rare disease in the law, still a small population but big enough to qualify many diseases ignored by industry because of poor market-return potential. As evidenced in the existing law, their arguments won the day.

The reasoning Meyers and Finkel followed typifies the general, common-sense, and practical approach to the overall writing of the ODA and its amendments. They had combined statistical projections of the patient population, including the likely undiagnosed, with a realistic assessment of the breakpoint for the industry where it would start to undertake development. The other practical lesson from the exercise is political: If you can't get everyone to agree on all the details before passing the law, get it passed first and settle on the details later.

But the core of the law was also boldly practical. "We knew orphan drugs were potential money-losers, so making them into profit-earners was very important," says Meyers. A rival proposal in Congress would have set up a revolving pool of funding for orphan-drug development, with the government issuing development grants, and companies surrendering profits for approved drugs back to the government. To Meyers, the industry's response could be summed up in one word: laughter.

"That was a very good learning point, because we turned around and asked ourselves, 'OK, what would satisfy these companies?' Let's say, 'We're going to give you a chance to make a profit and whatever profit you make, you'd be able to hold onto it yourself; you've earned it.' And we came up with the idea of seven years' exclusivity. Congressman Henry Waxman's staff went out and did the research on it and found, most of the time, companies apply for a drug patent very early in the process, way before it is even in clinical trials. By the time a company can get a drug on the market, it usually has only a few years left on its patent. And the ODA's seven years of exclusivity didn't start when you applied for an orphan drug designation; it started on the day the FDA approved your drug."

The Act also tied the exclusivity to indication, not chemical identity. The first FDA-approved drug for a rare disease has a monopoly on the indication for seven years. No "me-too" compounds, slightly altered from the original, can enter the market for the same condition during that period. Only entirely different molecules targeting the disease through a new approach can carry the same indication. Given those caveats, the Act would offer super-sized exclusivity, and Pharma stopped laughing — instead, it merely yawned. Fatefully, the industry's complacency led to an unexpected and overwhelming disruption.

"It took a long time for the industry to understand how important the ODA

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incentives are," Meyers says in witness. "The big companies really ignored the orphan-drug opportunity for the first number of years after the Act, so a whole new segment of the industry grew up around orphan drugs, consisting of little companies, many of them biotech. They were the first to recognize the importance of the law and its incentives."

She points to a particular incentive in the law that especially appealed to startups: tax credits. Pre-ODA, a company developing orphan drugs could use a tax credit only when it made a profit. If the company had lost money for its first years, it couldn't use the tax credit. "So years later we went back and passed another amendment saying the tax credits could be brought forward or brought back several years. A company could then apply them to a year when it is profitable. A mountain of small companies came into orphan drug development because of that change."

To Police Or Be Policed

You can't legislate everything. Even the best laws have loopholes, which is one good reason we are always left with plenty of moral decisions to make. But people of goodwill can come together to solve technical or tactical problems in applying the law, finding a balance of their multiple, sometimes conflicting interests they can all accept. Or one party or another can take off on its own and turn the law's gaps into open wounds.

Almost from the beginning, the ODA faced minor problems, most of which the later amendments mended. But one large unknown and uncontrolled factor in the incentives it offered was price and affordability. Although drugs developed from small patient populations had always cost more than large-market, primary care products, no one knew how a long period of orphan-drug exclusivity would affect the normal price parameters. NORD played a key role in helping companies and patients work through the initial challenges in both personal and practical ways, such as creating the first medication assistance program with Sandoz to ensure access to Sandimmune (cyclosporine), a critical drug for kidney-transplant patients.

I asked Meyers about the current row over drug pricing in the United States. Pharma companies respond to criticism of their pricing by saying it's the insurance companies' fault for not covering — and vice versa, the mega-sized private payers and PBMs blame the pharma companies for price gouging. So far, it is the drug industry coming across as the bad guy in the public eye, arguably aggravated by the self-serving tactics and outright bad manners of some new upstarts in public view.

"The scenario you just described really makes me so upset," she replies. "The pharmaceutical industry needs to police itself so it doesn't continuously get itself into these ridiculous circumstances that spur negative public relations. Who is being punished in the end? It's the patient. Pharmaceutical CEOs need a support group. They need to talk to each other, but not as a 'good 'ol boys' club,' not as a fraternity meeting, but as a group of people who have to face reality. One CEO should be saying to another CEO, 'You shouldn't charge a half-million dollars a year because most middle-class people in the United States can't afford to buy a half-million dollar house in their entire lifetime.' And the insurance companies have to do something or they're going to go broke, so they put their foot down and say they won't pay."

Meyers offers a suggestion for how the industry can "fix itself." By the existing tenets of the ODA, price-lowering competition among orphan drugs is still possible. When essentially the same or closely similar drugs can be used for more than one orphan disease, one of them may win first approval for a single rare condition, but another may win approval for a second rare indication, putting both drugs on the market at the same time. Once that happens, doctors are free to prescribe either drug for either indication. And the process is iterative — multiple drugs, all "me-too" molecules, each one approved for a single orphan disease, can thus enter the market simultaneously and compete with the other based on price. But the incentives for developing drugs for truly rare diseases that share no common mechanisms with any other remain intact.

She remains confident in the ODA's integrity and in the value of its accomplishments. "I believe the situation with orphan drugs is all very hopeful. I look back on 30 years and think, this is really extraordinary — the medical breakthroughs have come one right after another on diseases people can't even pronounce. There are a lot of kids alive today who would've been dead in infancy without orphan drugs, and no one is losing money developing an orphan drug anymore. Everybody makes money; it's a matter of making too much money that's causing the problems."

An Opening Horizon

What's next for Abbey Meyers? A book just published, "Orphan Drugs — A Global Crusade," and continuing advocacy for rare-disease patients and orphan drugs will surely fill her days. She is passionate about seeing the principles of the ODA expand further internationally, as they have already in Europe, Japan, and beyond. Regulatory authorities in many countries now have their own orphan-drug offices, and even numerous nations with no equivalent of the ODA legally expedite imports of orphan drugs for their own use.

Meyers does not seek legislative remedies that would imperil industry or orphan-drug development. She fiercely opposes attempts to amend the ODA, whether intended to stimulate more innovation or prevent price gouging. "To anybody who says the Orphan Drug Act needs to be changed, you have to ask one question: 'Why do you want to change something that works?' It works beautifully. Leave it alone. The major breakthroughs in medicine will continue to come through the Orphan Drug Act."

After all the years since that first letter I received from Meyers, I can see now that her approach has always remained the same: She accepts and works within the economic system and with the industry that has proved itself capable of producing orphan drugs, given the right incentives. At the same time, she has consistently nudged the industry's conscience with a positive spirit that reminds companies of their moral obligation to patients with rare diseases. For that, and for the entire sector she helped spawn, the industry owes her lasting recognition — and continued interaction. L

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HOT NEW THERAPEUTIC MOAs VERSUS NEURODEGENERATIVE DISEASES

A VIRTUAL ROUNDTABLE

PART ONE OF THREE PARTS: AIMING AT ALZHEIMER'S

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

The following key opinion leaders (KOLs) participated in this "virtual roundtable" on new therapeutic approaches in development for Alzheimer's disease.

MICHAEL WEINER, M.D.

Professor in Residence

Radiology and Biomedical Imaging, Medicine, Psychiatry, and Neurology

School of Medicine

University of California, San Francisco

JAMES A. HENDRIX, PH.D.

Director, Global Science Initiatives

Alzheimer's Association

GARY W. SMALL, M.D.

Director, Geriatric Psychiatry Division

Director, UCLA Longevity Center

Professor of Psychiatry and Biobehavioral Sciences

Parlow-Solomon Professor on Aging

UCLA Semel Institute of Neuroscience and Human Behavior

This series is our second "deep-dive" into a hot new therapeutic area, the first being "Combination Cancer Immunotherapy – A Virtual Roundtable." (September 2014 to January 2015, with a September 2015 update.) Here we dive into the neurodegenerative diseases (NDs) area – where a long, dark period of disappointment and frustration may be giving way at last to a flush of new therapeutic approaches based on previously unidentified or poorly understood mechanisms of action (MOAs).

Our virtual roundtable stitches together the separate inputs of participants into one comprehensive discussion, capturing the key players and issues at the dawn of revolutionary new modes of treatment. It brings together a panel of disease experts – key opinion leaders and scientists who are leading some of the most advanced research in the ND field. For comparison, and a closer look at the business side of the awakening ND space, we also cameo some of the companies in various stages of developing original agents that employ new MOAs.

Recognizing the considerable overlap of disease mechanisms and treatment issues among the many NDs, this series concentrates on the three most prevalent and representative of them: Here, Part One covers Alzheimer's disease (AD). In subsequent months, Part Two will explore Parkinson's disease, and Part Three, multiple sclerosis and other NDs.

Our limited sample of companies involved in the space suggests the range and variety of new MOA and drug development therein. (See the sidebar "Alzheimer's Advances — Development During Debate," and the table "New Therapeutic MOAs: Alzheimer's Disease.") Similarly, the small but prestigious panel of KOLs represents a range of leading views.

Our virtual panel discusses not only the scientific, regulatory, and other practical hurdles that lie before the new approaches, but also the issues that will affect any candidates that ultimately survive the development gauntlet and enter medical practice. Those include the possible use of therapeutic agents with different MOAs in combination, as well as the methods and authority for configuring combinations, along with pricing, postmarket regulation, and patient education.

MIRACLE OR MIRAGE?

Our KOL panelists, Drs. James Hendrix of the Alzheimer's Association, Gary Small of UCLA, and Michael Weiner of UCSF, begin by rating the chances and likely timelines of new MOA drugs in development for Alzheimer's disease. Their views vary considerably, reflecting the ongoing debate in the field as a whole.

What are the most promising therapeutic targets/mechanisms for Alzheimer's?

HENDRIX: The most excitement in the Alzheimer's field during the past year has been driven by the amyloid space. What made it exciting is the incorporation of amyloid imaging into some clinical trials, along with other amyloid biomarkers, such as CSF (cerebrospinal fluid). Those tools allow our clinical researchers to identify people with high levels of amyloid in their brain, so they can give an experimental drug to people who should respond to it — and that's new.

WEINER: I'm a mainstream Alzheimer's scientist, and I see the disease as closely associated with two misfolded proteins, amyloid beta and tau. By definition, to have Alzheimer's disease, you must have both proteins. Although not proven yet, there is a huge amount of evidence those proteins are the causes of neurodegeneration. The problem with developing a treatment aimed at general mechanisms such as neurodegeneration is that they are tied to the normal machinery of the cell. The more specific the target and the more specific the treatment, the less chance there is for side effects. That's what the industry is doing with passive immunotherapy, the monoclonal antibody (mAb) amyloid blockers such as solanezumab and aducanumab.

As people age, one reason they accumulate misfolded proteins is immunosenescence — the immune system ages to the point where it can no longer generate a strong antibody response to those proteins. How can we ramp up the immune system to respond better to these diseases? That's a long-term question. Meanwhile, we would like to see more efforts directed at preventing the formation of phosphorylated tau tangles, which is more closely associated with synapse loss and neurodegeneration than amyloid plaque.

SMALL: There are a lot of mechanisms in the brain besides amyloid and tau. In Alzheimer's disease, there's also evidence of inflammation. Despite the tremendous focus on antiplaque, so far it has not panned out. Even though we see a mechanism, we are not quite sure how to disrupt that mechanism to benefit the brain. Some of the changes we see may be just a result of some other neuropathic states underlying those mechanisms. I am a big advocate of diversifying our research portfolio, because we are not sure what will score a hit. In some of the clinical trials with anti-inflammatory treatments, there seems to be a benefit if used early, but exacerbation if used later.

HENDRIX: The biomarker studies, particularly the collaborative Alzheimer's disease Neuroimaging Initiative (ADNI) study, have shown that changes occur in people's brains as much as 10 years

ACCERA

Enrolling a Phase 3 trial of its ketone-based glucose-metabolic substitute.

Charles Stacey, President and CEO: *During the past 10 years, the failure rate for Alzheimer's drugs in Phase 2 and Phase 3 has been 99.6 percent, which is higher than for any other indication. One of the main reasons is the industry as a whole is really focused on the amyloid hypothesis, but whether the hypothesis explains a cause or effect has really never been established. We need to have more mechanisms of action. We need to diversify the targets we're looking at. As a company, we are addressing a different mechanism with our lead compound, AC-1204. It is well known that in Alzheimer's disease there is a metabolic deficiency within the brain — the brain becomes starved of its fuel, glucose, and goes into a neurotoxic decline, and the neurotoxicity leads to cell death. Our drug replaces glucose with ketone bodies that can serve as an alternative fuel to reverse the neurotoxic cascade.*

NEUROGENETIC PHARMACEUTICALS

Completed positive preclinical PoC (proof of concept) clinical safety study for a small molecule drug that modulates the gamma secretase complex in amyloid-plaque production to suppress toxic plaque.

William T. Comer, Ph.D., CEO and Chairman: *You can't treat people with advanced Alzheimer's; it's too late. You can't cure a dead brain. You've got to prevent the disease, but how? You must go back in the system and see what causes the problem in the first place. We believe it's the toxic form of amyloid plaque, but the first amyloid antibodies failed in trials – because the FDA limited them to patients who were too far advanced. But the anti-amyloid strategy appears to work when it targets an earlier population. It's well understood that cognitive impairment probably occurs years after amyloid deposition begins. Thus, if you use cognitive impairment as your early diagnostic, the amyloid and tau pathologies are already too advanced to reverse or prevent Alzheimer's disease.*

We should treat patients when we can prevent significant cognitive impairment by reducing the amyloid plaque so the condition doesn't get worse. Our company has a novel and maybe more effective way of addressing toxic plaque early. Our gamma secretase modulators (GSMs) are based on an innovative modulation of a key enzyme in the amyloid pathway, called γ-secretase. The approach with our lead product NGP 555 is to alter the production of amyloid proteins from the toxic form found in AD brains (Aß42) to nontoxic forms (Aß37 and Aß38), which do not contribute to plaque deposition.

before cognitive symptoms occur. If we can identify those people early and prevent the disease progression, we could have much better outcomes. Our hope is we'll eventually be able to delay the onset of the disease for a long enough period that people will live long enough to die of a different disease, and with their memories intact.

COCKTAIL CALL?

No one seems to argue for monotherapy in Alzheimer's disease, though the KOLs may disagree by degree about the therapeutic bandwidth of potential "cocktail" regimens. With so many non-exclusive targets in the long, complicated disease pathway, combination therapy for Alzheimer's seems inevitable.

How likely is it that some future drug therapies, each one hitting a different target, will prove complementary if used together? Could combination drug therapy then become the paradigm for treating a disease such as Alzheimer's?

SMALL: If I had to choose between a highly effective symptomatic treatment for Alzheimer's, taken for the duration of the illness, versus a disease modifier such as an amyloid blocker, where it takes longer for any modest benefits to kick in and side effects can be significant, I might

NEUROPHAGE

Positive preclinical PoC studies for its general amyloid interaction motif (GAIM)-based drug for neutralizing misfolded proteins such as toxic amyloid plaque.

Richard Fisher, Ph.D., Chief Scientific Officer: *The basic cause of Alzheimer's and other neurodegenerative diseases is toxic, misfolded proteins. Part of the toxicity of misfolded proteins in the brain comes from their aggregation. A misfolded protein ends up in a conformation that allows it to aggregate to other misfolded proteins of its kind and those eventually end up along a pathway to becoming oligomers, which are a relatively small number of subunits of the misfolded proteins stuck together. Those aggregates are very toxic and, in the brain, very toxic to neurons. The pathway can continue all the way to a fiber, so it's a large aggregate, a big polymer, and then the fibers can also stick together and they make extracellular plaque in Alzheimer's called A-amyloid plaque, and they can go on a similar pathway with tau, ending with neurofibrillary tangles. In Parkinson's disease, alpha-synuclein ends up being a misfolded protein that assembles along the pathway into aggregates that become fibers that stick together and form Lewy bodies in the brain – especially in the substantia nigra, the part of the brain involved in motor function.*

Misfolded proteins are sticky; they have sticky edges, unlike normally folded proteins, and they can spread through the brain no matter where they start, like a prion in Mad Cow or similar diseases. A misfolded protein causes properly folded proteins to misfold as well, acting as a template. That seems to be a general principle, even in misfolded proteins such as Abeta in Alzheimer's, alpha-synuclein in Parkinson's, and tau in Alzheimer's and other tauopathies. And it is probably going on in some peripheral amyloidosis outside the brain.

Our drug candidate, NPT088, leads to the elimination of misfolded proteins eventually in the mouse brain or in tissue, but if you look at it biochemically, first there's binding and then what we call remodeling of the structure, so essentially, the toxicity is neutralized. Our drug is a protein derived from a bacteriophage, a part of the virus that helps it enter bacteria cells. It has a shape that recognizes those misfolded proteins as they assemble.

choose symptomatic. But if I were free to prescribe both kinds of treatment, I would, because I want to do whatever I can to keep someone's brain healthy. So we may see a new form of polypharmacy emerging in this space.

HENDRIX: An Alzheimer's Association workshop in April 2015 brought together experts from pharma, government agencies such as the FDA and NIH, and academia to address the issue of combinations. The general feeling was the amyloid approach may provide some benefit, but the maximum benefit may come when you combine at least two different mechanisms such as amyloid and tau, and that could be the standard approach in the future.

Besides the disease-modifying drugs, there are also symptomatic therapies in the pipeline combining different mechanisms of action, such as 5-HT6 antagonists in combination with the already approved cholinesterase inhibitor, donepezil. A recently approved combination therapy, Namzaric, is donepezil with the NMDA-blocker memantine [Namenda]. But those drugs become less and less effective as the disease progresses, so we still need therapies that slow progression. A third type of drug in clinical trials addresses psychiatric symptoms of the disease. We need all of those approaches to treat the disease as a whole.

Could combinations of new drugs pose medical, regulatory, or economic issues for treatment of Alzheimer's?

HENDRIX: The most important issue from a regulatory approach is, if you're testing a drug in combination, does it need to be synergistic, or can it just be additive? To date, the regulators have indicated an additive effect is good enough, but safety is an issue with any drug in a combination — for example, avoiding a harmful drug-drug interaction. Of course, there is the issue of cost, and some drugs can be quite expensive, particularly the biologicals. But we know Alzheimer's disease is hugely expensive today and will be much more so in the future, so a combination drug therapy, though expensive, may still be a bargain compared to having no effective treatments.

SMALL: Companies are naturally concerned about how much payers will support how their products may be used or combined. A treatment algorithm will eventually evolve based on the data and determine access to any particular drug or set of drugs. But I doubt the companies or NIH grantees will be able to study that decision-making process systematically. Even in the medical community, I suspect reaching a consensus on the criteria will be a bit of a struggle.

HUMAN HEALTH

ENVIRONMENTAL HEALTH

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FOR INDUSTRY: DUTY & DIRECTION

The panel offers a variety of advice for how companies and the industry as a whole can speed the advancement of new therapies for Alzheimer's.

What does the pharma/biopharma industry need to do to ensure the new treatments reach patients, and soon?

WEINER: Companies must do successful clinical trials and get the treatments approved by the regulators, but the biggest single obstacle is recruitment of patients into the trials. Trials in this field enroll slowly and have high dropout rates because it's hard to get patients to continue, especially at early stages of the disease when we're after subjects who are not seeking treatment. To help solve the conundrum, we started The Brain Health Registry, thebrainhealthregistry.org, where we encourage people to sign up, take some tests, and answer some questions, and then we refer them into clinical trials. We already have 35,000 people enrolled. We believe this new Web-based approach will help accelerate clinical trails in this area.

HENDRIX: The drug development and the drug approval expertise in this country, and in the world, resides in the pharmaceutical industry. If we don't motivate companies and keep them interested in doing Alzheimer's R&D, we all lose. The whole ecosystem of research must be strong, from academia, to government, to the private sector as well, along with support from nonprofit organizations such as the Alzheimer's Association.

We need to continue to pressure our political leaders to provide more research funding because our researchers need help. The other advice I have for people in the industry is to make sure that you are an advocate for Alzheimer's treatment in your own community. Everyone in the United States can now have a "wellness" visit with a doctor, and if you're in Medicare, you can have a cognitive assessment done to check your brain health. Everyone needs to do that — physicians need to insist on it, and patients need to insist on it. We must distinguish between normal aging and disease.

A BROADER MOA AGENDA

Perhaps the efforts of researchers and developers in the Alzheimer's area will also contribute to progress in others, and vice versa.

To what extent might the underlying causes for multiple neurodegenerative diseases (NDs) be similar or the same — and thus perhaps respond to the same therapeutic MOAs?

SMALL: The brain is a very complex organ, and these diseases are also complex; many different neurotransmitter systems and brain abnormalities are involved, so there's tremendous overlap. Take the first drugs that were developed to treat the symptoms of Alzheimer's, the cholinesterase inhibitors. The cholinergic neurons are important for normal brain function, in general. Even though the indication for those drugs is primarily for Alzheimer's dementia, they still benefit some of the other conditions: Lewy body dementia, Parkinson's dementia, and so forth.

WEINER: There is a large class of neurodegenerative diseases that all appear to be associated with misfolded proteins: Alzheimer's disease, which is associated with amyloid beta and tau; frontotemporal dementia, with tau and other proteins; Lewy body disease and Parkinson's disease, with alpha-synuclein; amyotrophic lateral sclerosis, with SOD1 [superoxide dismutase 1] or TDP-43 [TAR DNA binding protein]; and a number of other neurodegenerative diseases. But the proteins involved in each disease are quite different. Neurodegeneration is the ultimate common pathway for a lot of diseases, so some laboratories have aimed at trying to block apoptosis or other neurodegenerative processes, but the majority of the field is aimed at specific proteins.

HENDRIX: The Alzheimer's Association has partnered with the Michael J. Fox Foundation, Alzheimer's Research UK, and the Weston Brain Institute in Canada,

COGRx (COGNITION THERAPEUTICS)

Going after various forms of protein misfolding and aggregation in multiple diseases, with its lead small molecule blocker of toxic beta amyloid in Phase I for Alzheimer's.

Hank Safferstein, Ph.D., CEO: *Our discovery and development program has delivered first-in-class receptor antagonists against the toxic forms of the Abeta protein. The company's novel biological and chemical platforms have been the driving force behind the discovery of first-in-class therapeutics and their novel mechanism of blocking the binding and signaling of soluble Abeta oligomers. Among those are first-in-class small molecules that directly target toxic Abeta oligomer proteins and their receptors and stop their bad effects on memory, with demonstrated dose-dependent knockdown in toxic Abeta binding. We have also identified a new epitope on a known membrane-bound protein to which our drugs bind and can block or displace bound oligomers. Our Phase Ia clinical studies are under way, having completed the single ascending dose and first cohort from the multiple ascending dose study. All data generated to date indicates we have a wide margin of safety going into our Phase 2 study in Alzheimer's patients.*

NEW THERAPEUTIC MOAs: ALZHEIMER'S DISEASE

A list of the numerous modes of action employed by drugs approved or in development for treating Alzheimer's disease, along with their company affiliations. Unless other indications are listed, all development stages or phases refer to the Alzheimer's indication.

DISEASE MODIFICATION/PREVENTION

Anti-Beta Amyloid (Abeta) Plaque

mAbs - (Passive immunotherapy)

- *Lilly: LY2062430 (solanezumab). Phase 3*
- *Biogen: aducanumab. Phase 3 enrolling*
- *Janssen, Pfizer: bapineuzumab. Phase 3 discontinued*

Selective beta secretase (BACE1) inhibitors

- *Merck: MK-8931 (verubecestat), Phase 2/3*
- *AstraZeneca/Lilly: AZD3293. Phase 2*

Gamma-Secretase Modulators (GSMs)

- *NeuroGenetic: NGP 555. Preclinical*

Sigma1 receptor (Sig-1R) inhibitors

- *Anavex: ANAVEX 2-73 and ANAVEX PLUS. Phase 2a*

Sigma2 receptor (progesterone receptor membrane component 1) inhibitor

- *CogRx: CT0109, CT0093, CT01344, and CT01346. Block soluble Abeta oligomer-induced toxicity on synapses. Preclinical*

RAGE (Receptors for Advanced Glycated Endproducts) inhibition

- *vTv Therapeutics: Azeliragon (TTP488). Phase 3 for mild Alzheimer's*

Fyn kinase inhibition

- *AstraZeneca: AZD0530 (saracatinib). Phase 2. (Also possible MS)*

PPAR-γ (Peroxisome Proliferator-Activated Receptor γ) agonist

- *Takeda/Zinfandel: AD4833 (pioglitazone, 2,4-Thiazolidinedione, Actos, Glustin, Piozone). Phase 3 (began 2013), Alzheimer's Mild Cognitive Impairment. Approved for Type 2 diabetes mellitus.*

Metabolic Stimulation (ketones substituting for glucose to promote metabolism of fats)

- *Accera: AC-1204. Preclinical, mild to moderate AD*

General Amyloid Interaction Motif (GAIM)

- *NeuroPhage Pharmaceuticals: NPT088. Preclinical*

Anti-immuno senescence (Active immunotherapy)

- *AC Immune SA, Janssen: ACI-35. Phase 1*
- *AC Immune SA: ACI-24 (Pal1-15 acetate salt). Alzheimer's disease Phase 1/2, Down's Syndrome. Phase 1*
- *Novartis: CAD106. Phase 2/3*

Anti-Tau (NFT: neurofibrillary tangles)

Small Molecule (prevent or dissolve tau aggregation)

- *TauRx: LMTX (leuco-methylthioninium). Two Phase 2 trials; data second half 2016 (mild, mild-to-moderate). Enrolling Phase 3, Alzheimer's disease, Frontotemporal Dementia*
- *Ogliomerix: Tau Oligomer Inhibitor; Tau Protease Inhibitor; Biomarkers for both programs. Alzheimer's, Preclinical*

Immunotherapy (Active)

- *AC Immune SA, Janssen: ACI-35. Phase 1*
- *Axon Neuroscience SE: AADvac-1*

SYMPTOMS/NEURAL HEALTH

Anti-cholinergic

- *Eisai/Pfizer: Aricept (donezepil). FDA approved 1996*
- *Also approved: Razadyne (galantamine), Exelon (rivastigmine), and Cognex (tacrine)1*

N-methyl-D-aspartate (NMDA) blockade

- *Actavis: Namenda (memantine). FDA approved 2003*

Type 4 phosphodiesterases (PDE4) inhibition

- *Tetra Discovery Partners: BPN14770. Phase 2*

5-hydroxytraptamine-6 (5-HT6) Antagonists

- *Axovant Sciences: RVT-101. Phase 3 (with donepezil)*
- *Lundbeck & Otsuka America Pharmaceutical: AE58054 Phase 3; Others: four in Phase 2; three in Phase 1*
- *Pfizer: PF-05212377. Phase 2 discontinued, October 2015*

Neuroprotection/Neurogenesis

- *Amarantus: MANF (mesencephalic- astrocyte-derived neurotrophic factor), Preclinical*
- *M3 Biotechnology, MM-201 – Modified Neurotrophic Factor, Preclinical*

ALZHEIMER'S ADVANCES – DEVELOPMENT DURING DEBATE

"The hallmark pathologies of Alzheimer's are the progressive accumulation of the protein fragment beta-amyloid (plaques) outside neurons in the brain and twisted strands of the protein tau (tangles) inside neurons. These changes are eventually accompanied by the damage and death of neurons." Alzheimer's Association Facts & Figures 2015.

Most likely, there is no one in this field without a stake in the development of some specific approach or agent. Nevertheless, the KOLs who participated in this virtual roundtable gave fair and widely focused views of current scientific thought in the ND area. Not that the field harbors uniform consensus. For every hypothesis about the progression of Alzheimer's, a contrary assertion seems plausible. Is Alzheimer's all about the accumulation of beta amyloid plaque? If so, why do so many people who never get the disease walk around with massive amounts of plaque in their brains? On the other hand, why did some patients with advanced disease seem to benefit from plaque-targeting mAbs (monoclonal antibodies) that produced poor overall results in Phase 3 trials?

It's important to note, however, that the Phase 3 trials have mostly happened under the wing of a Big Pharma company. It has been 20 years since the approval of Aricept (donezepil), the last major advancement in Alzheimer's therapy, however modest in effect. Lilly, Biogen, and Roche have all had their setbacks, but seem committed to the long haul, though Pfizer and Janssen have discontinued their late-stage programs. Still, it is now clear that ND drug development is no longer the lonely pilgrimage of small companies.

Beyond anti-amyloid, the next most powerful camp in scientific thinking is anti-tau, specifically, phosphorylated tau tangles. Tau proteins are normally straight and parallel fibers that stabilize microtubules inside neurons. Like the rails ripped up and left hopelessly tangled by Union troops as they marched through Georgia, tau fibers in Alzheimer's patients typically become "hyper-phosphorylated," or overwhelmed in binding with phosphoryl groups, detach from the microtubules, and misfold and intertwine, killing the neurons.

Anti-tauists point to the closer association of tau tangles with cell death and cognitive decline. But the pathway that leads to toxic Abeta plaque and tau tangles is the same – an evolutionary sequence that may encompass all the key steps in development of the human brain and its higher functions of thought and memory, yet somehow working in reverse to degenerate *the same structures. Almost all of the key points along the pathway have become targets of new therapeutic strategies and mechanisms for Alzheimer's – much like the continuum of checkpoints in immuno-oncology. A fair number of those targets, strategies, and mechanisms may apply to other NDs as well.*

But disease modification is only one of the goals for new Alzheimer's drugs. Much of the R&D effort in this space goes toward developing better agents for relieving symptoms or compensating for lost neurons and synapses by enhancing neurotransmission, delivering neuroprotection, or even promoting neuroregeneration. At the same time, as the Alzheimer's experts in this article emphasize, education in both the academic and public relations senses may still be the most powerful and essential tool available for preventing, forestalling, and treating the disease.

All of the new treatment approaches have one thing in common: the importance of early diagnosis and diagnostic tools. Another common denominator is drug delivery past the blood-brain barrier, and a quick search of Life Science Leader *and its sister Web portals will yield much on those topics. Imaging and blood testing for disease biomarkers have advanced, but so far they are mainly focused on amyloid plaque, and behind that, tau, and there is little that would guide use of drugs with other mechanisms. Diagnostics especially deserve their own chapter in this story. But the truth is, methods for detecting the earliest stages of Alzheimer's are still a long way from feasible and affordable availability and use.*

on grant opportunities for researchers looking at where the causes of different NDs could overlap, as in neuro-inflammation. If Parkinson's and Alzheimer's both involve misfolded proteins, do the proteins normally misfold but start accumulating instead of being cleared out of the brain as usual? If we understood that basic molecular question, we would have a better way to attack these diseases, including the orphan diseases that share the same effect. There has been some research about a hypothetical clearance mechanism, but we don't know whether the basic problem is clearance or inflammation.

What other issues or challenges in developing new drugs and MOAs for Alzheimer's disease concern you?

HENDRIX: Of the top 10 causes of death in the United States, Alzheimer's is the only one for which no way exists to stop or slow the disease, and even though we've recently seen additional funding of $350 million from the federal government for the NIH, we still don't fund Alzheimer's research at the levels of cancer, for example. In 2014, a blue ribbon panel convened by the Alzheimer's Association concluded we would need $2 billion a year in research funding from the NIH for the next 10 years to reach the national goal of an effective treatment or cure for Alzheimer's disease by 2025. We spend $226 billion per year on care for the disease right now; without therapeutic progress, care costs will balloon to $1.1 trillion by the middle of the century.

Alzheimer's disease funding had been stuck at just under $600 million per year, but even in this very partisan time, and with tremendous rancor in D.C., this year we convinced both sides of the aisle that Alzheimer's needs additional funding, so the funding is now nearly double of what it was just a few years ago, for which we are very grateful. But it's still not $2 billion a year. We have much more to do.

SMALL: One of the simple facts that motivates me is that we don't really have that much to offer Alzheimer's patients yet. It is frustrating and tragic and family members feel helplessness when they realize the doctors can do nothing more to help them. But I believe in time we can. It's a question of us being smart and pursuing a strategy that will be successful. It is not just about getting more candidates into your clinical trials, but also about being objective and meticulous in focusing on what makes sense in getting the right data.

Another area where improvement could help drug development is the interface between academia and the pharmaceutical industry. It can be awkward for academics, as they say in the industry, to go from bench to bedside, and I know our university and others have been working on how to make it easier. Although there are many intelligent and gifted investigators in our universities, they are not typically trained in how to make that journey, how to take their research to the next level. Basically, in academia, we are taught to publish or perish, not publish or produce.

WEINER: We need a whole big public awareness campaign — a big media, public relations campaign. We must get older people to start realizing Alzheimer's disease is a common problem, Alzheimer's disease runs in families, Alzheimer's begins with mild memory problems, and the only way we will see new treatments is for people to participate in clinical trials. Each time the FDA approves a new, effective treatment for the disease, there should be massive campaigns to get those treatments into practice, and the market will take care of that.

Please look for Part Two of this series next month, focusing on new therapeutic MOAs for Parkinson's disease.

TETRA DISCOVERY PARTNERS

This company, like many others, is an enterprise founded as the sole champion of a new therapeutic mode of action for Alzheimer's and other neurodegenerative diseases — PDE4 inhibition.

Mark Gurney, Ph.D., Chairman and CEO: *Our drug in Phase 1 development, BPN14770, modulates a biochemical mechanism of memory fundamental to the human brain, PDE4D [phosphodiesterase 4], to enhance cell signaling between neurons in the brain, while maintaining information flow through brain circuits important for memory. BPN14770 does not address a specific neurochemical deficit or disease pathway, so we believe it will have broad cognitive benefit across multiple neurologic and psychiatric illnesses.*

The PDE4 target had fallen out of favor due to the perception that a well-known side effect, nausea, could not be prevented. It also has been difficult to develop compounds that are selective for one of the four PDE4 subtypes, each of which have potentially distinct therapeutic profiles, but only one of which, PDE4D, appears to be associated with emesis. Our team solved the crystal structures of the PDE4 regulatory domains and developed PDE4 subtype-selective inhibitors based on this new knowledge. Because the drug has little effect on PDE4D in the off-state, it has very good tolerability.

3D Printed Medications Face Hurdles, But Growth Continues

JULIE DEARDORFF, PH.D., MPH Contributing Writer

3D printing of medications that meet regulatory standards is a reality, thanks to Aprecia Pharmaceuticals paving the road with the approval of the first 3D printed medication, SPRITAM (Levetiracetam), in August 2015. Although additional commercial products have yet to be approved, novel products made possible by the unique attributes of 3D printing, including "polypills," are being developed.

Specifically, using extrusion technology, which allows layering of different medications into the same pill, Clive Roberts' research group at the University of Nottingham, U.K., has successfully "printed" a polypill that not only contains five unique medications for the treatment of heart disease, but that also successfully allows separate medication-specific release profiles (either immediate or controlled release) within the same pill.

Thus, as Roberts, chair of pharmaceutical nanotechnology and head of the School of Pharmacy at the University of Nottingham, optimistically explains, "Developing 3D printing as a manufacturing tool for medicines is now becoming an engineering problem; the scientific principal has been proven. If it meets a clinical need and there are funds to do it, then as long as there is a will, it can be done."

This was successfully exemplified by the development team at Aprecia, who found an unmet clinical need that could be uniquely addressed by 3D printing. As explained by Don Wetherhold, Aprecia's CEO, with their proprietary ZipDose technology, "Aprecia is using 3D printing to make high-dose, 'fast-melt' preparations that are easy to take and that deliver medicines that remain unaddressed by other techniques for making fast melts. This approach is directed to ease of administration, regardless of dose." ZipDose technology allows delivery of doses up to 1 gram that can dissolve in the mouth within 10 seconds. Wetherhold added, "We believe there are numerous populations that can benefit from a 'fast-melt' formulation, such as children and the elderly, and those dealing with the complications of stroke, Alzheimer's disease, head and neck tumors, or certain other neurological disorders that may impact swallowing or self-management of care. Accordingly, we developed proprietary equipment to address that type of production need."

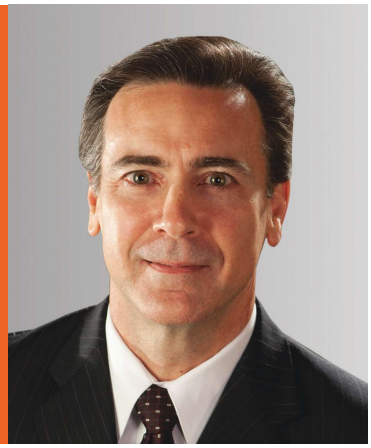
One of the promises frequently touted about 3D printing is that it allows for the customization and personalization of medications. Furthermore, 3D printing of medications is often seen as an ideal solution for niche clinical-need markets. But how large can these niche markets be? It's commonly acknowledged that 3D printing in general — not just with medications — is not economically suitable for large-scale production processes. So how will that limitation affect the 3D printing of medications?

Wetherhold agrees that 3D printing processes will remain smaller and more specialized than something like high-speed compression tableting. "But it is already well beyond the bench," he says. "If your primary goal is making unique strengths for each individual patient (e.g., such as a 90-day supply), then a bench-scale process rather than a full-scale production facility may meet the need. And, you can then focus on a different set of challenges such as demonstrating the extent of clinical benefit or clarifying regulatory requirements. We certainly believe 3D printing will have an impact at larger production scales than that. Our goals required considerable scaling of the process as a prerequisite, with a focus on creating value-added dosage forms to better meet the needs of substantial numbers of patients."

Indeed, the scale of production for SPRITAM is relatively not small. SPRITAM is approved for an indication that affects approximately 1.3 million to about 2.8 million in the United States, of which a significant subset may clinically benefit from the fast-melt formulation. Thus, the benefits associated with this technology can be applied to a larger segment of the population than is often envisioned when discussing the customization of medications. Wetherhold explained that the 3D printing of medications allows the "tailoring of functional attributes to better meet the common needs of certain subsets of patients. In this way, we hope to help larger groups of patients sooner." As such, Wetherhold added, "For our goals, it made sense to develop and build proprietary equipment that can mass produce our units with standardized dosing."

Roberts also shares this vision of 3D printing of medications not being limited to small production runs. "Larger production runs, particularly in the presence of decentralized manufacturing (such

> *"We are at the beginning of the technology adoption curve for 3D printing in our industry."*
>
> **DON WETHERHOLD**
> CEO, Aprecia Pharmaceuticals



as production at the point-of-service in pharmacies), will be feasible. Yes, you could make millions of tablets with 3D printing if you distribute the manufacturing. I think it's very realistic to imagine 3D printers in hospitals controlled by pharmacists that could make thousands of pills a day. I would expect that to happen at some point." He also pointed out that we need to put the field of 3D printing of medications into perspective. Namely, this field is very much in its infancy. "As such, the technology is being rapidly improved and optimized such that the cost per unit is decreasing, which promises that larger production runs will be increasingly more viable. Furthermore, as manufacturing costs are a relatively small component of the realized drug cost, if the clinical benefit delivered by the customization allowed by 3D printing is of sufficient value, the added manufacturing costs may not be prohibitive."

THE CLINICAL BENEFITS OF 3D PRINTING

Once we accept that the volume challenges associated with 3D printing can be overcome, we need to consider the potential clinical benefits of this method of drug manufacturing. Various possibilities exist ranging from greater access to medications, especially in developing countries and remote areas due to the decentralized production at the point-of-need, to customized and/or personalized attributes that will ultimately lead to improved treatment adherence. If 3D printing of medications does improve treatment adherence, that will be of significant clinical benefit. Roberts emphasized that one of the primary challenges to successfully treating chronic diseases is treatment adherence. For example, SPRITAM holds the promise of increasing treatment adherence among certain subsets of epileptic patients who have difficulties swallowing pills. One can imagine that personalization of pills could improve the likelihood that children in particular would take their medications. With 3D printing, a child could choose a color, flavor, and/or shape of their pill. Furthermore, personalization of medications may provide particular benefit for patients who have to take multiple pills a day, such as the elderly, by improving the ease of patient use. Polypills such as the one developed in Roberts' laboratory, which contain five medications, would allow a patient to take only one pill rather than five. These polypills would also deliver personalized doses that can be of considerable benefit, as currently some patients need to cut pills that come in standardized doses in order to receive the correct dose.

Another benefit is the ability to create solid-form medications at patient-specific doses. Currently, numerous medications that have a patient-weight-specific dose must be administered intravenously in a supervised setting. Thus, the 3D printing of medications could reduce the need for such infusions, allowing an improved patient experience and requiring fewer healthcare resources.

THE REAL CHALLENGES FACING 3D PRINTING OF MEDICATIONS

Now that Aprecia has successfully navigated the regulatory hurdles to gain approval for SPRITAM, the regulatory process is not considered a challenge. In Roberts' opinion, currently the most significant challenge is "the lack of options for the basic materials in the 'inks' (e.g., formulated medications). Essentially, there is a very limited dataset at the moment. We need to continue to develop materials that print well and produce suitable dosage forms." Again, putting things into perspective and emphasizing that the 3D printing of medications is just in its infancy, he points out that it took decades to optimize the inks that are in the inkjet printers currently used today.

Wetherhold feels the largest hurdle for the field right now is focus, as there are so many possible applications. He explains, "We are at the beginning of the technology adoption curve for 3D printing in our industry, and there are multiple versions of the technology that can each be deployed in more than one way. Each faces its own questions regarding regulatory requirements, quality assurance, and cost/benefit for the application. To achieve success, it is necessary to remain focused on clear goals to address the respective requirements and execute through to completion." It was this type of focus that led to Aprecia successfully developing its ZipDose technology and obtaining FDA approval for SPRITAM, which is made in a centralized manner, in scale, at Aprecia's own FDA-inspected facilities. The next step, the ability to achieve commercial success with a 3D-printed medication, will soon be put to the test. The field excitedly awaits as Aprecia plans to bring SPRITAM to market in the first half of 2016.

While the field certainly has its challenges, it's not stopping the activity or buzz associated with the potential for 3D printing of medications. It seems certain that it's not a matter of if these challenges can be overcome but rather a question of when. Companies — ranging from small startups to large established companies such as AstraZeneca and GlaxoSmithKline — are exploring the applications of applying this manufacturing technology to the creation of new medications. As the knowledge base and experience in this arena continues to grow rapidly, the development and approval of additional 3D medications is something we can expect in the relatively near future.

Insights For Creating A Combo Products Centre Of Excellence

DOUG ROE Executive Editor

The Centre of Excellence (CoE) business model has gained a lot of momentum over the last few years. Today's companies are looking for strategic long–term solutions, not just temporary fixes or tactical course corrections. An effective CoE can offer standardization of systems and processes across multiple businesses and disciplines throughout the company.

It becomes a centralized knowledge hub that develops best practices and governance, which facilitates repeatable and sustainable improvement. The CoE leadership become the company advocates of change. Their horizontal visibility, which reaches across all projects and teams, allows for consistent alignment with corporate directives.

If you are thinking about implementing a CoE, what are the real considerations? All companies will start in somewhat different places, and the development will take different paths to fruition. But one thing will stay the same: To have success, you will need to overcome some similar challenges.

There are some basic issues that have been summed up as the three Ps: people, product, and process. Does the current employee talent pool contain the required skills and technical expertise? Is there one clear company vision for current and future product strategy? How significant are the variations of existing systems and processes? Now, add in some complexities — senior management buy-in, earning/maintaining confidence from development and manufacturing teams, ego considerations, and cultural clashes, just to name a few.

Other than that, seems easy … right? Now here's the curve ball. What does it take to build that CoE structure in a life sciences company that also produces combination products? Talk about your culture clash. Historically, these two groups — drug and device — have existed autonomously. Each has its own regulatory path, quality standards, design and manufacturing controls, R&D obstacles, employee skillsets, department structure and career path, internal and external value proposition — and, of course — culture.

Even if you can overcome these systemic barriers that represent significant inequities, can you then bring the teams together and get them to play nicely in one very new, and very large, sandbox? Seems like a tall order.

I had the chance to discuss those issues with Susan Neadle, head of The Janssen Combination Products Centre of Excellence (a Johnson & Johnson Company). We discussed the reasons behind the 2014 launch of the CoE, some of the Centre's early challenges, the current improvement experience, and potential next steps in the Centre's evolution.

Can you describe the general scope and purpose of the Janssen Combination Products Centre of Excellence?

We established the CoE about a year and a half ago. Combination products at Janssen make up a good part of our portfolio. For a combination product, the critical aspects of the drug — to deliver the required therapeutic effect — and then the critical attributes of the device — to administer that drug effectively — are both key to overall patient outcomes. The Combination Products CoE was created to develop and implement the best practices and broad structure needed to be able to be strong in devices, not just pharma, ensuring we have the required resources and the skillsets, at all levels, to effectively be a pharma company and a device company.

What were the internal drivers that led to its creation?

I started at Janssen about two years ago. I transitioned in from another J&J Company (Device Sector). The timing was perfect. It was shortly after the time when the FDA released the final rule for combination products. I had just enough time to get my feet wet and realized we had an opportunity to improve our

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focus and core competencies for delivery devices.

I saw that the primary focus of the pharmaceutical company was about the therapeutic effects of the drug and making sure that those therapeutic effects were doing what they were supposed to do. Historically, it was less about making sure the device met the user needs for administering the product, as long as the drug was efficacious.

That was a key driver for the CoE's creation — it is about a pharmaceutical company learning that it needs to be a device company, too.

I also wear another hat; I head up the Design to Value (DtV) efforts at Janssen. DtV is a strategic initiative across all of the J&J companies. I lead the pharmaceutical sector, in addition to our combination products. DtV is an end-to-end life cycle methodology enabling customer-centric, high-quality products, made efficiently and reliably. DtV is built on five pillars: Customer Value, Quality by Design, Technology Platforms, Knowledge Management, and Governance. Customer Value is where it all starts, capturing, analyzing, and integrating customer insights to make sure that the products you are delivering and the services you are providing are customer-centric. When applying DtV to combination products, focusing on the customer need, the focus on ensuring the quality of the drug, is of course critical, because customers need to realize the therapeutic effect of the drug. From a customer value perspective, though, the device is equally important, because the device being used to administer the drug is the thing that the customer is seeing, touching, feeling, and interacting with.

We need to focus on understanding what specifically our customer needs — from a human factors and usability perspective and from a complete supply chain perspective — as well as who is administering care, be it the patient, or a caregiver. We need to determine what they care about when it comes to the device administering the drug and then build those things into the combined product.

Again, it comes back to the requirement to have the skillsets and core competencies that enable us to effectively deliver device constituents or combination products, not just the drug.

> *"There are cross-company differences that can really impede your progress, because you have people with different tolerances of risk working in devices, versus drugs, versus combinations."*
>
> **SUSAN NEADLE**
> Head of The Janssen Combination Products Centre of Excellence

What should a pharmaceutical company consider and understand before creating a combination product CoE?

I see three key considerations: business systems, cultural challenges, and product and process technology. From a product and process technology perspective, teams are composed of scientists and engineers accustomed to working through technical challenges. Technologies may fall outside of core capabilities, though, so those competencies need to be developed. It is likewise important for teams to effectively develop and characterize both constituent parts and the integrated product. These technical challenges may be magnified with business system and cultural challenges.

From a business systems perspective, consider the varied business cases. If you are a device company, the incentives, metrics, and strategies can be very different from those on the pharm side. Those management incentives, behind the business cases, may be very different.

From a quality systems perspective, you are dealing with multiple quality systems that have to be harmonized or potentially developed. There needs to be an understanding of the regulations that are uniquely interpreted under the Quality System Regulations (QSRs) compared to the Pharm GMPs. Much of the terminology used in the regulations is the same, but the interpretations may be different. If you are a pharma-centric organization, you need to ensure that these intricacies are incorporated into your quality systems.

With clinical and R&D systems, evaluate the governing project management. Do stage gate reviews include both device and drug subject matter experts? Was it designed for a pharma process, as is typical? Does it include the stages or the reviews that are required for the device at the right time? Treating these considerations as an afterthought could lead you to have to play catchup on the device, because the focus was on the drug.

Even with manufacturing systems, you have to implement the fundamental infrastructure and governance to make sure that your drug and device launches are synced. Do you have the systems built in to avoid manufacturability issues with your device? For example, devices require design validation. That design validation includes not just the device's performance, but also the device's interaction with the drug. More tests may equate to more time.

If developers focus primarily on how the drug is formed, that might impact your timeline. There are cross-company

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differences that can really impede your progress, because you have people with different tolerances of risk working in devices, versus drugs, versus combinations. "The drug matters; the device does not." This is a cultural divide. Product developers must be aware of, and accept, the differences between pharma and device and then be willing to educate themselves to get past that barrier.

Those culture aspects ... they are fun. How does each group perceive the other? If teams are collaborating on projects, is the cross-platform collaboration limited to, "I will consult with you when I need your opinion," or is it truly collaborative? You need to realize there may be blind spots. It may not even occur to one group that there are questions they need to be asking/ consulting about, and vice versa. You need to develop the understanding that each group probably knows some things that the other does not and then ensure that they hold hands the whole way to get the best outcome.

Was there an overarching dynamic at Janssen that made you believe, "yes, we can make this happen"?

This entire process has been top-down. Senior management understood and fully supported what we needed to do. Then, it was just a matter of education, so the broader organizaton could get it.

What are the various segments and disciplines of the CoE team?

The CoE is a large cross-functional team. It includes a leadership team of mentor experts in design controls, combination product regulatory compliance, complaints management, Corrective Action Preventive Action (CAPA), market safety reporting, and risk management + criticality analysis. That last group is unique, because it merges risk management for the device and criticality analysis for the drug into one function. We also have the DtV/Quality Engineering group. That is the leadership team, and then we have other CoE people distributed across the businesses. We have specially trained people in customer complaint vigilance, because the way you ask questions for combination products is going to be different from the query process for stand-alone drugs or devices. Our CoE also includes combination products subject matter experts for supplier quality. Then, in our R&D group, we have experts in human factors and combination product analytics, and combination products regulatory affairs. Some of the other experts in the CoE include Quality Systems and IT professionals, Reliability Engineers, and Device Engineers.

It has been set up so the CoE is integrated into all businesses and departments. We did not want it to be a separated governing group; we wanted it to evolve into, "This is just the way things are done," and the combination products are just part of it. This is about bringing in the right skillsets and embedding and ingraining those skillsets across the company.

"Much of the terminology used in the regulations is the same, but the interpretations may be different."

SUSAN NEADLE
Head of The Janssen Combination Products Centre of Excellence

What role do you play on the CoE team?

I have oversight for all programs and the overall center of excellence. My leadership team does weekly reviews of all of our initiatives, making sure things are moving forward the way we want them to. We focus on products currently on the market, making sure that they meet the quality the company expects, as well as any new products in development.

Has the CoE changed the way the company approaches combination product design and development?

We have updated or upgraded all of our combination product design and development processes. We have embedded the deliverables required for devices into our pharma chemistry, manufacturing, and controls (CMC) stage gate system. The process and the teams are fully integrated now.

Device experts are getting more exposure to the drug aspects, and the drug experts are getting more exposure to the device aspects. More people are developing that mutual understanding. You do not get customer-centric design by working in silos. We are achieving it by working together, and it will only get better over time. It just becomes part of the normal way of doing product development.

How do you see the function of the CoE transforming over the next 10 years?

It is going to shift from a focus on making sure that all the quality systems are aligned and integrated to a focus on proactive quality. We will make sure that we are building those customer-centric designs and design controls in conjunction with our Combination Products Development Process (CPDP) quality by design (QbD) protocols. The whole thing will be integrated. That way, the products released to market are the best products they can be.

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How Crowdfunding Can Expand Funding Opportunities For Biotechs

FRED OLDS Contributing Editor

Under new securities laws, biotech entrepreneurs gain increased access to potential investors. The Jumpstart Our Business Startups Act (JOBS Act) of 2012 authorizes biotechs and private companies to use general solicitation (public solicitation) of funds from accredited investors in exchange for equity in their companies using SEC-certified crowdfunding websites.

Amidst industry skepticism, some biotechs have succeeded in crowdfunding their startups. Their experience shows that entrepreneurs will need to hire legal expertise and select crowdfunding sites that cater to their science.

Crowdfunding is not new. Small startups have raised capital on crowdfunding sites prior to the JOBS Act, but legally only by soliciting donations, not selling equity. Think Kickstarter. These sites operate using short time frames and budgets in the thousands of dollars when biotech needs millions.

Biotech has special issues that crowdfunding platforms will need to accommodate. The most significant are the large amounts of money and the long time lines necessary for biotech drug development. Additionally, biotech startups need to protect their IP and find sophisticated investors who understand that IP. Raising large amounts of money through crowdsourcing implies large numbers of investors. But can a small biotech entrepreneur deal with "a crowd" of owners?

BE PREPARED FOR A STEEP LEARNING CURVE

Mike Moradi feels crowdfunding will probably be a large part of capital formation for biotech startups in the future. Moradi is cofounder and CEO of Sensulin LLC, a biotech developing a once-daily glucose-responsive insulin that may mimic a healthy human pancreas. He is a veteran of a number of startups through VCs, but he chose crowdfunding to fund Sensulin. "I had no idea what we were getting into, but we now have investors from all over the United States and sizable commitments from China, Luxembourg, Hong Kong, and England," he says. "I had a steep learning curve determining how to raise money using crowdfunding. It's safe to say a number of sites are on their own learning curves."

Sensulin looked at about a dozen platforms that dealt with healthcare or had a substantial investor base. The company registered with four. One of the four, a site focused on cutting-edge technology, was able to bring in an institutional and several private investors to join Sensulin's existing institutional investor. That essentially completed Sensulin's entire Series A round of funding.

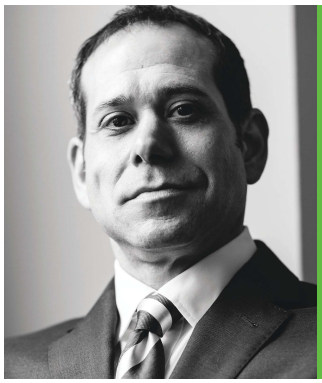
The lesson, says Moradi, is that it's critical, especially for biotech companies, to deal with sites that have expertise in the science your company is developing. "For example, we have proof-of-concept in animal studies. But the average angel investor may not easily understand the significance of that science."

Even platforms focused on technology may not focus on biotech. You want a platform that does more than simply attract investors who are willing to support your company. Find a platform that is familiar with your company's scientific space that will be able to provide the legal and business advice to make your proposal attractive to investors. As Moradi says, "You need an audience that knows the science." Of course, that audience is small and spread worldwide. Crowdfunding brings them to one virtual location.

ENLIST THE HELP OF EXPERTS TO AVOID BEING SUED

Erik Weingold, founder and general counsel at PPM LAWYERS, a law firm working exclusively in securities law and private placement, says biotech startups have had two primary routes to raise capital through equity transactions. A company could file a registration statement with the SEC to sell stock publicly or conduct a private placement under Rule 506(b), Regulation D of the Securities Act of 1933. "Registration is a very lengthy and expensive process," says Weingold, "so most biotechs use some form or combination of self-funding, debt/loans, warrants, or in the case of equity, a private placement."

Rule 506(b) authorizes and restricts companies to sell equity in a nonpublic offering to accredited investors and up to 35 nonaccredited investors. Accredited investors are those with a net worth in excess of $1 million, excluding their primary residence, and certain high-income earners. In this type of private placement, individuals can self-certify



> *"Most biotechs use some form or combination of self-funding, debt/loans, warrants, or in the case of equity, a private placement."*
>
> **ERIK WEINGOLD**
> Founder and general counsel, PPM LAWYERS

they are accredited investors. That is, companies can rely on individuals' statements that they are certified.

Private placement may require companies to provide investors specified disclosures about the offering. Weingold warns that companies should employ legal experts in corporate securities. Companies can be sued or even investigated by the SEC and state securities commissions for errors or omissions in these documents even without proof of intent.

A LOOMING MAY 16, 2016 DEADLINE

Title II and Title III of the JOBS Act reduce restrictions on equity transactions, but Weingold feels biotech entrepreneurs may find some provisions of the JOBS Act difficult and expensive, particularly in Title III.

Title II, under Rule 506(c), took effect in the summer of 2013. It generally follows the same disclosure, reporting, and accredited investor rules as private placement with three exceptions. 1) Title II allows general solicitations through accredited crowdfunding portals. 2) Funds can be raised only from accredited investors. 3) Startups have to certify that every investor is accredited. Companies can engage third-party vendor services, lawyers, or CPAs to preform certification; or the company itself can request supporting documentation from investors.

Title III goes into effect May 16, 2016. It opens equity sales to nonaccredited investors. "There are, perhaps, several million accredited investors in the United States, but there are nearly 250 million nonaccredited investors," says Weingold. That is a lot more opportunity, but there are some problems for biotech startups. A company can raise no more than $1 million annually, and an individual's investment is limited based on income. Simple math shows that company leadership might have to deal with hundreds of equity holders in making critical decisions, including dilutive funding issues, for instance.

Title III has a lot of regulation and restrictions built into it. "With a $1 million limit and robust disclosure rules," Weingold says, "frankly, I'm not sure how useful it will be for biotech startups where usually much more money is required. Although, it may be useful as a seed round."

FINDING "THE RIGHT" INVESTOR WILL BE A CHALLENGE

Crowdfunding sites can be so specialized or general that an entrepreneur's proposal might be ignored or get lost. Swati Chaturvedi is cofounder and CEO of Propel(x), a crowdfunding site dealing exclusively with deep (cutting-edge) technology. She says selecting the right specialized platform is critical for entrepreneurs developing these technologies, especially in esoteric sciences like those in biotech.

"These are companies that will change the world and lead us into the next century. They make good business sense," says Chaturvedi. "But there are difficulties investing in deep technology." Biotechnology is hard to understand. Both investors and startups are rare, making introductions very difficult.

There are few investors who understand life sciences and have a tolerance for technology risk. And those investors are dispersed globally. Chaturvedi says crowdfunding platforms serve as a global nexus for these investors and entrepreneurs. These sites can reach thousands, even hundreds of thousands of investors.

In addition, crowdfunding platforms can help entrepreneurs reduce the challenge of dealing with numerous investor owners.

KEY ELEMENTS TO LOOK FOR IN CROWDFUNDING SITES

Many platforms offer hands-on instruction and tools to improve the chances a company will catch the eye of an investor. Crowdfunding site EquityNet, for instance, provides a standardized template to help companies analyze the marketplace, develop business plans, and determine funding requirements. CEO James Murphy says, "A standardized business platform provides peer-to-peer evaluations. Entrepreneurs can compare their results to others in the same industry using that same template."

Choose a site that actively introduces investors to appropriate startup opportunities. Look for features such as database screening so investors can search for companies in their areas of interest, and entrepreneurs can identify likely investors. When an investor finds a company to discuss a possible deal, disclosures and due diligence should be well-formed virtually before the parties ever meet. "Imagine the time saved for both sides by eliminating a long series of lunch meetings to discuss terms," says Murphy.

Consumer feedback is very important when choosing a crowdfunding platform. Look for sites that provide some process for investors, peers, or experts to make suggestions to entrepreneurs on improving their business plans. Unlike presentations at investor meetings, these sites should offer companies the ability to correct missteps in their presentation and repromote their proposal to investors on the site.

"It's the quintessential American dream to change the world by inventing a new widget," says Moradi. "These platforms are a way to introduce innovators to investors who share that dream."

Life Sciences Companies Have Reason For Optimism In 2016

ALEX CASTELLI

Alex Castelli is the technology and life sciences industry practice leader at accounting, tax, and advisory firm CohnReznick LLP. Castelli also coleads the firm's National Liquidity and Capital Formation Advisory Group.

Even though the U.S. economy continued to strengthen in 2015, many public investors sat on the sidelines grappling with global economic and political concerns and uncertainty surrounding the Fed's policy concerning interest rates. Because of these and other factors, middle-market IPO transaction activity (IPOs completed by companies with market caps between $10 million and $2 billion) in 2015 decreased versus the previous year. Contributing to the downward pressure on IPO activity was the availability of capital and high valuations from private financial and strategic investors.

In 2015, IPO transaction activity for middle-market life sciences companies followed the pattern of broader middle-market IPO activity. The number of life sciences companies that accessed capital by issuing an IPO was down 39 percent in 2015 when compared to 2014. When examining overall middle-market IPO activity in 2015, there was a 43 percent drop when compared to 2014.

While middle-market life sciences IPO transactions decreased in 2015, one positive sign is that the proportion of life sciences IPOs compared to total middle-market IPOs increased. In 2015, life sciences issues represented 34 percent of middle-market IPOs compared to 32 percent in 2014. Additionally, 41 percent more public middle-market life sciences companies raised additional capital through follow-on transactions. In 2015, a full 42 percent of all middle-market follow-on transactions involved a life sciences company (compared to just 24 percent in 2014) — an indication that investors see promise in the future of these growing companies.

Although the decrease in life sciences IPOs could lead one to believe that there was less investor interest in the industry, the decrease may be more a function of broader market volatility than lack of interest in the industry as a whole. From an investment perspective, when comparing biotechnology and pharmaceutical company investments to investments in other industries, investors can measure the progress of these companies by milestones achieved through the discovery, preclinical, and clinical trials.

As life sciences companies achieve milestones and move closer to regulatory approval, valuations tend to increase, as does the continued need for capital. This industry-specific dynamic is attractive to investors as it helps when evaluating the risks and rewards of a prospective investment. Also, the achievement of milestones helps investors establish a prospective timeline to commercialization, which could help build investor comfort and confidence. The development process is unique to the life sciences industry, but can be an attractive tool to investors when making investment decisions.

Communicating timely and transparent information relative to the achievement of scientific milestones and relative to the growth and development of the company may support pharmaceutical companies seeking higher valuations. Disseminating such information helps to build relationships with the investment community, leading to greater investor confidence, which is critical to successful fundraising.

REASONS FOR OPTIMISM IN 2016

Despite 2015's lag in IPO activity, life sciences companies in need of raising capital should have reason for some optimism in 2016, with several options to consider. For many of these companies, the IPO will remain a viable form of capital. In addition, strategic acquirers with cash on their balance sheets and pressure to grow will be aggressively searching for new acquisitions.

In 2016, the IPO window will be open, but to an increasingly selective group of issuers. As was the case in the second half of 2015, we are likely to see increasing public investor scrutiny before new issues come to market, resulting in moderating valuations and careful pricing. Those companies with a proven track record of achieving milestones and that are further along in the development and approval processes may find a greater opening of the IPO window. A valuation premium will be placed on those companies whose management teams have successfully commercialized their products and services.

In the near term, private financial and strategic investors will continue to woo some companies once destined to become public. Capital from venture capital and strategic investors should remain plentiful in 2016, as will their appetite for quality investment opportunities. Some life sciences companies should be well-positioned to negotiate a private capital raise that includes many of the benefits associated with an IPO.

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Gigi Hirsch, MD
Executive Director, MIT Center for Biomedical Innovation

Featured Sessions:

- Disease Interception: Shifting the Paradigm from Treatment to Prevention of Disease
- Expedited Reviews and Other Pathways to Speed up Access to Medicines
- Lessons Learned from Eight Years of Drug Development Tool/Novel Methodology Qualification
- Regulatory Science Considerations Applying to Novel Biologics and Bifunctional Biologics Development
- Infectious Disease Containment and Lessons Learned

Agenda Now Available

Featured Highlights

- Global regulatory presence with representatives from FDA, EMA, PMDA, Health Canada, and more
- NEW Engage and Exchange Sessions: Engage with fellow attendees in a new, collaborative learning environment
- Increase your knowledge while allowing for small group interaction with DIA 2016 Preconference Tutorials
- Hear from the top thought-leaders in drug development discuss topics such as 21st Century Cures, biologics/biosimilars, patient engagement, mobile/wearable technology, big data, personalized medicine, approval pathways, pricing, reimbursement and access, plus much more

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How Social Media Will Upgrade Your Leadership

PAUL SOHN

Over 1.5 billion people are on Facebook, 400 million on LinkedIn, and 300 million on Twitter. While the world is becoming more social, top executives haven't seemed to join the bandwagon. According to a study conducted by CEO.com in 2014, more than 68 percent of CEOs still have no social presence on the five social networks.

Many leaders don't seem to have time to manage their social media. A growing number of executives expressed their doubts of using social media since they couldn't see the ROI of social media. Besides, for many, figuring out how to manage the multifarious features on different social media platforms is mind-baffling.

As the face of the business and brand, all executives should consider four important reasons to have an active social media presence.

1 CONNECT, CONNECT, CONNECT

The adage says there are "six degrees of separation" between any two people on earth, meaning that any two people would know each other through no more than six contacts. On Facebook, however, the average user is only 4.74 degrees away from any other Facebooker.

If executives take the time to intentionally connect with followers, that means the next person they connect with may be their next prospective client, business partner, or collaborator. You have the opportunity to connect with people from any and all of the 196 countries, and even all seven continents.

2 ESTABLISH THOUGHT LEADERSHIP

Successful business leaders actively engage in thought leadership surrounding their industry. By sharing knowledge and insight, executives gain the trust and respect of clients, their peers, and their staff. Additionally, thought leadership is an important route to establishing a personal brand.

Paul Sohn is a leadership transformation consultant at GiANT Worldwide. His latest book is *Quarter-Life Calling: How to Find Your Sweet Spot in Your Twenties.*

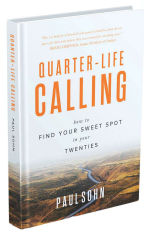
According to the BrandFog survey, 61 percent of U.S. respondents are more likely to purchase from a company whose values and leadership are communicated through executive participation on social media. Clearly, executives should choose to make their relationships on social media count because customers are paying attention.

3 ENGAGE IN TWO-WAY FEEDBACK

Social media gives executives the opportunity to remain in touch with their wide range of stakeholders, including customers. Customers want executives who are real and visible, who are available to reach out to, and they want to understand the executives' opinions and thoughts about the company and the products. With one tweet or one Facebook post, you'll immediately get a plethora of instant feedback from your customers.

4 IMPROVE BRANDING

When Cisco CEO Chuck Robbins tweets a compliment to his company's global head of executive talent or thanks a customer for a great meeting, he's doing more than just saying casual praise. He's reinforcing a culture and brand that matters to his business. Compliments are one of the most powerful ways to maximize social media and earn greater support from followers. Executives have special leverage in this way. By recognizing an employee's or business partner's qualities or achievements in public, they are not only doing them a favor, but creating a culture of trust and a brand that people want to follow. L



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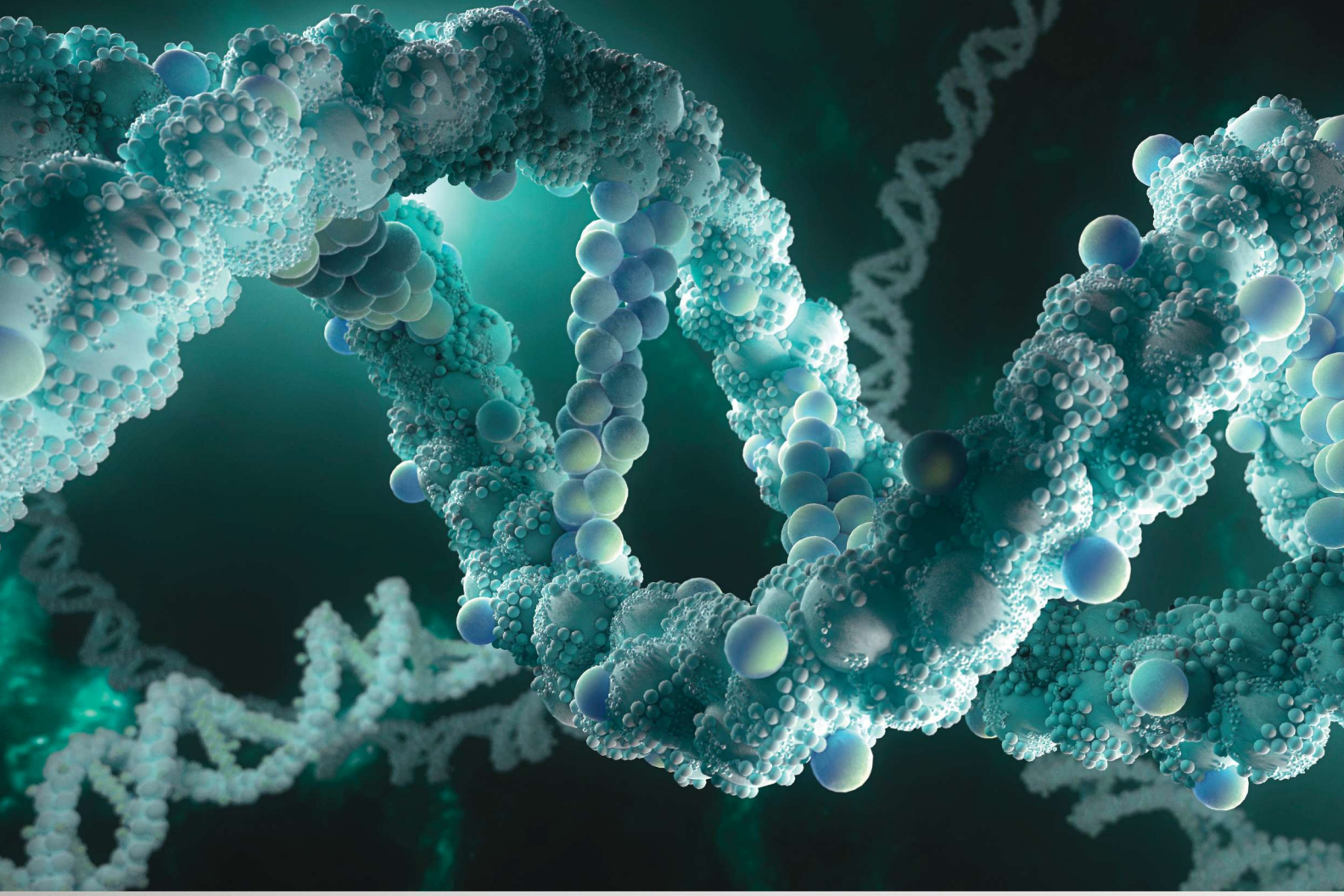

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