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FEBRUARY 2017

PAUL PERREAULT
CEO, Managing Director
CSL Limited

The Secrets to CSL Limited's Incredible Revenue Growth

p. 14

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CONTENTS

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THE ENTERPRISERS

Insights:

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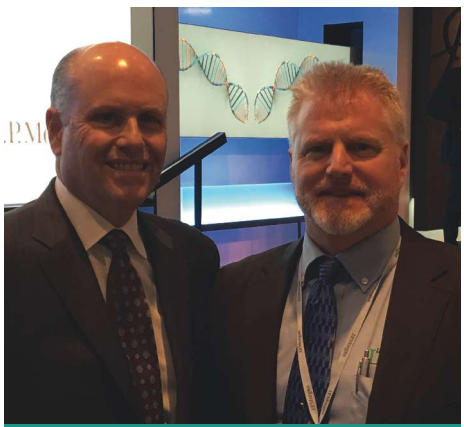
What JPM 2017 Revealed To Me

ROB WRIGHT Chief Editor

As I walked into a breakout session on Jan. 11, 2017, at the J.P. Morgan Healthcare Conference (JPM) in San Francisco, I couldn't help but overhear a number of people discussing the latest negative news to hit the biopharmaceutical industry. In his first press conference as president-elect, Donald Trump slammed the biopharmaceutical industry for corporate inversions, overseas production, and yes — drug pricing too. And as is often the case during this annual event, the news spread like wildfire. Though the NASDAQ Biotechnology Index (NBI) declined 3 percent by day's end, the tone of conference conversations remained confident, and in my opinion, rightfully so. Despite no biopharmaceutical executive wanting to end up on the wrong end of a Donald Trump tweet, there seems to be a strong sense of industry optimism. And why not, for we work in an industry focused on creating life-saving and life-improving therapies.

That being said, drug pricing continues to remain a very hot topic. For example, during at least three JPM breakouts on Tuesday that I attended, almost the exact same question on drug pricing was posed to three different biopharma leadership teams. During AbbVie's Wednesday morning presentation, CEO Richard Gonzalez addressed the drug pricing issue proactively, announcing plans to raise product prices only one time during 2017, and to do so by only single-digit percentages. But perhaps most telling was the poise demonstrated by 2016's most embattled drug-pricing CEO — Mylan's Heather Bresch. When asked what lesson she had learned from EpiPen price increases that placed her and Mylan under the media's microscope, she replied, "That the pricing model has got to change." Bresch went on to state that she thinks the change can't be incremental and that it needs to involve truly rethinking the business model. She also gave her plan for Mylan to be part of the solution. I for one admire Bresch's willingness to face the drug-pricing heat head on. For she could have easily cancelled conducting a breakout Q&A, something one top-five Big Pharma seems to do rather consistently during recent JPMs.

Every year during JPM there are those who argue that the real action takes place outside the four walls of the Westin St. Francis (JPM's annual host hotel). What cannot be debated, though, is this — the reason BioWeekSF (i.e., term used by the greater San Francisco biopharma community to refer to the time period surrounding JPM) exists is because of JPM, not in spite of it. And though there are plenty of worthwhile adjacent activities that have sprung up around, I prefer to spend the bulk of my time within JPM. After all, there's so much to be gained if you just pay attention. L



With CSL Limited CEO, Paul Perreault, at the 35th Annual J.P. Morgan Healthcare Conference in San Francisco

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Founder, President, and CEO, ImmusanT

Q Are there teachings from a small company that can help big company executives?

A TRUE BIOTECHS TYPICALLY have a single program driving value and capital expenditure. Functioning as pods of innovation, small biotechs are struggling and striving to find the next breakthrough. Their resources are limited, organizational structure flat, and decision making efficient. In a small biotech each person is laser focused, has a sense of urgency, and is empowered to work on tasks beyond predefined responsibilities. Big companies could benefit from adopting a similar mentality that empowers teams to not only take calculated risks, but reward those that are successful. Disincentivize the stagnant status quo and eliminate legacy baggage, waste, and redundancy (i.e., costly check-and-balance "safety" mechanisms). Communicate regularly, lead by example, and eliminate the ability of personnel to hide in bureaucracy.

LESLIE WILLIAMS
is president, CEO, and founder of ImmusanT, Inc., an early-stage company focused on peptide treatments for autoimmune diseases. She has more than 20 years of industry experience.

Q Knowing what you know now, what would you do differently in managing teams?

A I WOULD PUT GREATER EMPHASIS on giving my staff challenging responsibilities. We talk about celebrating failure and letting people learn from their mistakes, but it is difficult to not tighten control as the stakes get higher. Letting people practice on low-risk activities is fine, but everyone needs to be put into a situation where the risk is real, the pressure is high, and the responsibility for outcomes is their own. Interestingly, the tougher the situation, the bigger the learning and, in my experience, the better the performance. Strong employees respond to big challenges. Empowering staff members to lead and control their own projects has brought success with employee development and the projects themselves. However, it is an ongoing struggle to remember to do this, and to do it in such a way that the possibility of failure does not become a guaranteed failure.

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

Q What is the most interesting post-retirement experience you have had, and why?

A AFTER 30+ YEARS OF 50+ HOUR WORKWEEKS, my intention was to retire but do some industry consulting. While I didn't miss the intensity of a Big Pharma job, I did miss the passion that drives improving healthcare. Coaching a few small firms has helped me to fill that void. Interestingly, as a coach there is little I need do to set companies up for success. I share experiences, ask questions to clarify intentions and approaches, and thereby help others to lead. Though leaders face a choice of how much they do versus how much they allow others to do, coaches do not. In my opinion, the role of a leader should be much more aligned to that of a coach – creating the conditions for success. While this was my approach in industry, retirement provided me the opportunity to relearn this valuable lesson from a new perspective.

JAMES ROBINSON
is the former VP of vaccine and biologics technical operations for Merck

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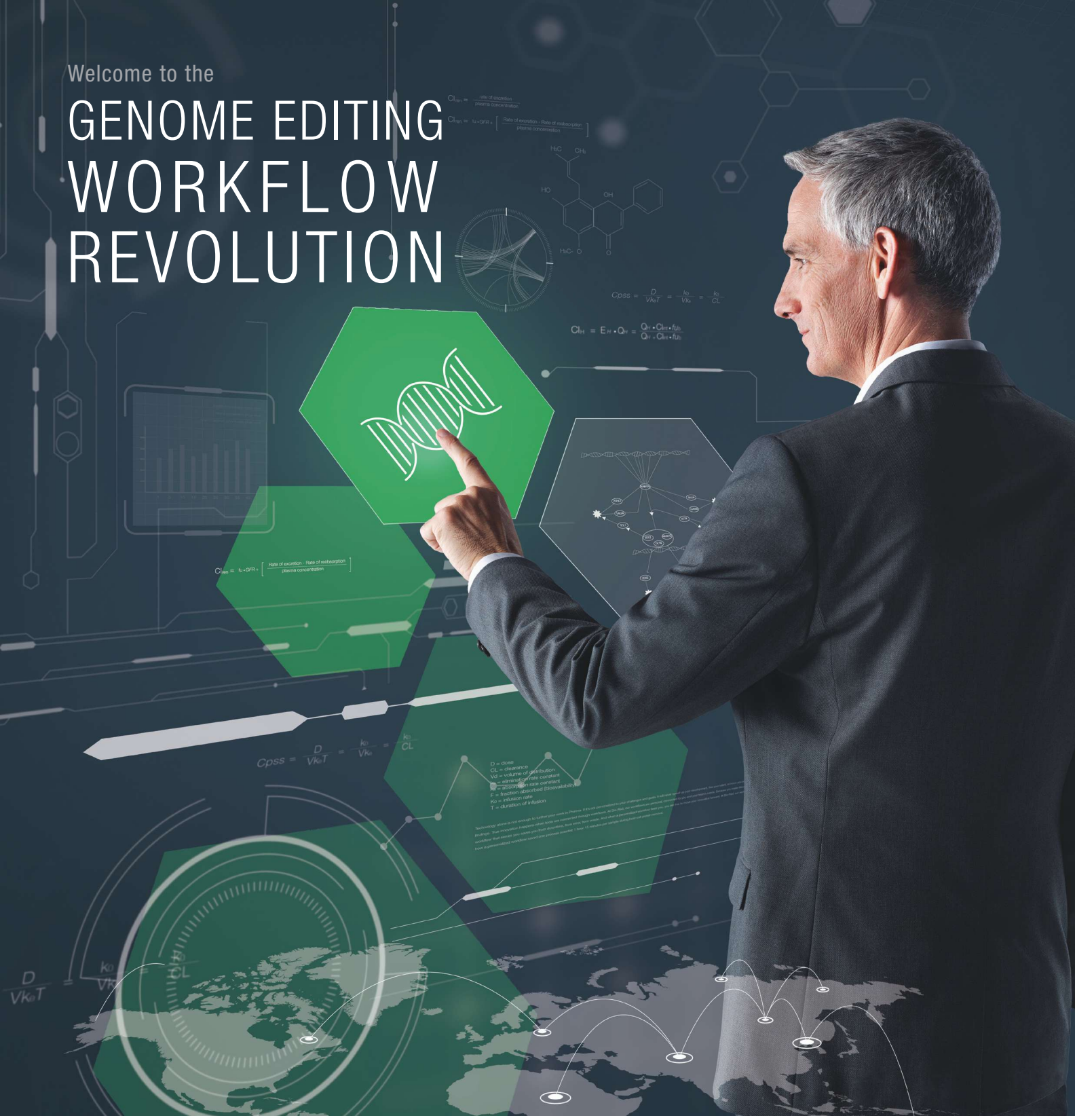

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Trump Targets
The Pharmaceutical Industry

JOHN MCMANUS The McManus Group

A few minutes into a freestyle press conference on Jan. 11, ostensibly called in response to a specious and salacious intelligence report on his ties to Russia a mere week before his inauguration as the 45th U.S. president, Donald J. Trump launched an unprovoked broadside against ... the pharmaceutical industry!

He seemed to criticize recent inversions, but more importantly vowed to go after the industry: "Our drug industry has been disastrous. They're leaving left and right. They supply our drugs, but they don't make them here, to a large extent. And the other thing we have to do is create new bidding procedures for the drug industry, because they're getting away with murder. Pharma has a lot of ... lobbyists and a lot of power. And there's very little bidding on drugs. We're the largest buyer of drugs in the world, and yet we don't bid properly. And we're going to start bidding, and we're going to save billions of dollars over a period of time."

The nine biggest pharmaceutical companies promptly lost roughly $24.6 billion (or 1.7 percent) in market cap in 20 minutes.

And then over the following weekend, Trump doubled down in an interview where he said he will demand Medicare and Medicaid negotiate directly with drug companies and vowed to use his bully pulpit (read: Twitter feed) to lower drug prices, like he has been attempting to do against Lockheed Martin for its over-budget F-35 program.

Nervous pharmaceutical executives across the country braced themselves for Twitter attacks on their companies and blockbuster products. Should they respond to an attack or just hunker down and hope to work the legislative process where a generally friendly Republican Congress might provide some respite? Trump made his view clear on the latter approach, referring to pharmaceutical companies, "They're politically protected, but not anymore."

Some may dismiss the Trump fusillades as populist hyperbole. But he inherits considerable executive authority ceded by the then-Democratic Congress when it created the Center for Medicare and Medicaid Innovation (CMMI), which can ignore and override long-standing statutory law to "test" new nationwide demonstration projects in Medicare and Medicaid.

How about a test of a new Part D plan that uses Veterans Affairs prices, which are limited by statute and also severely restrict the choice of drugs? Professor Joanna Shepherd, professor of law at Emory University School of Law, recently observed, "Private Medicare Part D plans cover an average of 85 percent of the 200 most popular drugs, with some plans covering as much as 93 percent." She also stated that "The Department of Veterans Affairs (VA), one government program that is able to set its own formulary to achieve leverage over drug companies, covers only 59 percent of the 200 most popular drugs." Most seniors would not take kindly to that type of rationing.

In addition, an (certainly less than) Independent Payment Advisory Board (IPAB) this year is expected to have the ability to exert its power to extract an arbitrary amount of savings from Medicare. We will find out if that power is triggered when the CMS Office of the Actuary issues its report in Q2. If IPAB is not appointed (as appears likely), Trump's Department of Health and Human Services (HHS) gets to develop and implement the policies to achieve those savings. Taken together, we're in for a very wild ride.

But are Trump's attacks misdirected? In its January meeting, the Medicare Payment Advisory Commission (MedPAC) noted that the Part D monthly beneficiary premium has remained remarkably stable from 2009

to 2016 — rising just $2 in that period (from $29 to $31).

But it expressed concern that reinsurance payments, which finance 80 percent of the spending in the catastrophic part of the benefit, are growing much more rapidly, rising 25 percent per year between 2010 and 2015. Less than 9 percent of Medicare beneficiaries have enough spending to reach the catastrophic threshold, yet they account for 53 percent of the spending, up from 40 percent in 2011. MedPAC suggests reducing the 80 percent reinsurance subsidy, but the underlying subsidy for the initial benefit is 75 percent — not much difference.

"We're the largest buyer of drugs in the world, and yet we don't bid properly. And we're going to start bidding, and we're going to save billions of dollars."

PRESIDENT DONALD J. TRUMP

MedPAC notes that growth in prices of single-source drugs is overwhelming the effects of generic use. A key factor is that "Plans have incentives to put high-price, high-rebate drugs on their formularies." Why is that, and where is that pharmaceutical rebate revenue going?

The National Community Pharmacists Association (NCPA), representing 22,000 independent pharmacies across the country, fingered pharmaceutical benefit managers (PBMs). In a January letter to Trump to respond to his press conference, NCPA pointed out that half of the 400 percent price increase for the EpiPen went to PBMs, and "Similarly, insulin prices have also skyrocketed, yet the net revenue per prescription received by drug manufacturers is reportedly falling sharply."

NCPA's letter goes on to state: "Little–known PBMs have grown over the past few decades from prescription-processing companies into enormous corporations that hold the key to rising drug costs and operate in a virtual black box. Three large PBMs now control 80 percent of the market. ... Over time these companies have morphed into little-regulated entities that exploit their strategic position at the middle of nearly all drug transactions in the U.S., to extract profits from the upstream and downstream participants in the drug supply chain while providing questionable value to the consumer."

A key problem is the percentage rebate large PBMs typically demand of pharmaceutical companies. This gives PBMs an inherent incentive to prioritize higher-cost products on their formularies — the higher the price, the more revenue the PBM can extract. This pricing scheme also hampers competition, as new entrants who may have a drug of equal or superior clinical value cannot obtain patient access because PBMs protect high-volume legacy products that can generate more rebate revenue. Products launched at a cheaper price are at an inherent disadvantage because of reduced profit potential to the PBM.

Robert Goldberg, cofounder and VP of the Center for Medicine in the Public Interest, points out, "Cash rebates that drug companies give to discount [their] products are now pocketed by insurance companies or used to subsidize other line items. ... Rebates now make up 30 percent (or $115 billion) of total drug spending. Indeed, 77 percent of the retail price increase in drugs since 2006 goes to rebates."

He goes on to state, "When auto companies offer new car rebates, the cash is applied to reduce the price of the car in the dealership. In our healthcare system, the cash rebates go to the insurance companies and pharmacy benefit management firms. And when we pay for our prescription at the drug store, we are charged the list price."

To President Trump's point — can the "bidding" process be improved in Medicare? Absolutely!

1. Congress should ensure that patients are actually benefitting from price negotiations between pharmaceutical manufacturers and PBMs that contract for Part D plans. The Medicare statute requires Medicare plans to provide a mechanism for patients to benefit from negotiations at point of sale, but that has never been enforced.
2. Similarly, the 340B drug discount program has certainly benefitted qualifying hospitals, but the statute does not require those discounts to be passed on to patients. Mega-hospital systems are reaping millions in 340B discounts by charging their customers full price for these products, but their patients — even those who are uninsured and indigent — are not experiencing any savings. 340B is ripe for reform!
3. Finally, a reformed tax code that substantially reduces the corporate rate will do much to deter inversions that were initiated only because U.S.-based multinational companies could not repatriate offshore earnings without substantial penalty. 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.

Why More Incentives Are Needed To Tackle Antibiotic Resistance

ANKIT MAHADEVIA, M.D.

Antibiotic resistance is a real and immediate threat that is beginning to garner the global attention it needs and deserves. During a meeting of the United Nations in September 2016, the entire General Assembly — 193 nations — reaffirmed its commitment to developing national action plans on combatting antibiotic resistance. Speaking at the meeting, UN Secretary-General Ban Ki-moon said antibiotic resistance poses "a fundamental, long-term threat to human health, sustainable food production, and development."

Currently, approximately 700,000 people around the world die every year from so-called "superbugs" or multidrug-resistant infections. This number is expected to rise with the emergence and spread of superbugs across the globe. A strain of E. coli resistant to colistin and carbapenem has now surfaced in Europe, China, and the United States. Without an urgent and coordinated global effort, we run the very real risk of falling into a post-antibiotic era in which surgeries and treatments that depress the immune system, such as chemotherapy, are too dangerous to perform, and minor injuries can kill again. According to the final report issued earlier this year by Britain's Review on Antimicrobial Resistance, if we fail to find effective antibiotics, across the globe, 10 million people each year will die by 2050. This would make antibiotic resistance the world's biggest killer, with a cost to the global GDP of $100 trillion.

Until recently, there has been little incentive for drug developers to invest in antibacterials, which are designed to be used as infrequently as possible. Additionally, the American consumer has come to expect antibiotics to be very inexpensive, which further discourages the development of new antibiotics. The high cost of development and the low rate of return leave little room for profit. In May 2016, The PEW Charitable Foundation found that there are only 37 new antibiotics in clinical development and only a fraction of those will make it to market. In 2001, Eli Lilly and Bristol-Myers Squibb left the market, while Roche spun-off its antimicrobials unit into a separate company. Only five traditional pharmaceutical companies (GlaxoSmithKline, Novartis, AstraZeneca, Merck, and Pfizer) are currently pursuing antibiotic R&D at a time when the world is in desperate need of new antibiotics. An area of particular need is new solutions for Gram-negative bacteria. The unique outer membrane of Gram-negative bacteria protects them against many of the currently available antibiotics and makes them generally less susceptible to antibiotics than their Gram-positive counterparts. There hasn't been a new antibiotic class approved to treat Gram-negative infections in more than five decades.

GOVERNMENTS ARE TAKING NOTICE

Today, governments around the world are taking steps to encourage responsible use of antibiotics to control the spread of drug-resistant infections. In the United States, the CDC has found that not only are people misusing antibiotics, but that at least 30 percent of antibiotics prescribed in the United States are unnecessary. The CDC, the U.S. FDA, United States Agency for International Development (USAID), and Systems for Improved Access to Pharmaceuticals and Services (SIAPS) have all implemented educational campaigns encouraging doctors not to overprescribe antibiotics and to inform patients about the dangers of antibiotic overuse and misuse. Local public initiatives on hand washing and the importance of compliance with antibiotic prescriptions have been enacted to help stop the spread of infections and reduce the emergence of antibiotic resistance. Updated antibiotic stewardship guidelines have been recommended by numerous professional organizations including the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA).

Public education campaigns and antibiotic stewardship programs play an important role in reducing further damage, but they do little to address the current limited number of effective antibiotics for the toughest-to-fight infections.

Governments are also beginning to fill in these gaps with additional funding and support for antibacterial development. In July, the U.K. established a new Antimicrobial Resistance Center to provide research and funding for startups working in the field. The center has a £180 million (U.S. $236 million) plan with the ambition of getting 20 products into preclinical development by 2020 and advancing 10 of those to clinical trials by 2022.

As another step in realizing the goals set forth in the White House-led National Action Plan on Combating Antibiotic-Resistant Bacteria (CARB), CARB-X was launched in August 2016. CARB-X is a biopharmaceutical accelerator to help move projects from the lab to clinical trials. In the first year, CARB-X will commit $50 million to research with the goal of getting at least two new drugs into clinical trials in the next five years.

In addition to providing direct funding for R&D, governments have also begun to take a serious look at the regulatory hurdles faced by antibiotic developers. Passed in 2012, the Generating Antibiotic Incentives Now (GAIN) Act provides an accelerated approval pathway and a five-year regulatory extension of exclusivity for novel antibiotics that address serious or life-threatening infections. Companies such as Allergan and The Medicines Company have begun using the benefits of the GAIN Act. Without the GAIN Act, biopharmaceutical startups would not have been able to raise the capital needed to begin development as a company. More recently, the 21st Century Cures Act was passed in December 2016 and establishes a new FDA-limited population-approval pathway for antibiotics that treat serious or life-threatening infections with unmet medical needs. The Cures Act provides a streamlined regulatory process for medicines treating rare illnesses for which there are few or no available alternative treatments.

THE POTENTIAL OF PUSH AND PULL INCENTIVES

Accelerators, additional funding, and public-private partnerships are critical "push" incentives that reduce a company's R&D expenses, but more can be done to transform the entire economic model. In addition to incentives that "push" new drugs to market, we also need incentives that will "pull" larger companies into the space to ensure there is a sustainable ecosystem that will continue to deliver new antibacterial solutions well into the future.

Pull incentives reward successful development of a drug by increasing or ensuring future revenue. Pull mechanisms include outcome-based rewards such as monetary prizes and advanced market commitments or policies that accelerate the market approval process, extend market exclusivity rights, and increase reimbursement prices. Some specific pull incentives that have been discussed and should be considered to help drive and sustain antibiotic development include:

- Market-Exclusivity Vouchers — Upon approval, the company that developed the new antibiotic could be granted a voucher that would extend market exclusivity for the newly approved antibiotic. The company could retain and use the voucher or could sell it to another company for use on another drug. In order to be eligible for the voucher, the new antibacterial would need to meet stringent criteria for innovation and its ability to address an unmet medical need.
- De-Linkage — The concept of "de-linkage" refers to separating a company's return on investment from the number of product units it sells (vials, pills, etc.). Instead, companies would receive one or more lump-sum payments upon product approval and/or other developmental milestones in exchange for agreeing to marketing constraints and stewardship provisions.
- Value-Based Reimbursement — Value-based pricing would price products according to their value for patients based on a health-technology assessment. Society would pay for what it benefits from and values, which would better reflect the lifesaving and societal value of these medicines. An opportunity for reevaluation of reimbursement rates to reflect changes in antibiotic effectiveness would be worked into the proposal, and the higher prices may also minimize inappropriate use of antibiotics.

WE NEED A COOPERATIVE ECOSYSTEM

Innovative medicines that truly address unmet needs do not need policy solutions to get to market and be successful, whether in antibacterials or otherwise. However, a healthy ecosystem where biotechs, academic labs, regulators, policymakers, and pharma work together to advance new drugs treating infection is crucial. Any exits from the ecosystem make biopharmaceutical companies' jobs harder.

We support incentives that solidify the momentum we have in the field by continuing to increase parity between therapeutic areas. With dozens of public policy proposals, now is the time to move forward with a set of solutions. L

ANKIT MAHADEVIA, M.D., is president, CEO, and a member of the board of directors of Spero Therapeutics, which he founded in April 2013.

THE SECRETS TO CSL LIMITED'S INCREDIBLE REVENUE GROWTH

ROB WRIGHT Chief Editor @RfwrightLSL

Like any pharma CEO today, Paul Perreault talks a lot about the importance of the "voice of the patient" in drug development. Patient-centricity is, after all, a prerequisite industry buzzword these days. But when Perreault talks about this topic, it doesn't have the usual hollow ring of marketing fluff; he cites examples and specifics that add credibility to this "strategy."

But part of that credibility comes from the man himself. Since taking over as CEO and managing director of CSL Limited in 2012, the 36-year industry veteran has helped the company increase revenue by 33 percent. Did he slash R&D or perhaps hold off on making capital improvements just to make the numbers? Not according to CSL's most recent financial reports. Instead, the company has increased R&D by 73 percent and capital investment by 83 percent. Perreault admits there are multiple drivers to this level of success, but it all starts with a focus on patient education.

START EDUCATING EARLY, AND TOUT THE DATA

"Within the United States we have developed close collaborations with all of the relevant patient disease organizations, as well as those more broad-reaching groups [e.g., the National Organization for Rare Disorders]," Perreault says. Those efforts are intended to help educate patients and providers toward better diagnoses. In addition, the company educates Washington insiders on the need to make sure orphan and rare diseases legislation is in alignment with commercial efforts.

"Before Phase 3 of clinical trials, we also like to talk to insurance companies because, by then, we have a good idea of what the therapeutic will cost, so we want to make sure patients are going to have access," he explains. "If you don't start that conversation early, you can go through a heck of a lot of development and get products approved that nobody is willing to pay for." He says he's seen it happen in both Europe and the U.S. And it's not just having those conversations early; its providing data on how a new therapeutic is going to impact the lives of patients and lower the long-term costs of care.

For example, in December 2016, *The Lancet Respiratory Medicine*, a specialty journal, published findings of the CSL-sponsored RAPID Open Label Extension study. Conducted in patients with alpha-1 antitrypsin deficiency (AATD), the study data demonstrated that the use of Alpha-1-Proteinase-Inhibitor

PAUL PERREAULT
CEO, Managing Director
CSL Limited

(A1-PI) therapy slowed the progressive and irreversible loss of lung tissue. "Alpha-1 is one of those diseases where it looks a lot like COPD, so the awareness and diagnosis is tough," Perreault contends. "I've spoken to pulmonologists who have said they have never seen an alpha-1 patient. When I ask if they've ever tested for it, they usually say no."

He says in the alpha-1 space both physicians and payers needed a lot of education. But having the data from this study, which demonstrates disease modification, certainly helped the discussion. "When designing clinical trials today, you need to make sure the data you collect supports your pharmacoeconomic proposition," he says.

EDUCATING PAYERS WITH PATIENT ADVOCATES

"We know that not every patient is going to be a perfect fit for our products," says Paul Perreault, CEO and managing director of CSL Limited. "Sometimes patients have reactions after being switched to a new drug."

And while having a 100 percent market share would be great, he is not interested in the use of closed insurance formularies to achieve such an end. "We want to make sure that formularies have multiple options," he states. "In the rare disease communities, patients need choice." To help achieve this, CSL has patients advocate on the company's behalf. "We've brought patient advocates to speak to payers on the importance of choice," Perreault shares. "Not only does this help educate the payers, it provides patients an opportunity to have a loud voice at a high level within the payer community."

Perreault and his team are also trying to encourage payers to think more long term, which is hard. "They're trying to save money *today*, so it's not easy to pull costs out of the system." He says CSL talks with payers about their business model and seeks to understand what they are trying to accomplish as an organization. "Drug companies have to look beyond drugs when working with insurance providers," he explains. "We need to ask what's happening in terms of care, tests, and utilizations. We also need to know what we can add regarding how to diagnose certain diseases." In doing so, CSL hopes to help prevent people from wandering through a healthcare system for many years trying to get diagnosed. "We need to understand their model of delivery if we want to help them better deliver care for patients with rare diseases," he concludes.

GLOBAL AND INTERNATIONAL ARE *NOT* THE SAME THING

Although focusing on education for patients, payers, and legislators is a key part of CSL's business strategy, the enormity of that task isn't immediately evident until you consider that this is a *global* company conducting business in more than 60 countries, yet is headquartered in Australia. "We are one of the few companies that have successfully globalized out of Australia, because Australia is a long way away from anywhere," Perreault quips. "The difference between us and a lot of Big Pharma companies is that they talk about being global, but are actually *international*, operating independently in all of the countries in which they do business."

To further explain how this global moniker impacts the company's business, he says decisions aren't made based on one market without first checking with all the other markets. It's more of a long-term view, meaning, for instance, that the company wouldn't abandon a market simply because product sales are struggling. Similarly, the promise of a high price for a product shouldn't be the sole reason to enter a market. "Neither customers nor patients like such approaches since each represents a lack of commitment to a medical community," Perreault explains. "If you're going to enter a market, you need to know that you have a sustainable platform and strategy, and you don't leave when you have a problem or need a better price to raise profits."

"Getting into the flu business is not for the faint of heart, and to be successful requires you to be highly focused."

Outside of the United States, which represents the bulk of CSL's business and a key growth area, the company has operations in Argentina, Brazil, Chile, Europe, and Mexico, just to name a few. "All of these have been good growth platforms for us, built on the back of initiatives we have for awareness and diagnosis of various rare diseases," he says. "Areas like Latin America and some of the other countries I mentioned are really starting to come into their own as a result of the patient advocacy and education we have supported."

Japan, though, required some customized attention when it came to developing those education initiatives. "Japan is a really tough place to do business," Perreault admits. In particular, the company wanted to educate the older Japanese medical professionals about primary immunodeficiency, a group of more than 300 rare, chronic disorders in which part of the body's immune system is missing or functions improperly. To do so, CSL helped establish the Primary Immunodeficiency Database in Japan (PIDJ). "We found some younger Japanese immunologists who were more on the cutting edge of what's happening in immunodeficiency," he explains. "Now, with the PIDJ, it has become a reference center of excellence, enabling younger and older immunologists to share new information and best practices."

GROWTH BY ADDING ONTO A CORE BUSINESS

Beyond its global education initiatives, CSL achieved growth in recent years a more direct way — through acquisitions. On this topic, Perreault is also effusive, lobbying for a more thoughtful approach. "I frequently say, don't get entertained by stuff you don't understand," Perreault counsels. "For example, say a company is facing a big patent cliff. So, looking for future growth, they decide to buy another company's product. But two or three years later, they want to jettison it because it's no longer 'core' to what they do. Often, the end result is a lot of wasted time and effort."

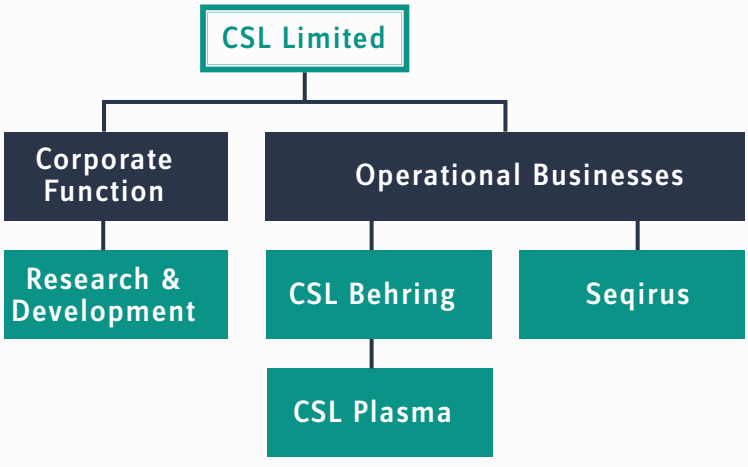
So why did CSL — a specialty biotherapeutics company that primarily develops biotherapies from human blood plasma — decide to buy the Novartis flu business for $275 million in 2014? To answer that question, you first need to understand the flu business.

Unlike most vaccines, which are developed and pretty much stay the same for 50 years, when you develop flu vaccines you develop and register a new product about every six months. You've got one flu vaccine for the Southern Hemisphere and another one for the Northern Hemisphere; different strains require flu companies to do safety trials in both hemispheres every year. "In other words, getting into the flu business is not for the faint of heart, and to be successful requires you to be highly focused on the flu business," explains Perreault.

He contends that CSL's acquisition of the Novartis flu business was a good strategic decision because they were the only manufacturer in the Southern Hemisphere, of any scale whatsoever, in influenza. "We have pandemic contracts with the Australian government, and that

CSL LIMITED COMPANY DIAGRAM

With major facilities in Australia, Germany, Switzerland, United Kingdom, and the U.S., CSL Limited has more than 16,000 employees working in over 30 countries.



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flu infrastructure also supports some of our antivenoms and antitoxins [medicines of national importance for Australia] work." According to Perreault, when people in Australia get bit by snakes or spiders or are stung by jellyfish or other sorts of creatures, it is CSL that makes *all* of the remedies. Purchasing the Novartis flu business gave CSL the necessary scale to go global with its existing flu business.

Besides scale it was also a good deal. "They had great cell culture assets in Holly Springs, NC, a facility that cost over $1 billion to build," he relates. "Novartis also had a facility in Liverpool that's a former Chiron plant that they had put a lot of money into." In early 2016, the company announced the combination of the former Novartis flu business with CSL's existing vaccine business would operate under the brand Seqirus, making the company the second-largest influenza vaccine provider in the $4-billion global market. While not yet profitable, Perreault anticipates getting to break-even by 2018. "The goal is to be profitable by 2020, having about 20 percent EBIT margins, and around $1 billion in sales," he says. In the meantime, the focus is on ramping up flu doses. "The first season we got out 8 million," he concludes. "We need to get to 25 million, then 30 million, and eventually 60 million flu doses to really achieve scale."

While Perreault acknowledges CSL's future success begins with a focus on patient education, it ends with looking beyond plasma. "Having launched two new recombinants this past year, we certainly have capabilities in this area," he reiterates. "But we've added competencies in others as well." For example, back in 2006, the company acquired an Australian antibody company (Zenyth Therapeutics) for $104 million. And while this added a lot of antibody assets to the company's portfolio, it also brought a lot of knowledge on which CSL can build. "We're not looking for bolt-ons that provide a one-year positive raise to revenues. We are looking for things around our core capabilities, competencies, or adjacencies that we can add value to and can grow over time, and this requires disciplined decision making," he concludes. L

CSL CEO STRESSES NEED FOR "GENERAL MANAGEMENT"

CSL CEO and managing director Paul Perreault says he never set out to be the CEO of anything and certainly never aspired to head an Australian biopharmaceutical company. "I am surprised as anybody to be in charge of this company." He says his rise to the top position at CSL happened through teachable moments, as well as unexpected opportunities.

Shortly after graduating college, Perreault began his biopharmaceutical career as a field sales representative with A.H. Robins. "I learned early in my career the importance of taking on additional responsibilities," he shares. While still a rep, his boss told him there was an opening for a regional trainer and asked if Perreault wanted to apply. But he was reluctant, primarily because he didn't want to leave his customers. His manager assured him that he'd continue to have a sales territory, though it'd have to be shrunk to accommodate his training responsibilities. "The one thing I learned from my regional trainer experience is that not everybody worked or was motivated the same way I was," he admits. This lesson was even more evident when he took his next job as district manager.

"I took over a district that was 45 out of 45 in the country," he recalls. "I started my first meeting with motivational posters on the walls — which all went over like a lead balloon." Perreault shares that he failed miserably in his first year as a manager. "I was clueless when it came to people," he admits. "Understanding the importance of having the right people motivated around the right things was a key teachable moment for me as a young district manager. After a year I realized I had to get the right people working in the company to do the job that needed to get done." Over the next two and a half years he ended up turning over about 10 out of the 12 sales representatives, and the team moved from worst to first.

Other teachable moments occurred as he continued throughout his career. "Today, everybody wants to be a specialist," he asserts. "General management seems to be a declining skill, yet one greatly needed in today's environment." For example, Perreault has experience in operations, sales, marketing, training, management, and finance. "When it comes to leadership, I think the broader your experience, the better," he explains. "If you don't have enough breadth to understand the big picture of a business, how are you going to be able to ask the right questions or see the interplay and intricacies critical to making it successful?" But don't only aspire to take on different roles in an organization. "The more diversely you read, the better your thinking will become," he says. "Teachable moments are all about the learning, not the lesson."

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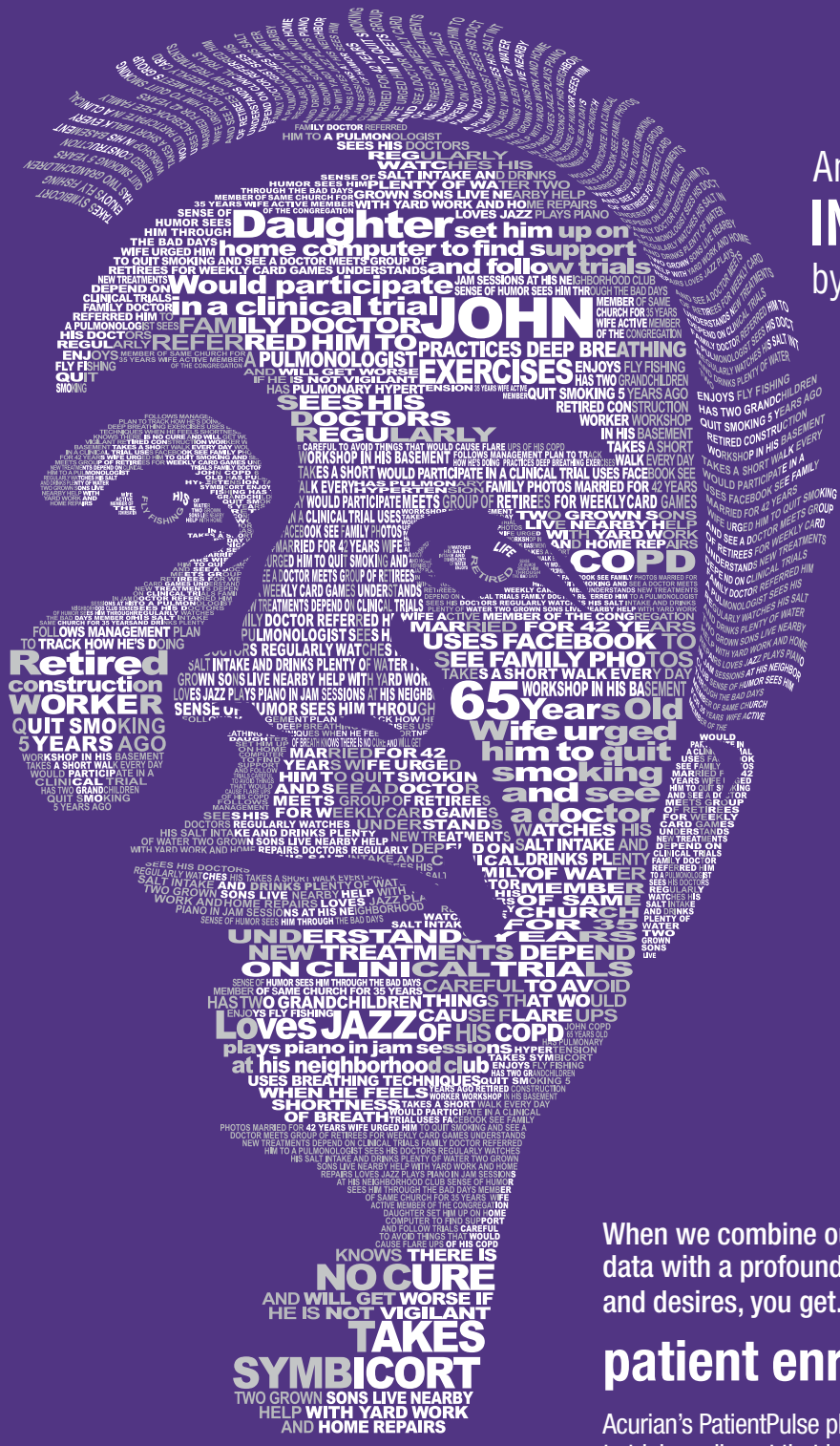

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COMPANIES TO WATCH ROUNDUP 2016

BY WAYNE KOBERSTEIN Executive Editor

There is no grand plan for a whole year of Companies to Watch (CtW). Each month, a single candidate makes the cut for a single column. Nevertheless, patterns emerge among the CtWs as the year progresses and come into focus as it ends. Perhaps I make them half consciously. Every year so far, I have made a wide selection of possible CtW candidates according to the simple criteria — small company, developing new therapies, little press coverage, interesting and instructive story. A CtW might come from the larger group of my meetings and interviews or out of the constantly churning pool of startups and upstarts in this wondrous industry. As I write this, I have just scheduled more than a dozen meetings during the week of the 2017 J.P. Morgan Healthcare conference, selected from more than 300 PR pitches, and am preparing for a trip in February and more interviews at the BIO CEO and Investor event. Many of those conversations will form the basis of CtWs, but many will also contribute to other series, features, columns, or blogs produced during the year.

This year, some clear patterns showed themselves in the 10 CtW columns we published in 2016. First, the featured companies range fairly evenly from just-off-the-bench early to regulatory-submission late. It is safe to say that every company reflects the characteristic risks that come at each stage along the development path. At the earliest points, hopes are high, success or failure lies far in the future, and merely communicating and "proving" your concept is the immediate challenge. Further along, though, as you approach testing in humans, the pressure rises; get the trial design wrong, and you may have sown the seeds of your own defeat. And with each new phase, the ante jumps higher — you must raise and spend more money, hire more people, batten down your IP, and work through the racket raised about your product by the usual crowd of hypesters and doubters.

The 2016 CtWs report making progress at their stage — all, that is, except one, felled by safety issues, otherwise known as the vagaries of the human body in reacting to new therapeutic agents. Not as random as roulette, but often as unpredictable. In truth, our exception is closer to the rule than the rest of our CTWs, seen in mid-development, and still working toward their end goal. In the following, we let the companies update their stories as we continue to watch them in 2017.

JANUARY

Catalyst Pharmaceuticals

At the FDA's door this year with Phase 3 data and a planned NDA for a licensed drug developed as the first treatment for a rare neuromuscular disease — and maybe others.

"In 2016, Catalyst continued to focus on bringing Firdapse [amifampridine phosphate] to patients with Lambert-Eaton myasthenic syndrome (LEMS) and other neuro-

muscular disorders through the FDA approval process. In December 2016, Catalyst launched a confirmatory Phase 3 clinical trial of Firdapse in patients with LEMS. This Phase 3 trial, which received a Special Protocol Assessment (SPA) from the FDA, will support Firdapse's new drug application (NDA) to the FDA. Catalyst expects data from this trial and its NDA submission in the second half of 2017.

Catalyst also has continued to evaluate Firdapse in patients with congenital myasthenic syndromes (CMS) and MuSK-antibody positive myasthenia gravis (MuSK-MG), with clinical trials running for both indications. In December 2016, the company expanded its CMS clinical study to include adults with CMS, in addition to pediatric patients with certain genetic mutations of CMS. Data is expected later in 2017. In 2016, Catalyst also proudly published case reports of clinical efficacy of its GABA-AT inhibitor, CPP-115, in patients with infantile spasms.

Catalyst will have multiple clinical milestones in 2017, including data from its second Phase 3 trial of Firdapse and data from studies of Firdapse in CMS and MuSK-MG. The company expects to submit the NDA to the FDA for approval of Firdapse in patients with LEMS later in 2017 as well. The FDA approval will allow, for the first time, all patients with LEMS to have access to the only effective treatment for this debilitating disease."

PATRICK MCENANY
COFOUNDER, CHAIRMAN, PRESIDENT, & CEO
CATALYST PHARMACEUTICALS

FEBRUARY

Symic Bio

Completing midstage trials for its two lead bioconjugate drugs in critical limb ischemia and osteoarthritis, and preparing for some serious money raising.

"*Symic Bio has experienced rapid growth since February 2016, nearly doubling in size. We've relocated (to Emeryville, still in the Bay Area) to expand our office and lab space. Our trial for osteoarthritis of the knee, initiated in June, completed enrollment in November. Our program for vascular interventions in critical limb ischemia continues to progress. This allows us to look forward to two efficacy readouts in 2017: results from SB-061 in osteoarthritis in the second quarter, and results from SB-030 in vascular interventions in the second half of the year. SB-061 is designed for both disease modification and pain management in osteoarthritis, while SB-030 is designed to block inflammation following cardiovascular procedures to prevent serious complications. Demonstrating efficacy in either trial will validate the potential of our library of compounds as a new therapeutic class in humans for the first time and hopefully draw attention to the distinct possibilities of therapeutic approaches based on matrix biology. We continue to explore applications for our platform in oncology, fibrosis, and CNS disorders. In addition, we expect to complete a significant Series B financing early in 2017. If conditions permit, we may move toward an IPO in 2017 as well.*"

KEN HORNE
CEO
SYMIC BIO

MARCH

Egalet

Progress by an upstart startup in taking on the world of abuse-deterrent pain treatment as opioids of all kinds come under increasing fire.

"*2016 was a momentous year for Egalet. In August, the company went through its first FDA advisory committee for Arymo ER (morphine sulfate), where the committees recommended approval of Arymo and voted that, if approved, it should be labeled as an abuse-deterrent product by the intravenous, nasal, and oral routes of abuse. Leading up to the potential approval of Arymo, the company has experienced a period of growth in the United States, including the addition of 16 new employees in 2016, bringing the total employees in the United States to 62 (88 globally), with plans to add another 75 employees in just the first quarter of 2017. The company also submitted an sNDA (supplemental new drug application) to the FDA in December for Oxaydo (oxycodone HCl, USP) tablets C-II, to support an abuse-deterrent label claim for the intravenous route of abuse, and received pharmaceutical composition patent protection for Oxaydo through 2024. As the company looks into 2017, the first half of the year will be focused on launching Arymo ER, once approved.*"

ROBERT RADIE
PRESIDENT & CEO
EGALET

APRIL

Osel

Completing and launching Phase 2b trials for a "microbiome modulator" to treat and prevent vaginosis, urinary tract infections, and infertility, while aiming longer term at HIV and GI.

"*Osel continued to advance clinical development of its lead product, Lactin-V (Lactobacillus crispatus, CTV-05) in 2016 with two Phase 2b clinical trials. An NIH-sponsored*

study to investigate Lactin-V for treatment/prevention of recurrent bacterial vaginosis was initiated at four U.S. sites in 2016. In addition, an ongoing Lactin-V study for treatment/prevention of recurrent urinary tract infections continues at the University of Washington. Both of these indications are major unmet medical needs associated with dysbiosis of the vaginal microbiome, characterized by a diverse microbiota low in protective Lactobacillus. Lactin-V is a microbiome modulator that restores vaginal Lactobacillus. A third Lactin-V study is scheduled to begin in 2017 in Europe to improve the success rate of in vitro fertilization (IVF) for infertile women with abnormal vaginal microbiota (AVM). AVM has been shown to significantly reduce the clinical pregnancy rate of IVF patients.

Osel's genetically engineered Lactobacillus product, MucoCept-CVN, is advancing toward the clinic. A pre-IND meeting was held with the FDA in 2016 and an IND will be submitted in 2017. MucoCept-CVN contains a vaginal strain of Lactobacillus jensenii that secretes a potent HIV inhibitor, cyanovirin-N. The product is being developed in conjunction with UCSF (University of California at San Francisco) and the NIH to prevent HIV infection in women.

Osel is also developing a GI microbiome product, CBM588 (Clostridium butyricum Miyairi 588). Collaborations are ongoing to test a new high-potency formulation of CBM588 in HIV-associated diarrhea and graft-versus-host disease. CBM588 is known to have antidiarrheal and immunomodulatory activity.

PETER LEE, M.D.
CHAIRMAN
OSEL

MAY

Addex Therapeutics

Prepared to launch a Phase 2 program with its lead drug candidate for levodopa-induced dyskinesia and various forms of spasticity with a stronger, experienced team.

Progress made since May 2016:

Lead program, dipraglurant for levodopa-induced dyskinesia associated with Parkinson's disease (PD-LID): POC (proof of concept) data published in peer-reviewed journal, Movement Disorders; and significant progress made in the preparation to start registration trials, including interactions with regulators and completion of registration trial designs. Preparation of a Phase 2 POC clinical trial with dipraglurant in focal cervical dystonia was also completed. Our second clinical-stage asset's (ADX71441) preclinical profile was published in a peer-reviewed journal, Neuropharmacology; our NIDA (National Institute on Drug Abuse) collaboration generated spectacular data in a nonhuman primate model of cocaine-seeking behavior; and preclinical data in a model of spasticity was also generated. Our discovery programs also made significant progress with a new collaboration with NIDA, under which NIDA will test ADX88178 in models of cocaine addiction. At the corporate level, we increased equity research coverage, with David Sherman of LifeSci Capital and Marcel Wijma of Van Leeuwenhoeck Institute picking up coverage. In addition, we strengthened the team with the hiring of Roger Mills as chief medical officer. Dr. Mills is the ex-CMO of Acadia and credited with the development of pimavanserin for Parkinson's Disease Psychosis.

Plans for 2017:

We plan to secure resources through collaborative arrangements or capital raising to execute our strategy to develop dipraglurant in PD-LID and dystonia and ADX71441 in addiction and Charcot-Marie-Toothtype 1A neuropathy. We also plan to continue to advance our preclinical programs through collaborative arrangements with patient advocacy groups, governmental organizations, and academic institutions.

TIM DYER
CEO
ADDEX THERAPEUTICS

JULY

Tunitas Therapeutics

Now an example of how many, really most, drug development programs end early.

Tunitas is in the process of winding down due to some safety issues in the recent Phase 1 clinical trial for its lead candidate Epsi-gam, a genetically engineered bifunctional human fusion protein for allergic reactions.

NOLAN SIGAL, M.D. PH.D.
FOUNDER, PRESIDENT, AND CEO
TUNITAS THERAPEUTICS

AUGUST

Enteris BioPharma

Continuing a move from supplier with novel oral-formulations to developer of a pipeline of urinary and gynecological drugs in mid-stage clinical trials.

Since being featured in Companies to Watch, Enteris BioPharma has completed dosing patients in our Phase 1

study of Tobrate, an oral tablet formulation of tobramycin for the treatment of uncomplicated urinary tract infections (uUTIs). The initiation of the Tobrate clinical program was a significant event for Enteris as it provides the company with an opportunity to advance a potentially high-value and highly differentiated therapeutic for the treatment of uUTI, a condition that affects approximately 10 million U.S. women each year. Tobrate is an expansion of Enteris' internal drug pipeline, which includes Ovarest, a Phase 2a-ready oral peptide for endometriosis. In 2017, Enteris expects to announce data from the Tobrate Phase 1 study and plans to initiate a Phase 2a study of Ovarest in the first half of 2017. Additionally, Enteris anticipates securing two or more license agreements involving the company's proprietary Peptelligence platform, a novel formulation technology that enables oral delivery of molecules that are typically injected, including peptides and BCS class II, III, and IV small molecules.

JOEL TUNE
CEO
ENTERIS BIOPHARMA

SEPTEMBER

Quark Pharmaceuticals

Virtually sneaking up on the RNAi space with late-stage ophthalmology and renal therapies.

Quark continues to advance its two pivotal Phase 3 studies and one Phase 2 study of RNAi-based therapeutics for kidney and eye indications. In the second half of 2017, Quark expects to announce:

- *Results of its Phase 2 study of QPI-1002 for the prevention of acute kidney injury in patients undergoing major cardiovascular surgery.*
- *An interim analysis of its Phase 2/3 study of QPI-1007 for the preservation of visual acuity in acute nonarteritic ischemic optical neuropathy, or NAION.*

DANIEL ZURR, PH.D.
CEO
QUARK PHARMACEUTICALS

OCTOBER

ViewPoint Therapeutics

Pushing preclinical testing of molecules to correct protein misfolding in cataracts and other conditions by preventing and reversing aggregation of alpha crystallin.

ViewPoint Therapeutics is making progress as planned. In 2017, the company will continue to carry out preclinical studies on its lead candidate, VP1-001, as well as second-generation molecules targeting alpha-crystallin for the treatment of cataracts and presbyopia.

LEAH MAKLEY, PH.D.
PRESIDENT & CSO
VIEWPOINT THERAPEUTICS

NOVEMBER

Catabasis

Completing a Phase 2 trial and hoping to launch a pivotal Phase 3 trial of its lead drug in DMD, with clinical data set for release this year.

Catabasis has continued to make significant progress. The company held its first Investor Day on Nov. 17, 2016, on edasalonexent (CAT-1004), for the treatment of Duchenne muscular dystrophy (DMD), and its rare disease pipeline. This event included guest speakers Craig McDonald, M.D., and H. Lee Sweeney, Ph.D., in addition to the Catabasis executive team. Catabasis presented the MoveDMD trial design and their expectations for the upcoming important clinical trial results on their lead program in early 2017. In the first half of Q1 2017, the company expects to report top-line safety and efficacy results from the placebo-controlled portion of the MoveDMD Phase 2 trial of edasalonexent in DMD. Assuming positive Phase 2 results, Catabasis anticipates initiating two additional clinical trials in DMD next year, a pivotal Phase 3 trial, as well as a trial in nonambulatory patients. Catabasis expects to report periodic results from the ongoing MoveDMD 36-week open-label extension in 2017. There are also additional diseases in which edasalonexent may be beneficial; therefore, Catabasis expects to initiate a Phase 2 trial for an additional rare disease for edasalonexent in Q4 2017 or Q1 2018. The company also discussed the rare disease pipeline, including the recent announcement of CAT-5571, an activator of autophagy, as a potential treatment of cystic fibrosis. Catabasis expects to initiate a Phase 1 trial with CAT-5571 in Q4 2017 or Q1 2018. Preclinical research with CAT-4001 has continued in diseases such as ALS and Friedreich's ataxia and further research is expected in 2017.

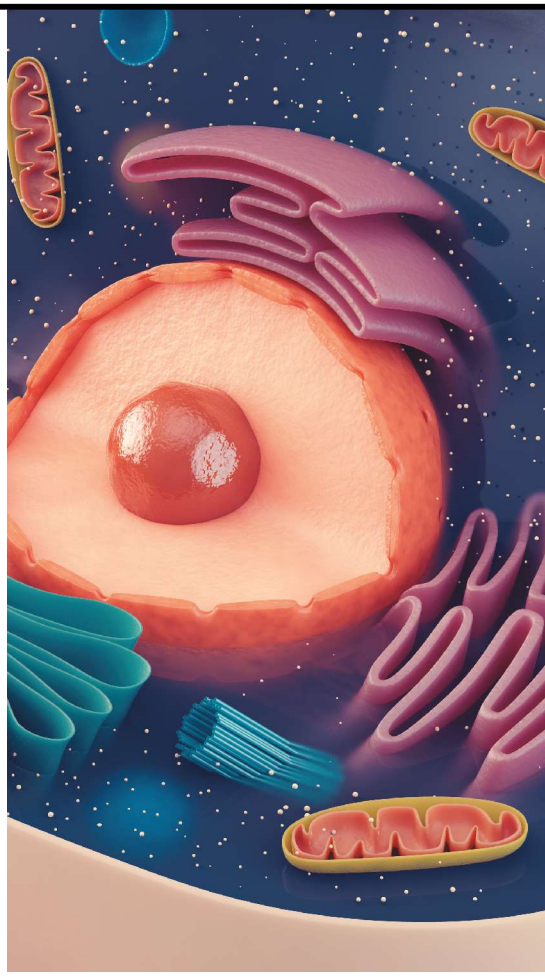
JILL C. MILNE, PH.D.
COFOUNDER & CEO
CATABASIS (L)

THE
ENTERPRISERS

Life Science Leadership In Action

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

COHBAR:
Mitochondria Medicine



Why shouldn't our mitochondria want us to live long, prospering in good health? Why shouldn't they — as symbiotic microbes turned cellular organelles with their own mini-genomes — carry genes that help ensure our healthful survival? After all, they ride around inside our cells, living on what we feed them, as they transform those elementals into the chemical fuel that powers us. In a variety of ways, they reach out and help keep our bodies whole and healthy as well. Many companies have sprung up around the idea of making medicine based on mitochondria's role in health and disease, and one of them, CohBar, has chosen a unique way that avoids the common challenge of invading the cell's interior to achieve therapeutic effects.

Mitochondria also play a big role for many of us in our imaginations. Children and adults who have read and related to the classic fantasy, *A Wrinkle in Time*, can envision the organelles as a forest of tiny, self-aware creatures who can be summoned to action against an invading evil. "Everybody's got a parallel to *Wrinkle*," says Albion Fitzgerald, chairman of CohBar. The book had just enough science, based on the current knowledge when published in 1963, to teach and touch off interest in the inner workings of the living cell. For many, it was the first step in a lifetime quest to look ever deeper inside the biology of cellular life.

For others like Fitzgerald, the book may have simply accelerated an interest in the principles that govern organized systems, including the computer-based applications and business startups that preoccupied most of his career. An interesting part of CohBar's singular story is how it attracted the IT architect and entrepreneur onto a new professional path as an involved board chairman in a biopharma enterprise.

Fitzgerald and CohBar's CEO, Simon Allen, joined me for a conversation at the October 2016 BIO Investor Forum to offer the company's novel take on the mitochondria. CohBar creates analogs of certain peptides produced by mitochondrial genes to generate health-maintaining proteins the natural peptides normally express. It systematically discovers, analyzes, optimizes, patents, and produces selected mitochondrial-derived peptides (MDPs) as therapeutic agents. Founded in 2007, but with its origins going back 20 years, the company recently emerged from a long period of research and refinement to enter preclinical drug development, building on the considerable body of science its founders created.

As they walk into the room, Allen has just made the company presentation at the Forum, and Fitzgerald temporarily takes the lead in explaining the company's start-

PUBLIC COMPANY

MARKET CAP: $95 MILLION

CASH: $8.1 MILLION at 9/30/16

STARTUP DATE: 2009

NUMBER OF EMPLOYEES: 12

FOCUS: Identifying, characterizing, selecting, and creating analogs to mitochondrial peptides as therapeutics for metabolic diseases.

ing premise, offering a layman's version of its scientific foundation. "Our founders, Dr. Pinchas Cohen and Dr. Nir Barzilai, discovered a whole class of peptides coded inside the mitochondria that affect metabolic regulation and protection," he says. "They had just discovered the new genes in the sequence of the genome and were trying to figure out the function and beneficial effects of each gene."

The genome sequencing and discovery of a new class of peptides dramatically increased the long-believed number of known mitochondrial genes, from 37 to over 80, and greatly expanded the number of possible peptides they encode. The founders' next thought, prompted by some serendipitous clinical data, was to identify which of the MDPs might represent the most useful proteins for therapeutic purposes in conditions related to metabolic regulation and protection.

Subsequently, CohBar made a further, enterprising leap ahead: Synthesize analogs of the MDPs for development as mitochondria-based therapeutics (MBTs). To date, research studies have identified potential MBT candidates for treating Type 2 diabetes (T2D), Alzheimer's disease, obesity, fatty liver, and certain cancers. CohBar's lead candidates, coded CB4209 and CB4211, are analogs of the MOTS-c (mitochondrial open reading frame of the 12S rRNA-c) peptide discovered by Cohen and his USC colleagues that show strong therapeutic potential for obesity, T2D, and NASH (non-alcoholic steatohepatitis, associated with fatty liver) in the company's preclinical models. Clinical testing remains more than a year away; CohBar plans to launch a Phase-1a trial in early 2018.

That means the initial human trial will start more than 15 years after the first MDP, humanin, was discovered and the CohBar founders began to investigate its effects. In 1998, Barzilai founded (and currently oversees) an ongoing study to identify genes that promote long life called the Longevity Genes Project. Among the findings from this study, using a novel assay developed by Cohen, was that centenarians and their offspring exhibit much higher levels of humanin in their blood than individuals with average life expectancy; the same subjects also had extraordinarily disease-free lives. Suspecting the two trends were related, the CohBar founders studied how humanin acts to promote lifespan and healthspan.

"They found humanin had all kinds of neuroprotective and cytoprotective capabilities," Fitzgerald relates. "In cells, it appeared to promote healthier cell metabolism to an extraordinary level. In animals, it improved endothelial function enormously — preventing them from developing clots and atherosclerosis. It also reduced amyloid beta plaque in their brains, and had many other observable benefits."

Fitzgerald says the MDPs are encoded in a conserved area of the mitochondrial genome that, with some variations, is shared across most mammalian species. "In our laboratory tests, we're using the human versions of these mitochondrial peptides, which have some differences from the animal versions, in mice. That is very significant as context for the amazing effects we saw. It means the possibility of our results happening by coincidence is extremely small." The peptide analogs are secreted by cells, and some evidence suggests they not only act cell-to-cell, but also participate in the cytoplasmic interaction between different sections inside the cells.

STAGING UP

By 2014, CohBar had obtained a total of eight MDPs from Cohen's lab and shifted gears to a level that required more serious investment. Fitzgerald joined the company and brought his business acumen and assets to the table in May of that year, becoming chairman of the board a few months later.

During the past four years, a new, experienced management team has taken form. Allen came aboard as CEO in March 2016 with a long track record in building biopharma companies. Kenneth Cundy, Ph.D., a noted veteran of Gilead and Sterling, joined in late 2014 as chief scientific officer. Jeff Biunno became CFO in 2013, moving to CohBar after the sale of Fitzgerald's previous company, ManageIQ. Jon Stern, a longtime entrepreneur in several other industries, joined the company in 2013 and became COO in 2016. In a sign the company is looking ahead to clinical drug development and manufacturing, Cundy has led the development of major medicines and invented the Nanocrystal technology used in some drugs now on the market.

Fitzgerald has a wealth of experience in business, but his entry into the life sciences began with CohBar.

"I'd had three of my own companies, and I'd taken one of them from zero to a multinational, internationally deployed public company, with my own ideas," he says. His approach to IT, however, presaged his life sciences migration. He describes how one of his software companies used a "cybernetic genome model" in its successful design of global IT systems. "I typically applied biological models to the management and creation of very large computer systems."

Fitzgerald had planned, as customary, "to take a year off and get an idea for another company" following the sale of ManageIQ in 2012. His 30-year business partner, Rob Anderson, had just met with Barzilai and Cohen and was so excited by their work he pushed the idea of joining CohBar at the clinical-critical moment. "Why would I change fields, after 45 years and starting three companies in the IT industry? But Rob said, 'You have to talk to them,' and I said, 'Well, OK,' and here we are three and a half years later."

Initially, the new chairman helped CohBar complete a Series B financing along with a venture public offering on the Toronto Exchange. "Those financings enabled us to put the team together and do the kinds of things a biotech company needs to do to take a drug beyond the research stage — where you have the excitement of scientists and researchers in the lab but not the deterministic predictability you need for getting through clinical trials." CohBar saw additional warrant funding from its initial venture offering by early 2017, and is now laying the groundwork for its next big funding step during the current year.

> *"When I first got involved in the company's development strategy, it took me a while to get up to speed with the science."*
>
> ALBION FITZGERALD
> Chairman, CohBar

In the less than two years since the venture financings, the company opened a lab, hired new staff, and put the development program in motion. It moved two of the founders' discoveries into pre-IND status with numerous preclinical studies while also discovering and acquiring a large number of additional mitochondrial peptides that show potentially useful biological activity. Overall, the company's strategy is to focus with its initial clinical candidates on the area where morbid obesity, Type 2 diabetes, and NASH overlap in the same patient set, within the grander global market of age-related metabolic disease. Those three indications together represent about 67 million patients and markets worth about $84 billion worldwide, the company estimates.

"When I first got involved in the company's development strategy, it took me a while to get up to speed with the science," Fitzgerald says. "This is theoretical science and leading-edge research stuff, so it was challenging. I started looking at the concept of the connectivity and the underlying metabolic enablement of age-related disease." Age-related diseases, not communicable diseases, pose the largest global health challenge, he says. "During the next 15 years, there will be five times as many deaths from noncommunicable diseases as from the old historic communicable diseases, and most noncommunicable diseases are metabolic diseases. Those may include some you wouldn't even think of as metabolic diseases, such as cancer and Alzheimer's."

SYMBIOTIC MECHANISMS

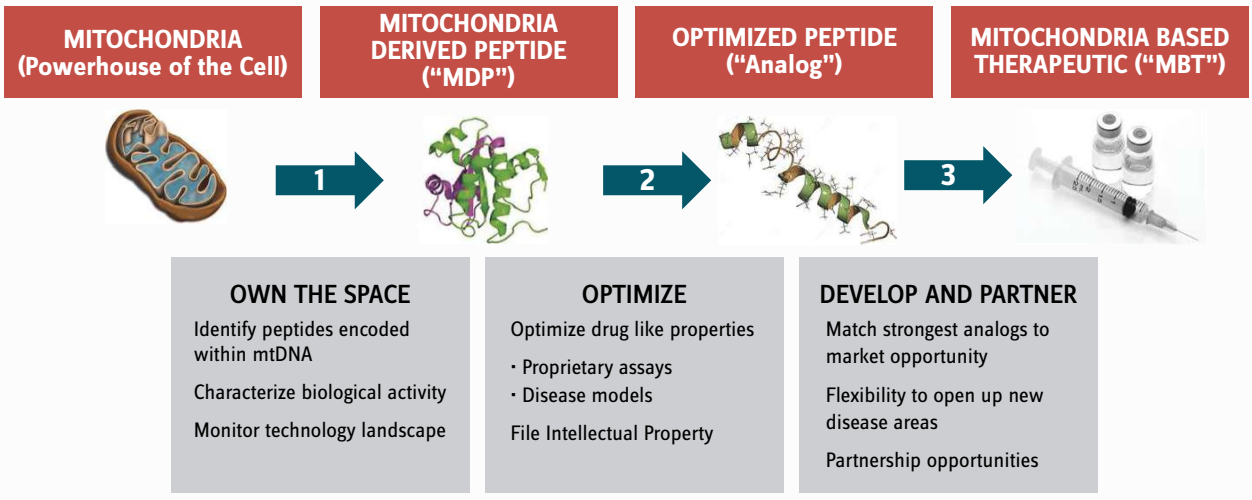
CohBar's obesity models relate to how cells metabolize fat. As Fitzgerald observes, humans whose genomes evolved in cold climates generally burn fat more efficiently than those with genomes evolved in warm or hot climates. Global displacement of peoples, exposing them to new nontraditional fatty diets, have therefore challenged the metabolic, fat-burning capacity of millions of human beings — driving obesity and digestive issues to peak levels around the world.

Human genomes evolve and adapt to such challenges slowly, but mitochondria genomes appear to change in response much more quickly. With each mitochondrial adaptation and production of related peptides, the cell receives new signals to produce proteins that promote, say, more efficient fat burning or other healthful metabolic changes.

"In mitochondrial peptides, we are finding important parts of the body's protective mechanisms," says Fitzgerald. "One seems to work like exercise in the metabolic sense — doing, metabolically, what happens when you are exercising. Another one seems to be a caloric deprivation mechanism. It's pretty well established that caloric deprivation may extend life expectancy."

Allen adds: "The mitochondrial genome and its peptides have been known for decades. Why didn't somebody else connect the dots? Eons ago, a bacterium invaded the cell and created a vital symbiotic function of converting nutrients into energy in exchange for using

COHBAR'S TECHNOLOGY PLATFORM: IDENTIFY, OPTIMIZE, AND DEVELOP MBTs



the cell mechanisms to build and replicate itself. Yet the consensus view was the nuclear genome had everything of therapeutic relevance and the mitochondrial genome had nothing. What we're finding is mitochondrial peptides cross species and, in very validated animal models, create biological impact. That is a paradigm shift."

Research studies in the cardiovascular area have identified some MDPs that appear to prevent plaque buildup in arteries or suppress cardiac fibrosis, according to Fitzgerald. "And the majority of people who have fatty liver, obesity, and/or diabetes die of cardiovascular disease or stroke," he says. "Fatty liver and NASH were not even on anyone's radar screen two years ago, but they're as pervasive as obesity, almost in the same population."

"Everyone knows being obese is not healthy," says Allen. "But they don't know how unhealthy it actually is. The FDA and many physicians now understand obesity captures a lot of people who will end up having NASH, Type 2 diabetes, or cardiovascular complications. We see a growing body of evidence that, when you treat obesity, you're not just reducing fat, you're actually treating a whole host of metabolic disorders that can lead to these other diseases. That is our central tenet."

CohBar has used liraglutide (Victoza), approved for treating obesity, as a comparator to its two lead MBTs because its mechanism of action as a GLP1 agonist is a well-defined biological pathway for fat metabolism. In contrast, in addition to regulating GLP1, the MBTs show the broader effect of reducing fat deposits and triglycerides in the liver. "As a physician, I'd be saying, 'If I treat someone for obesity, I would also like to have much less fat and reduced fat-metabolizing enzymes in the liver because that is really what needs to be treated.' It's not just about losing weight; it's about restoring endocrine balance again."

With aging, mitochondrial activity declines, Fitzgerald adds. "You may get away with being obese and your body will manage the problem for a while. But once your mitochondria and their related peptides start falling off, you start demonstrating symptoms of the other diseases such as heart failure and diabetes. Of course, that stimulates faster aging." He cites the FDA's TAME (Targeting Aging with Metformin) Study led by Barzilai as supporting recognition of the metabolic relationship of many age-related diseases.

"People who study age-related diseases know they're related. You try to treat one, the problem just moves to the next one. Sometimes, in pharmacotherapy, the drugs themselves precipitate the movement to symptoms of the next disease. But a patient can't go to a doctor and say, 'I'm aging poorly, can you help me?' Physicians have to translate the symptoms into a particular disease, but that is only one facet of the problem. Why aren't we looking at the process of aging itself, so a company like us could develop therapeutics that simultaneously treat multiple diseases underlying poor aging? Instead, each agent must still go through the regulatory process one indication at a time."

Nature has a way of juggling many different tasks with single, simple mechanisms. CohBar will also have to maximize its efficiency as the inherent risk of development rises in entering the clinic and deploying all of its capabilities. Enterprise, well demonstrated in the company to date, must move from building to advancing its programs through the wrinkles of tough times ahead. But if its tested concept holds, we may all be among the beneficiaries — as hosts of the mitochondria.

Getting An Accurate Count Of Counterfeit Drugs

CAMILLE MOJICA REY Contributing Writer

This is the first article in a four-part Life Science Leader series examining the current state of the counterfeit medicines problem. Upcoming stories will examine the issue from the perspective of industry giant Pfizer, look at what is being done by one international coalition to fight the crime, identify efforts to educate patients, and profile a company working to put unique identifiers on individual pills.

Experts in pharmaceutical crime describe it as a global game of cat-and-mouse that can be deadly for patients, costly for pharmaceutical companies, and challenging for government agencies responsible for health and safety. What they are referring to is counterfeit drugs. The Center for Medicine in the Public Interest, a New York-based research group partially funded by the pharmaceutical industry, estimates that the sale of fake medicines will generate $95 billion this year, an increase of 26 percent since 2010.

It is a problem that continues to grow in scale and complexity, says Thomas Kubic, CEO of the Pharmaceutical Security Institute (PSI), a Washington, D.C.-based nonprofit organization. "We have seen medicines marked as donations to African nations end up in a Caribbean-based online distribution system targeting U.S. customers," Kubic says.

According to Kubic, the biggest problem facing the industry 15 years ago was that pharmaceutical crimes were not being pursued by law enforcement, largely because the magnitude of the problem was unknown. In response, industry leaders in 2002 created PSI, taking it upon themselves to provide law enforcement with a more accurate picture of the global pharmaceutical crime problem. Prior to the institute's creation, the WHO was reporting an average of 50 law-enforcement events involving pharmaceutical crimes per year. Last year, PSI reported 3,002 incidences.

"These numbers more accurately reflect the scope of the problem," Kubic says. "Nobody knows for sure how big a problem it is; we only see indicators. But, for years, we lacked those basic numbers."

According to Kubic, the current data indicates that the industry is making progress. "We have seen a significant increase in seizure activity, as well as the dollar value of goods that have been subject to enforcement activity," Kubic explains. In 2011, PSI reported 18 tons of illegal drugs seized by customs agents, police, and drug regulators. By 2015, that number grew to 423.9 tons.

TRACKING CRIME

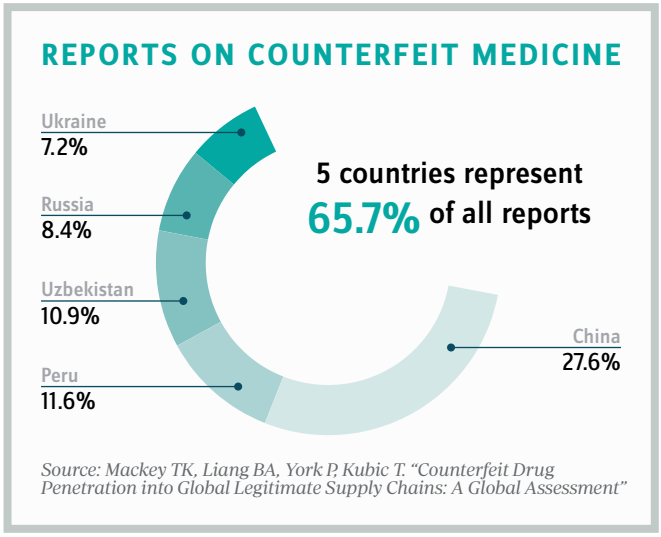
One can assume that PSI has been so effective because the organization employs the likes of Kubic. He was once head of operations at the FBI's Salt Lake City office and, later, was in charge of what was known as the FBI's white-collar crime division.

Kubic and his similarly trained colleagues at PSI developed their Counterfeit Incidence System (CIS) in 2002. By using case report details, such as the amount of counterfeit product seized, the system tracks the number of law enforcement cases involving pharmaceutical crimes.

"One of the first things we wanted to do was identify the extent of the problem," Kubic says. That led to the creation of CIS.

Using this system, Kubic and his colleagues analyze data for trends that can pinpoint the source of batches of counterfeit medicines so that they can then alert the appropriate authorities.

Kubic and his colleagues can also help law enforcement officials decide where to focus their efforts. Recently, they began defining as "commercial" those incidents of pharmaceutical crime involving more than 1,000 dosage units. Anything less than that is now classified as "noncommercial." Last year, one-third of the



seizures was commercial in size, while 56 percent were noncommercial. (The rest were of unknown size.)

In addition to surveillance and trend analysis, PSI offers law-enforcement training to customs agents and other authorities. These trainings have increased the number of seizures made by those who have completed training, Kubic says.

COOPERATION AMONG COMPETITORS

PSI began in 1992 as an informal meeting of 14 security directors from drug companies. These directors realized that the counterfeit drug problem was not one that any single drug maker could tackle on its own. Cooperation was required.

The group originally focused on conducting its own investigations and then sharing its results with local agencies. Many of these agencies were unaware that pharmaceutical crime was taking place in their own jurisdictions.

Working individual cases themselves, however, was not having the global impact needed to truly curtail pharmaceutical crime. It became clear that hard data was needed to get international law enforcement to devote the resources to apprehend the perpetrators of pharmaceutical crime.

PSI defines counterfeit medicines as branded or generic products deliberately and fraudulently produced.

Counterfeit medicines are also authentic products that have been mislabeled to obscure true identity or source.

Data that goes into the CIS include incidents of counterfeiting, theft, and illegal diversion of pharmaceutical products worldwide. CIS incidents come from a variety of sources, including open media reports, PSI member company submissions, and public-private sector partnerships.

GETTING GLOBAL BUY-IN

Today, PSI is made up of 33 pharmaceutical manufacturers from around the world and has additional offices in London and Hong Kong. The organization has been able to raise awareness about the magnitude of the global pharmaceutical problem, and that, in turn, has led to increased global cooperation among law enforcement organizations. For example, Interpol began its Operation Giboia in 2013. In 2015, the operation involved 2,100 police, customs agents, and health officials who conducted raids in seven countries. Authorities raided markets, shops, warehouses, pharmacies, clinics, and ports in more than 50 cities and seized more than 150 tons of counterfeit and illicit medicines worth an estimated $3.5 million.

In addition to data collection, Kubic and his colleagues continue to conduct their own investigations, sharing information with law enforcement officials about criminal activities in their jurisdictions. Getting the authorities to act on that information, however, can sometimes be difficult. Pharmaceutical crimes are competing for resources with more urgent cases involving violent crimes, he says.

PREVENTION MAKES SENSE

The fight against pharmaceutical criminals is a multifaceted one that requires not only law enforcement, but also prevention. Kubic says efforts by manufacturers to track-and-trace goods have been good and are getting better. "The big discussion among manufacturers is about the unique identifier," he says. "I think it is a good idea."

Criminals are now going directly to doctors to try to sell their goods. The ability to do that would be greatly reduced if every package has a unique identifier and every doctor, pharmacist, or wholesaler has access to a scanner that can verify that unique number in a database. No one can predict whether such a system will be adopted on a global scale. But, if doctors choose not to utilize this system to verify authenticity, they are knowingly putting their patients in jeopardy.

"If you're a doctor and you're buying medicines that are unapproved for sale for whatever reason, that's a federal crime. You don't want to lose your license," Kubic says.

In the United States, visits to doctors' offices by the FDA's Office of Criminal Investigation (OCI) have come under scrutiny — even by some of its own agents. In a September, Reuters reported that some FDA agents complained they had become the "Botox Police." They charged that few of the doctors who purchased authentic versions of the antiwrinkle drug that were labeled for use in other countries were ever prosecuted. One reason that happens, Kubic says, is that federal prosecutors from different regions have different thresholds for deciding when they will file charges. If the threshold is $25,000, for example, a person could technically escape charges if they were responsible for a theft totaling $24,999.

"We have seen a significant increase in seizure activity, as well as the dollar value of goods that have been subject to enforcement activity."

THOMAS KUBIC
CEO, Pharmaceutical Security Institute

Despite OCI's record on federal charges filed, it is not a waste of time for FDA agents to visit doctors' offices. "If they don't know they are buying illegal medicines, then they are going to get some good advice," Kubic says. "If they do know, they need to be held accountable."

Other experts interviewed say it is precisely because the United States has such tight regulations that we don't have problems like the ones seen in Asia and Africa, which have hundreds of thousands of deaths due to widely circulated fake malaria drugs.

Here in the U.S., the real problem is people buying counterfeit medications off of the Internet. One illegal organization often operates thousands of websites. Drug companies and others fighting pharmaceutical crime are using complex algorithms to locate these distributors and put them out of business.

Another way to track down those selling counterfeit drugs on the Internet is to screen patients who complain to the manufacturer of adverse events. "Those folks in the customer care centers need to be asking consumers where these people got their medications," Kubic says. PSI is working on a larger detection strategy that includes training for call center staff.

Kubic also says emerging methods to use plant DNA in inks used directly on individual pills offers promise. "That would go beyond putting numbers on boxes and would tell us what's inside of the box." L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Most U.S. Pharmas Ignore Cuba, Despite Relaxed Rules

GAIL DUTTON Contributing Writer @GailDutton

The Cuba trade embargo has almost ended, but American pharmaceutical companies have barely noticed. In a quick survey I did of 13 pharmaceutical companies ranging from Big Pharma to small generics manufacturers, plus two industry associations, all 15 organizations declined to comment about Cuba's potential role in their business strategies or opportunities and challenges involved with doing business with that nation. Only one of those claimed the silence stemmed from competitive interests.

Two American organizations, however, are going on the record to discuss their work with Cuban researchers and their efforts to bring innovative research involving cancer vaccines and levels of consciousness (e.g., comas, brain death) to American patients.

IN-LICENSING A NOVEL CANCER VACCINE

In late October, Roswell Park Cancer Institute became the first American organization to receive FDA approval to launch a clinical trial treating American patients with a Cuban-made therapy.

Roswell Park's upcoming Phase 1 trial will test CIMAvax-EGF, a lung cancer vaccine that is both developed and manufactured in Cuba and has been administered to thousands of patients globally. "This vaccine is based on an antibody-based strategy designed for mass production. It's a completely novel vaccine approach that we haven't seen in the U.S.," says Thomas Schwaab, M.D., Ph.D., who is chief of strategy, business development, and outreach at Roswell Park.

Approval to begin trials came soon after the FDA inspected the Cuban vaccine manufacturing facility. Cuban life sciences facilities are accustomed to meeting international requirements, Schwaab says. For instance, "Japan's Pharmaceuticals and Medical Devices Agency (PMDA), widely considered the strictest of regulators, also has approved Cuba's vaccine manufacturing facilities."

To further development of CIMAvax and other biotech products, the U.S. Treasury Department also authorized Roswell Park to form a joint venture with Cuba's Center of Molecular Immunology (CIM) for product research, development, manufacturing, and marketing.

The groundwork for these collaborations began about three years ago under the Cuba trade embargo when Roswell Park obtained a license from the U.S. Treasury Department's Office of Foreign Assets Control (OFAC) to exchange scientific material and information with Cuba. Specifically, Schwaab elaborates, "The license allowed us to conduct basic research and Phase 1 clinical trials for a limited set of drugs that includes CIMAvax and some preclinical development candidates." The business relationship was fast-tracked in early 2015 when Roswell Park leaders participated in New York Governor Andrew Cuomo's trade mission to Cuba.

"We had to move mountains to get CIMAvax to U.S. patients," Schwaab recalls. Obtaining an OFAC license,

> *"Japan's Pharmaceuticals and Medical Devices Agency (PMDA), widely considered the strictest of regulators, also has approved Cuba's vaccine manufacturing facilities."*
>
> **THOMAS SCHWAAB, M.D., PH.D.**
> Chief of Strategy, Business Development, and Outreach
> Roswell Park Cancer Institute

MANUFACTURING SECTORS IN CUBA THAT EXPERIENCED AN INCREASE IN PHYSICAL PRODUCTION LEVELS FOR THE YEARS 1989-2014

State Department permits, and FDA inspection are not trivial endeavors. "Throughout it all, the Cubans have been incredibly cooperative and professional."

EVEN EXEMPTED EXCHANGES TAKE TIME

BioQuark isn't as far along as Roswell Park, despite starting earlier. It has worked with an OFAC attorney for the past four years to formalize relations with Cuba's Calixto Machado, M.D., an internationally recognized expert in the niche specialty of brain death and disorders of consciousness.

"Our relationship with Dr. Machado is governed by the OFAC's exempted informational materials exchange regulations," says Ira Pastor, BioQuark CEO. "Dr. Machado has a five-year visa to lecture throughout the U.S., so we are allowed to talk with him but not to share proprietary technology or to compensate him." Recent changes to U.S. rulings specific to Cuba may change those stipulations.

BioQuark wants to apply Machado's insights into brain death to BioQuark's studies of epimorphic regeneration in humans, for example, restoring function to the central nervous system or regrowing damaged organs. "There's not a lot of research on brain death, so conversations with Dr. Machado have been invaluable," Pastor says. "We'd like to become more involved with him, either through a consulting arrangement in the U.S. or through joint research in Cuba."

As the U.S. trade embargo against Cuba gradually relaxes, bureaucratic hurdles remain. "We still need to obtain permits from the OFAC and State Department," Pastor says, as well as comply with Cuba's research regulations. "This area requires extensive legal expense and consultation."

CHANGES EXPAND U.S. OPTIONS IN CUBA

The new, more open relationship with Cuba is in its early days, and regulations are in flux, so it's no wonder American companies hesitate to formulate strategies involving the communist nation. One of the most recent revisions to the embargo took effect Oct. 17, when the U.S. departments of Treasury and Commerce amended section 515.547 of the Cuban Assets Control Regulations.

The changes allow Cuban companies, and American companies working with Cuba, to seek FDA approval for drugs originating in Cuba. They also enable a range of collaborations and partnerships at all levels of research and development from discovery to post-marketing and importation. Furthermore, the changes allow Cuban nationals to conduct research in the United States and permit American organizations to award grants and scholarships for scientific research to Cuban nationals. (Educational and humanitarian grants and scholarships already were permitted.)

"I don't expect Cuban companies to apply to the FDA directly," says John Caulfield, consultant on business in Latin America and head of the U.S. Interests Section (now Embassy) in Cuba until his retirement in 2014. "They probably would have experienced partners that would in-license rights to products."

In Roswell Park's case, "The October amendments to the Cuban Assets Control regulations haven't affected our work. Our specific OFAC license allowed us to do many of those things that now are feasible under a general license," Schwaab says.

The changes, however, will make it easier to expand projects and to incorporate new research findings. "The license we have is very specific," he continues. "Before the new regulations took effect, we would have had to apply for a new license to incorporate new research developments. Now we can move forward easily. Easing the licensing requirements accelerates research."

It's important to recognize that only certain regulations regarding Cuba have been relaxed.

Other regulations remain intact. Therefore, for example, the Bureau of Industry and Security within the U.S. Commerce Department still requires special licenses to export high-tech goods or equipment to Cuba or to

import Cuban materials into the United States. General tourism remains prohibited, so travelers to Cuba must comply with OFAC's general license for travel.

OPENING CHINA WAS DIFFERENT

It's natural to assume that entering Cuba commercially is similar to entering China in the mid-1990s. For instance, "Cubans are extremely capable scientists who are very proud of their country and culture. It's very important to them to deal with those with whom they have a personal relationship and trust," Schwaab says.

So, one of the biggest challenges of doing business in Cuba is to build strong personal relationships with business partners. Forming those connections has become easier since Cuba removed travel restrictions on its citizens in 2013. Now scientists can travel freely to international meetings, some of which are hosted in Havana, and meet potential business partners.

More often, however, Cuba and China are more dissimilar than alike, Caulfield says. For instance, "When the U.S. entered China, we were looking to sell things to a very large market. That's not the case with Cuba. With a population of 11 million people, it doesn't have a large market." Cuba, therefore, requires a different strategy.

Although Cuba and China both are communist, the execution of that philosophy is very different. China, for example, incorporates capitalism into its business model, while in Cuba, all businesses are owned by the state. Therefore, all negotiations, whether to in-license a product from Cuba or export a product to that island nation, are conducted with government officials. "The people actually doing the negotiations won't have the final say," Caulfield explains. "That must come from a government minister or from the Council of Ministers. That's very different from dealing with other companies throughout the world."

Schwaab, however, characterizes the chain of command differently. "We are negotiating with employees at the CIMAB – the commercial arm of the CIM. They have final authority to make decisions but may need approval from a board of directors."

Cuba's relatively small market, limited buying power, and complicated business environment have contributed to the implosion of its manufacturing base. Between 1989 and 2014, its manufacturing output fell more than 45 percent.

Pharmaceutical manufacturing is one of the few areas with positive growth. It increased 892 percent during that time frame because of the Cuban government's interest in building its genetic engineering prowess (at the expense of other sciences), according to The CubanEconomy.com. Since Cuba has staked its future on its biotech industry, it recognizes the importance of secure intellectual property rights. The Chinese, in the 1990s, did not.

KNOW BEFORE YOU GO

"Everything involving Cuba is a little different than in the rest of the world," Caulfield notes. Those in charge of its businesses aren't as informed about pharmaceutical validation, financial requirements, and financial terms as their counterparts internationally. Therefore, American companies attempting to bring a Cuban drug to the U.S. market must anticipate a learning curve for all parties.

Companies can shorten the education process by hiring an OFAC attorney early in the development of any potential strategy involving Cuba to help understand what's possible, what's impossible, and the time frame to accomplish anything. But as Pastor says, no matter who you have helping you, "nothing occurs overnight."

English speakers are rare among the populace. Although the island was a U.S. protectorate and American companies flourished until they were nationalized in 1960, the English language is less prevalent than in other nations. After the revolution ended in 1959, schools began teaching Russian rather than English. Although that has changed, "For business, take a translator," Caulfield advises.

"Everything involving Cuba is a little different than in the rest of the world."

JOHN CAULFIELD
Consultant On Business In Latin America

Cuba isn't frozen in time. Visitors to Cuba typically return talking about the classic 1950s-era cars that still are being driven, but "there are plenty of Toyotas and Hyundais on the streets," says Marc Hoffman, M.D., chief medical officer for the clinical trial patient-matching service Patient identification Platform, who toured the island last August. It is, nonetheless, a very poor country. The highest earners in the country still gross little more than $1,000 annually, and most are closer to $500. Its gross domestic product (GDP) is $77.15 billion at the official exchange rate.

Despite this poverty, there are opportunities in Cuba, mainly in the form of in-licensing Cuban therapeutics. Regulations are still in flux but are gradually normalizing. If American life sciences companies decide Cuban options are worth investigating, patience will be a necessary virtue. L

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What Gets Funded, What Dies Before It Gets To Pharma R&D

SCOTT FISHMAN

Lots of people in our industry are wondering how to simultaneously bring value to patients and the organization. It's a reasonable aspiration, but one that faces an environment emphasizing lucrative opportunities among small but desperate populations and stratospheric prices.

Informing company decisions with patient input sounds great but doesn't shift internal priorities when it is being treated as a tool to enhance revenue instead of a fundamental driver of financial performance. We need to redirect attention from the tactical marketing tactic of patient-centricity to the foundational proposition of customer-centricity. If a business develops things that create great value, and it does so for lots of people, then it doesn't have to fight for customers, credibility, or profits.

It's worth taking a close look at just how the industry is going about sourcing these things of great value, and more specifically, how the products of early-stage discovery find their way into clinical and market development within pharma.

My co-author and I noted in our book, *Preserving the Promise: Improving the Culture of Biotech Investing*, that the primary reason something gets funded or dies in the early stages of development is the ability of the innovation to support an investment thesis that stakeholders will buy into. Whether that's an internal or external assessment, the opportunity is going to be subjected, at some level, to a process of due diligence.

That process has everything to do with establishing and self-reinforcing the perception of a *good bet* and little to do with the reasons stuff usually gets invented (e.g., scientific curiosity, passion to solve a personal or societal problem, search for a clinical solution). Investment motives are complex — neither solely rational, emotional, nor financial. But because they are always underpinned by a calculation about ROI, the potential is real for important discoveries to go unrealized while shaky clinical propositions get funded.

DUE DILIGENCE IS SUBJECT TO COMMON HUMAN BIASES

Most people understand due diligence conceptually as a process of pressure testing an opportunity. That opportunity has to pass muster scientifically and in market potential. It also has to offer an attractive payout, such as an internal rate of return for an internal development opportunity or an ROI for investors.

But this apparently rational analysis masks the foibles of human decision making. I'm looking at something right now in which I have limited domain interest and am fairly equivocal about the technological prospects, but it's got an absolute surge of interest from colleague investors because the CEO just made a lot of money for a lot of people with a high-multiple exit in a completely unrelated therapeutic domain. The impetus for investment here has relatively little to do with the intrinsic clinical value of the technology, its prospect of scientific validity, or an admittedly enormous potential market. Instead, it's all about the ability of a particular CEO to attract money.

Despite the presumed formality of the due diligence, the diversity of opportunities and practical constraints of timing can favor intuitive attraction over hard analytics and inductive over deductive decision making. It's not crazy that investors "bet on the jockey" and rely heavily on a leader's prior accomplishments; experienced people are more likely to be able to adapt, know how to solve problems, and have a network of connections. But it's still crucial to know if the horse the jockey is riding is a champion or lame.

Due diligence consistently overweights variables other than the clinical implications of new healthcare technologies, and that's where the patient-centricity

argument breaks down. Value from a human-health perspective may be entirely disconnected from value as an investment proposition. Value pricing may be a hell of an argument for funding a development program, but no amount of feinting to patients' "interests" is going to convince them you're on their side when you're planning to charge the cost of their house for the therapy.

GETTING ON PHARMA'S RADAR

In the world of early-stage technologies, seed-funding decisions may happen very quickly. It's painful to inventors but unsurprising that a "no" can be sudden and final, because there is a huge disparity in risk for founders and investors. Everything is at stake for the inventor, but considerably less is on the line for pharmaceutical business developers or angel investors whose financial stake in an early-stage company is hardly going to break the bank.

As any primer on negotiation will tell you, leverage is always a function of who has more to lose, and here's the prospect facing an early-stage company: Inventions at this point are not significantly differentiated by the nature of the technology but by the strength of their promise of financial return. They're collateral.

Yet they need to be nurtured and sustained long enough to even appear on the pharma industry's radar. Here's how it goes: Tech transfer offices filter what comes out of the university based on scientific reputation and serendipitous interest from prospective investors. Business advisers or transitional CEOs get attached to the venture with a promise of equity and deferred compensation. The same companies make the same rounds to prospective investors in a region. The gatekeeping mechanism is a 15- or 20-minute presentation followed by a Q&A session and maybe due diligence by a committee impressed enough with the pitch to volunteer time. The decision to commit is often dependent on the presence of a lead or co-investor. A good impression, a relatively large target population, and apparent technical and operational skill go into the plus column. An uninspiring pitch, a lack of obvious customer need, a small target population, or a lack of backing by capable people may doom the investment.

And this is just to get to due diligence — a subjective process that examines not just the science but also the founders' motives, competence, and ability to succeed. Ultimately, what is available for pharma to invest in, what has even a *possibility* of getting onto a genuine commercial development track, is the result of scientific credibility, financial cogency, whim, and serendipity. You could argue that this applies to much in life, but is that really the way we want to address human health?

WE NEED TO REDEFINE DUE DILIGENCE

I believe a redefinition of the parameters of due diligence could be helpful. Consider three traditional areas of due diligence: unmet need, size and growth of addressable market, and sustainable competitive advantage. These are crucial to an assessment of opportunity, yet the component most often missing from pitches and even fully developed business cases is solid understanding/characterization of market opportunity.

First, what if we think about unmet need as what is good for the most number of people? Is that a poor basis for a business model just because it echoes the concept of distributive justice (fair distribution of scarce resources)? Or is it a disruptive and potentially game-changing definition? What happens if we concentrate scarce development resources on whatever rises to the top as a crucial human and societal problem, instead of what sorts to the top of a net present value (NPV) spreadsheet? Wouldn't we potentially make even more money by doing the most good for the most people? And wouldn't that intrinsically make a stronger and more sustainable value proposition than a multibillion dollar windfall on an overpriced drug sold to a few thousand people that is ultimately going to experience formulary refusal?

Or what about size and growth of addressable market? I've spent decades advising people on optimal development based on the largest and most receptive targets. But what if we recast that slightly and make our target the biggest human need in a particular category? Maybe it would make more money, maybe less in the NPV calculation. But what would be the intangible value of resurrecting the stature of pharma as the singular industry focused on making us healthier? What's the relative value of next quarter's dividend against being the company that provides a massive public good and *mitigates* instead of increases the cost of good health?

And how about sustainable competitive advantage? What's the sustainable advantage of a nearly six-figure drug to cure hepatitis C, raced after by other similarly priced drugs that do the same thing because everyone's chasing that gigantic margin? I'm not taking anyone to task here, just wondering what would be the worldwide financial, societal, and yes, industry public relations impact of solving a huge problem with an affordable solution.

REASSESSING PRIORITIES

A recasting of assessment priorities is a realistic proposition and could form the basis of a better business model. I'm talking about a fundamental rethink that would begin at the earliest stages of a development decision, not as some post-launch marketing strategy. It follows that assessing an opportunity by due diligence would mean accounting for a broader range of criteria, not all of which are subject to green-eye-shade analysis.

The case I'm making here includes three primary recommendations:

- Stop trying to convince people that you're reorganizing business priorities around something like "patient-centricity," when you aren't. Everyone knows business is about business, and if a number of constituencies are well served, that's both a good thing and a driver of financial return. But it's not a rethinking of the essential business model unless we've gone so completely off the rails that marketing 101 has suddenly emerged as the industry's future.
- If you're going to model on what's good for customers, then carry through with development programs that take care of lots of people instead of rationalizing astronomical pricing with discredited arguments about the cost of development. Build a model on doing well by doing good. It's not a new concept, but it seems to be increasingly rare, despite its being just a return to pharma's historic foundations.
- Don't just search for useful things coming out of the funnel of seed investment. Due diligence needs a broader perspective, one that both scans the environment for really good but really early technology — just like the historic model of internal discovery — and one that vets technologies with a more balanced template than NPV alone. The early-stage funding community doesn't have pharma's resources and can't be expected to do it alone or operate with a broader perspective than ROI. If we're going to really talk about customer-centricity, doesn't that come down to prioritizing innovation based on merit rather than margin?

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Brexit Presents Opportunity For U.S. Life Sciences Companies

CAMERON COOLEY AND CHRIS JANES

The United Kingdom's decision to leave the European Union (E.U.) in June 2016 sent economic shockwaves throughout international markets. While Britain is taking time to understand the impact of adopting Article 50 of the Treaty of Lisbon, which will trigger its exit from the E.U. (the so-called "Brexit"), U.S.-based companies may have a unique opportunity to expand and take advantage of operations in the U.K.

Immediately following the Brexit vote, the value of the pound declined significantly. At one point, sterling reached its lowest value in nearly 30 years, and over the past year it has been one of the world's worst-performing currencies. Poor performance from the pound is good news for the U.S. dollar, which has historically had an unfavorable 1.5 to 1 exchange rate.

There continues to be uncertainty over the future of Britain's economic landscape following the official exit of the E.U.; however, Britain has not yet left and is still expected to be a fully functioning member for a number of years.

It will take two years to exit the E.U. once Britain has adopted Article 50. U.K. Prime Minister Theresa May has indicated that she would like to trigger this by March 2017. May's timeline received some early pushback, including a High Court ruling that Parliament would have to approve the adoption of Article 50, but it now appears that the March 2017 date is solidifying. The House of Commons recently voted to support May's plan, removing a significant roadblock to Brexit.

Even if Article 50 is triggered in March 2017, the reality is that the U.K. will continue to experience the same access to European resources and trade deals for a number of years until the country finally leaves the E.U. Also, many arrangements will continue for a longer period in the form of transition agreements. In the meantime, U.S. companies may be able to operate in the U.K. at reduced costs.

Setting up a location in the U.K. may be particularly beneficial for U.S.-based life sciences companies. The U.K.'s talent pool, networking and support services, corporate tax incentives, government and private investments in the sector, world-class banking systems, and established life sciences infrastructure make it ripe for U.S. life sciences companies. The exchange rate may just be the tipping point.

ADVANTAGES FOR LIFE SCIENCES COMPANIES OPERATING IN THE U.K.

R&D often is one of the largest expenses life sciences companies incur. Although the U.S. research and development tax credit has been enhanced over the past year with the passage of the Protecting Americans Against Tax Hikes Act of 2015, similar tax credits and arrangements in the U.K. may offer more benefits.

The life sciences sector has several benefits working in its favor. By moving operations to the U.K., companies can receive credits of up to 230 percent of their eligible R&D expenditures. Small- to mid-sized companies in a loss position can trade this in for 14.5 percent of the credit's value in physical cash, which can be a significant advantage for cash-strapped start-ups.

Several of the Big Pharma companies, including GSK and AstraZeneca, have their headquarters in the U.K. Between Big Pharma and the research locations, there is a wealth of CROs for U.S.-based companies to access. A snapshot of CRO resources can be easily vetted through online searches or using tools such as the Contract Research Map.

The U.K. also has a highly skilled talent pipeline that is readily available. Cambridge and Oxford attract international talent and produce high-caliber graduates. Add to that the employees from the Big Pharma

companies and other research institutions, and you have a local workforce that not only understands the sector and local market, but also includes potential collaborators, key network contacts, and sources of other support services.

With one of the world's premier banking hubs based in London, investors are within close geographic reach. Several U.K. investment firms specifically look for opportunities in the life sciences sector, which may provide critical access to funding and financial support.

> *"Setting up a location in the U.K. may be particularly beneficial for U.S.-based life sciences companies."*

Aside from tax credits, the U.K. government offers financial support for life sciences companies looking to grow their operations or expand their service offerings. Innovate U.K., a government-sponsored organization, supports science and technology activities and start-ups and has assisted more than 7,600 organizations and provided more than £1.8 billion in funding for the sector. The government announced in November 2016 that it would be committing an additional £2 billion to life science and technology investments, of which £400 million would be injected directly into venture capital funds. Innovate U.K. recipients have significantly less red tape with their awards than comparable funding in the U.S. A wide range of organizations can provide advice and access to government funding at relatively low costs.

Another advantage to the infrastructure is that U.K. companies register patents with the European Patent Office. Patents facilitated through the European Patent Office become registered across all 27 E.U. member countries in a single application, thereby reducing the time and cost to commercialize new products across Europe.

Selecting the U.K. over another overseas location also comes with some practical benefits. Because of the existing infrastructure and the shared language, establishing operations in the U.K. would not be wholly different from establishing a new location in the U.S. Company formation and maintenance are relatively inexpensive, and taking advantage of CRO services requires a comparable time investment as doing the same thing in the U.S. Nevertheless, an international tax professional can assist with the transition, particularly for U.S. employees who will be working overseas.

HOW BREXIT AFFECTS U.K. OPERATIONS

Members of the E.U. function as one country, with limited restrictions on travel and trade among E.U. countries. As part of Brexit, the U.K. will be negotiating specifics on trade and travel with the E.U. Many of the Brexit negotiations will have a limited effect on U.S. companies operating in the U.K.

The "how wll Brexit affect trade?" question would not be relevant for U.S. companies using the U.K. for intellectual property development or other types of research because the U.K. location would not be physically exporting or importing products. The European Patent Office is also not expected to be significantly interrupted by Brexit.

Issues relating to the international skilled workforce in the U.K. may be something for U.S. companies to monitor but not in the near term. Some U.K. life sciences companies have already raised questions about what Brexit will do to their talent pool and influx of international investment capital. The U.K. life sciences sector has long benefited from a pan-European workforce; however, indications are that the U.K. government is pursuing a "Hard Brexit," which would end the right for other E.U. nationals to work in the U.K. without visas. As a result, in the future it may be more difficult for U.K.-based life sciences companies to attract a multinational workforce and multinational funding than in the current environment.

THE TIME TO ACT IS NOW

If your company is considering exploiting overseas interests in the U.K., it should do so in the near future. The British pound continues to perform at historic lows compared to the U.S. dollar and is expected to weaken further as Brexit negotiations progress and Article 50 is triggered. The U.K. is also still enjoying the benefits of being in the E.U. Workers and E.U. capital will continue to flow freely to Great Britain at least until March 2019. Finally, it is uncertain how President Trump's views on trade may affect the tax and regulatory environment. L

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The Ethical Implications Of Right-To-Try Laws

JENNIFER PAUL COHEN

There is a determined and thus far extremely successful effort in this country, endorsed by both the FDA and the pharmaceutical industry, to enable terminally ill patients to obtain drugs which have not been approved by the FDA. A recent development in this trend is right-to-try laws passed by state legislatures that are designed to provide patients access to nonapproved drugs directly from drug manufacturers.

The first right-to-try law passed in 2014 in Colorado, and since then 32 states have passed one. These laws reflect the perception that the FDA is holding back both innovation and life-giving drugs from people facing a terminal illness who are desperate to try them.

Contrary to the promise contained in their names, right-to-try laws do not establish any rights for or impose any obligations on patients, physicians, pharmaceutical companies, or the FDA. But they have three extremely problematical features:

- These laws are redundant, as the FDA already has a process that allows terminally ill patients to obtain these drugs. Consequently, these laws are most likely unconstitutional, as they violate the Supremacy Clause of the U.S. Constitution, therefore placing at risk patients who are obtaining drugs as a result of these laws. This violates the ethical duty of beneficence and nonmaleficence, as well as the duty of truth-telling, which respects the patient's autonomy.
- Secondly, by skirting the FDA's regulatory authority, these laws diminish the requirement that medicines be safe and effective and undermine the authority and legitimacy of the FDA.
- Finally, these laws, which indemnify the doctor, the pharmaceutical manufacturer, and the insurance company from claims of mistreatment, increase the danger of unnecessary overtreatment at the end of life. In the name of providing hope to the terminally ill, they promote unproven therapies with very little chance of therapeutic benefit.

WHAT ABOUT THE EXPANDED ACCESS PROGRAMS?

Right-to-try laws give the impression that no other mechanism allowing access to experimental drugs exists. To the contrary, the FDA has had a mechanism for obtaining such drugs for nearly 30 years. The FDA's expanded access programs include multiple categories ranging from individual patients asking for an investigational new drug (IND) application that has a 30-day waiting period, or requesting inclusion in an existing IND that does not have a 30-day waiting period, or applications for an emergency IND where treatment can be authorized by telephone prior to written submission. In February 2015, in response to pressure from the right-to-try movement and high-profile cases in the media, the FDA streamlined its policies for obtaining drugs through what the industry refers to as "compassionate use." The FDA estimates that the revised, one-page form the agency requires should take approximately 45 minutes for a physician to complete. The FDA approves 99 percent of the expanded access requests it receives, and it receives roughly 1,000 requests per year. While this approval percentage rate is high, the argument proponents of state right-to-try laws make is that the numbers of patients applying to the FDA for investigational drugs represent "infinitesimally small numbers of requests." Darcy Olsen, author of *The Right to Try: How the Federal Government Prevents Americans from Getting the Lifesaving Treatments They Need*, compares the number of people dying from cancer in 2015 (1,615 per day) to the number of requests the FDA receives (1,200 per year) and concludes that the FDA's expanded access model is a failure, causing patients to die pre-

maturely. However, the reason for the discrepancy is unclear. We will have to see if the increased publicity around expanded access and the streamlined FDA approval process results in more people applying for experimental drugs.

Another argument against the FDA's expanded access program is that it slows down the general approval process for a drug. However, the FDA estimates that out of the roughly 10,000 approvals granted under the expanded access program, two drug applications were delayed as a result.

THE FDA NEEDS MORE OVERSIGHT, DATA COLLECTION

The right-to-try laws are an attempt to use state law to nullify the federal law that outlines the FDA's expanded access programs. The Supremacy Clause of the U.S. Constitution provides that states are bound by federal law. This means that state laws such as right-to-try laws that are designed to evade federal regulations should be unconstitutional. In addition, federal case law does not recognize the right of terminally ill patients to access investigational drugs.

By skirting the FDA's regulatory authority, these laws diminish the requirement that medicines be safe and effective and undermine the authority and legitimacy of the FDA, whose mandate is to protect and advance public health. A critical function of the FDA is its oversight of the pharmaceutical industry. Rather than reduce the role of the FDA in the expanded access program, the public should be pushing for the FDA to take on *more* oversight and data collection. The FDA does not know how many of the 10,000 requests for drugs over the last 10 years under the expanded access program have resulted in any therapeutic benefit. A requirement that data from expanded access be reported to the FDA so that safety and efficacy could be optimized would aid in assessing the therapeutic value of the program. Simply assuming that terminally ill patients are facing no meaningful additional risks when they take an unapproved drug is an abdication of the ethical imperative of nonmaleficence and respect for patient autonomy. As Arthur Caplan writes, the perception that drugs that are out of Phase 1 testing are safe is misleading. Phase 1 testing is done on healthy people. He warns:

> "Trying an experimental drug on sick people who are already significantly compromised in their health status, and who are receiving myriad other medications, may well kill them more quickly or more painfully."

GO BEYOND SATISFYING THE DEFINITION OF "LEGAL"

The compassionate use or expanded access systems in place now to make drugs available to terminally ill patients are already ethically problematical, and state right-to-try laws have the unfortunate result of further muddying the waters. The constitutional and misleading aspects of the right-to-try laws are the most troublesome, but the larger issue is the statement they make about the ethical treatment of the terminally ill. By removing the requirement that the FDA approve a request, the laws imply that there is less need for an unbiased, oversight authority to agree that a drug is safe and effective for use. Under the right-to-try paradigm, as long as the company that makes the drug (hardly an unbiased actor) agrees to allow the patient access to the drug (after being indemnified against legal redress) the transaction is legal.

It is critical that a program based on giving investigational drugs to dying patients be one that goes beyond satisfying the low bar of "legal." Such a program should aim to provide a therapeutic benefit to patients beyond that of hope. The right-to-try movement as well as social media pressure on drug manufacturers has begun an important dialogue on the ethical treatment of terminally ill patients. Drug manufacturers have responded with more transparency and codification of their policies on their websites and, in the case of Johnson & Johnson, the establishment of an outside Compassionate-Use Advisory Committee (CompAC).

The larger ethical dilemma is how far physicians, the FDA, and drug manufacturers want to go in privileging hope for individual patients over proven therapeutic benefit. Olsen admits that we are discussing a system of extremely long odds designed to give patients hope: "Dying patients are not looking for a 100 percent guarantee the drug is effective. They are looking for hope. They are looking for a fighting chance." The truth is that dying patients will have nowhere near a 100 percent chance that investigational drugs will produce a therapeutic benefit. Without solid data on the patients who have benefited from expanded access and those who have not, it is simply a roll of the dice. The FDA should be collecting such data and continuing its oversight of the expanded access process. Right-to-try laws that remove the FDA as a participant in this ethically challenging area do not represent a step forward. L

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What To Know About Post-Grant Review And The Biotech Industry

BRIAN KWOK, NICHOLAS MARTINI, AND NICOLE JOHNSON

Patent litigation can often be a costly, lengthy, and resource-intensive endeavor. Recognizing the frequency, duration, and potentially debilitating effects of patent litigation, Congress passed the America Invents Act (AIA) in 2011.

The AIA made several significant changes to United States patent law, including the establishment of post-grant proceedings before the Patent Trials and Appeals Board (PTAB) where patents have the potential of being invalidated in a much more efficient and expedient manner. In the five years since the AIA was enacted, two types of post-grant proceedings, Inter Partes Review (IPR) and Post-Grant Review (PGR), have become increasingly popular tools for biotechnology companies to resolve patent disputes.

A COMPARISON OF LITIGATION, IPR, AND PGR

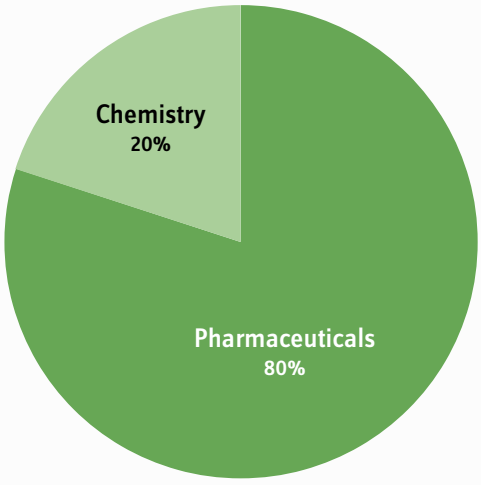
To use post-grant proceedings before the PTAB effectively, it is important to observe how patent invalidity challenges in district court compare to post-grant proceedings (i.e., IPRs and PGRs) before the PTAB. Some sophisticated strategies integrate both district-court proceedings and post-grant proceedings before the PTAB to effectively stage a multifront attack during patent disputes. For example, some strategies may employ a combination of both district court litigation and an IPR proceeding before the PTAB to increase the likelihood of a favorable outcome and oftentimes increase the motivation for parties to settle sooner or position a case for success should litigation ensue.

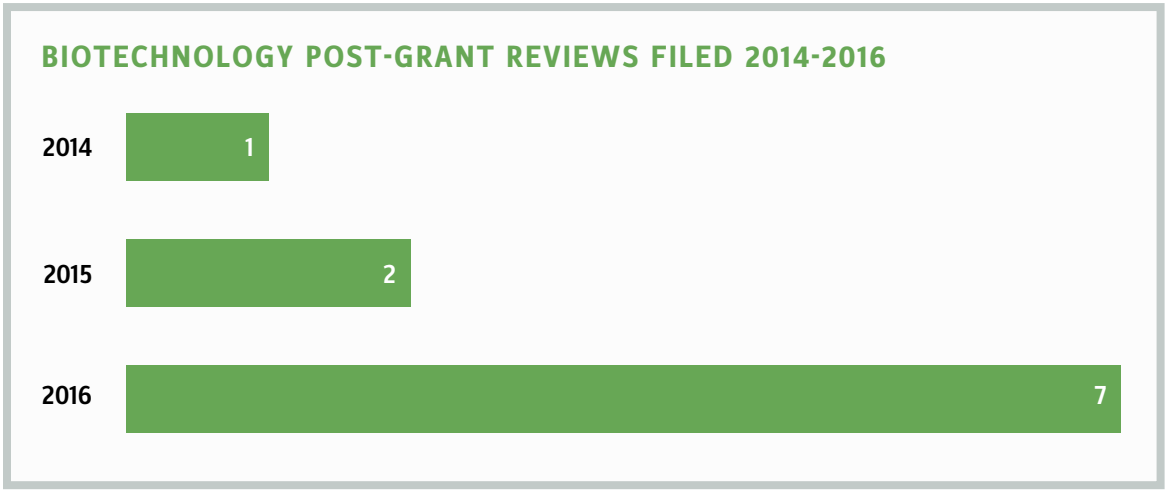
CURRENT TRENDS FOR BIOTECHNOLOGY PGRs

A total of 10 PGRs have been filed in the biotechnology space. From 2015 to 2016 the number of PGRs filed in this space has more than tripled from two to seven petitions filed within the year, which is significant because the number of patents eligible for PGR (those with a priority date on or after March 16, 2013) are just starting to be issued in greater numbers. Some commentators (including judges) predict that PGR will continue to increase in popularity as the number of eligible patents continues to grow. Getting ahead of this trend and considering PGR as part of an overall patent strategy would behoove any company faced with patent disputes.

Currently, about one-fifth of all PGRs filed have been in the biotechnology space (1,600), making that the most popular field for PGR filings.

EIGHTY PERCENT OF BIOTECHNOLOGY PGR PETITIONS RELATE TO PHARMACEUTICALS





Of the 10 petitions relating to biotechnology that have been filed, three have been denied, two have been granted, one is awaiting institution decision, and one final decision was issued. The remaining three PGRs were terminated by the parties — two before institution and one after institution. The PGR petitions that have been filed in the biotechnology space have been related to either chemistry or pharmaceuticals, with the majority involving pharmaceutical-related technologies.

TYPES OF CHALLENGES IN BIOTECHNOLOGY PGRs

Perhaps not surprisingly, challenges to the written description of a patent, including enablement and indefiniteness, have been the most popular invalidity challenges in PGR petitions in biotechnology. When patents claim large genera of chemical or pharmaceutical compounds, questions can arise as to whether the patent adequately permits a skilled artisan to make and use all of the compounds claimed. These types of challenges are particularly suited to PGR challenges, especially when stakeholders are more interested in invalidating a patent based on written description and enablement challenges than traditional prior art challenges.

INSIGHTS FROM PTABs TO BIOTECHNOLOGY

Altaire Pharamceuticals, Inc., v. Paragon BioTeck, Inc. was a PGR filed on May 11, 2015, instituted on November 16, 2015 and decided November 14, 2016. In this decision, the PTAB held that the petitioner did not meet its burden of proof to demonstrate that the challenged claims were unpatentable. Therefore, the PTAB ruled in favor of the patent owner.

In this case, the petition challenged U.S. Patent 8,859,623, claiming that it was unpatentable as obvious over the petitioner's product. The case turned on whether the evidence provided by the petitioner was sufficient for the PTAB to find unpatentability. The issue with the petition was that the tests and data it submitted did not meet the requirements of 37 C.F.R. § 42.65 (the petition failed to explain how the test was performed and how the data was generated) and other data used by the petitioner was unreliable. Thus, the problem for the petitioner was not that the PTAB did not find its PGR petition flawed; it was that the underlying evidence supporting its arguments did not comply with the relevant procedural rules.

With more patents being eligible for PGR, we will likely see filings in this space continue to increase. If the trend in biotechnology IPRs is any indication of what is to come with PGRs, stakeholders need to be prepared to defend themselves if they are faced with a PGR or, alternatively to have considered PGR as part of their current patent strategy. L

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How To Navigate Pharma Collaboration And Licensing Agreements

MATTHEW HOLIAN, MELISSA WHITNEY, AND ANDREW GILBERT

Collaboration and licensing agreements are an indispensable business strategy for both pharmaceutical companies with commercial capabilities and biotech companies developing novel therapeutics. With collaboration agreements, efforts to develop, seek regulatory approval, manufacture, and market a product are conducted jointly at one or more stages along the drug development pipeline.

Under typical licensing or asset purchase agreements, the licensee or buyer typically agrees with the licensor, seller, or (former) owners of a compound to develop and commercialize a drug or device in exchange for an up-front fee and/or the payment of royalties upon completion of milestones along the development and regulatory timeline.

While parties' expectations are typically aligned at the outset of the collaboration and licensing relationship (following an initial, robust negotiation process, of course), expectations can become increasingly misaligned when the information and incentives available to one party diverge from the other over time. This is especially true in the pharmaceutical industry, where multiple projects must compete for limited development funds and there are strong financial incentives to launch promising new therapies as quickly as possible and to scrap less successful projects just as quickly. Disappointments in drug development happen frequently, even among the most promising compounds in a company's development pipeline. For reference, an estimated 50 percent of all Phase 3 trials fail, with the average cost of a single Phase 3 trial ranging from $11.5 to $52.9 million, depending on therapeutic area, and increasing each year.

When collaboration and licensing agreement disputes arise, the repercussions can be costly. In the event of a dispute, companies should think very carefully about whether litigation is the best tool for resolution. Drug discovery and development is an incredibly lengthy, expensive, and uncertain process — but so is litigation. And unlike clinical development, which is at least subject (in part) to the rules of science, litigation results often depend on factors outside the parties' control. Recent jury verdicts demonstrate that the failure of a single development program can result in licensing disputes worth hundreds of millions of dollars.

More and more, biotech and pharmaceutical companies are taking active steps to (1) avoid collaboration and licensing disputes; and (2) resolve disputes that do arise without resorting to litigation. There is a variety of nonlitigation strategies to help companies navigate the uncertainties surrounding collaboration and licensing arrangements, including:

DEFINE MILESTONES IN CLEAR TERMS

The parties should make sure that milestones are established in clear, objective terms in the agreement to avoid any ambiguity and subsequent dispute regarding when a milestone has been achieved or when payment for meeting that particular milestone is due. Common objective development and regulatory milestones might include the first dosing of a human subject, filing a first NDA (new drug application), or achieving first regulatory approval. Other commonly used milestones, for example, "progressing to Phase 3," should be further defined to provide a clear triggering event for when payment would be due.

MAKE "REASONABLE EFFORTS" CLAUSES REASONABLE FOR THE DEVELOPMENT PROJECT AT HAND

The issue of how to measure whether a licensee has exercised the efforts required under the agreement to develop or commercialize a product is one of the most important (and most frequently litigated) issues surrounding a licensing agreement. Depending on jurisdiction, whether the licensee agrees to exercise

"commercially reasonable efforts," "reasonable efforts," "best efforts," or any other standard in developing or commercializing a product can have real implications on the likelihood of success in litigation. It also impacts whether expert testimony, within-company comparisons to other development projects, and/or industry-wide comparisons will be necessary later to determine whether a licensee's actions met such a standard, should a dispute arise. The parties should be very deliberate in their choice and work at the outset to articulate clear guideposts in any agreement for what efforts will be required to avoid future uncertainty.

VIEW REPORTING OBLIGATIONS AS OPPORTUNITIES

Periodic reporting obligations are a common feature in milestone-structured collaboration and licensing agreements. These are obligations on the licensee to keep the licensor, seller, and/or former shareholders apprised of the status of the licensed product's development and efforts undertaken to date to further develop or commercialize the product. These reports should be treated as far more than a formality with language cut and pasted from prior reporting periods. Rather, periodic reporting is an invaluable, proactive opportunity to diligently and contemporaneously record the efforts undertaken by the licensee to achieve certain milestones or other obligations under the agreement. It is also a means to document a company's reasoning in a thorough, well-thought-out manner, should it decide to eventually cease development. By keeping the licensor abreast of development efforts, the licensee can manage expectations and hopefully avoid a costly milestone dispute. Should a dispute arise, such reports will be crucial evidence for demonstrating that the licensee exercised the diligence in development required under the agreement.

THINK STRATEGICALLY ABOUT CHOICE-OF-LAW, FORUM SELECTION, AND ARBITRATION CLAUSES

A collaboration agreement can refer disputes to arbitration or remain silent on this issue, sending any disputes to a court by default. The parties should think strategically about which option would serve them best at the outset. Court proceedings generally allow greater opportunities for discovery, jury trial rights, and greater rights to appeal decisions. Jurisdictional differences in contract law, and in particular the interpretation of what constitutes "exercising reasonable efforts" in drug development, can have real consequences on the likelihood of success in litigation. In contrast, arbitration generally ensures greater speed in resolving disputes, confidentiality, the ability to choose the decision maker(s) in settling the dispute, and the finality of limited judicial review of the arbitral process. Additional considerations arise when the parties are not headquartered in the United States. Arbitration can provide an opportunity to significantly limit the amount of discovery that will be required, should a dispute arise. This may be particularly helpful for companies operating outside the U.S., with workforces less familiar with, or prepared for, the demands of U.S.-style discovery procedures.

UTILIZE DISPUTE RESOLUTION CLAUSES TO SETTLE ISSUES AMICABLY

Even in the event that a dispute arises, the parties can preemptively agree to strategies to resolve the dispute long before they reach trial or arbitration. During the contract negotiation process, consider requiring that the contracting parties initiate a multi-stage dispute resolution process before any party can initiate a lawsuit or commence arbitration. Known as an escalation clause or multistage dispute resolution clause, this contract provision requires that the parties first negotiate in good faith to try to resolve a dispute amicably before they can initiate proceedings. This opportunity can provide invaluable time to exchange information, renegotiate arrangements that no longer serve the interests of the parties, and avoid rushing to court or arbitration.

As the costs of developing and commercializing drugs and devices continue to rise, the emphasis on collaboration and licensing arrangements is only expected to grow. A company's efforts to structure and implement sound, effective collaboration and licensing agreements have the potential to pay off enormously down the road. Of course, the best time to plan for potential collaboration and licensing disputes is at the outset, during the term-sheet phase and contract negotiations. However, reassessing existing agreements and proactively documenting drug development measures and decision-making processes are also effective tools in curbing future potential disputes and minimizing costs, should a dispute arise. L

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Considerations For The Use Of Wearables In Clinical Trials

MARIE MCCARTHY

With wearables, we now have the means to innovate the "where" and the "how" of patient data capture, creating a 24-hour digital map of physical behaviors. The recent Sanofi-sponsored VERKKO trial (a fully remote trial), for example, highlights the possibility of creating patient-centric virtual studies, eliminating the need for the subject to travel long distances to sites. Thus, wearables could become an integral component of this place-shifting strategy.

However, integrating wearables into a trial is more complex than simply giving the patient a smartwatch and generating clinically relevant data. Wearables are already subject to negative commentary; critics say the huge quantities of data generated by them add to the complexity of trials.

Before integrating wearables into a trial, you should first make sure their inclusion fits with the clinical hypothesis. Will adding them add value? Will their inclusion offer data not available from other sources? Wearables can generate primary, secondary, and exploratory endpoints. They have value in screening and compliance (e.g., inclusion/exclusion criteria require patients to have specific activity and sleep patterns).

Of course, patient acceptance is critical; if the device is not worn, there is no data. Design, ease of battery-recharging, and water-resistance all impact compliance. The more a patient removes the device, the greater the risk of their not wearing it in the future. To further improve a wearable's acceptability, its materials need to be hypoallergenic to avoid any skin irritation or burns.

ENSURING GREATER COMPLIANCE, ACCEPTANCE

The selection of a device class depends on the intended use, labelling claims, and supporting scientific evidence. It's more common to use medical devices for the generation of clinically significant primary and secondary endpoints and wellness or investigational devices for less-critical data generation. Here again, patient acceptance is crucial. In the past, medical devices tended to be uncomfortable to wear and designed based on functional engineering principles rather than the user experience. In contrast, wellness devices tend to be more design-focused, although bulky, targeting mostly men and not always suitable for the elderly or children.

A number of companies that are members of the Consumer Technology Association (CTA) Health & Fitness Technology Division are developing industry standards that address the issue of data and device quality. In addition, companies such as Withings, iHealth, and Philips are creating devices that meet consumer demands and are medical devices. This new development could ensure greater compliance and acceptance.

THE CHALLENGE OF DATA TRANSMISSION

One of the challenges associated with wearables is data transmission. Each method of data transmission (e.g., apps, hubs) has cost and regulatory implications that need to be mapped and risk assessed. Data management processes need to be in place to manage the flow of data into a validated clinical data management system, to perform data quality control, and to map to data standards when required.

Regulators are struggling to keep pace with the digital explosion. The FDA recently added a page to its website dedicated to digital health and sought input from stakeholders regarding the use of digital technology in clinical trials. The agency also issued a number of guidance documents on the subject.

But just focusing on technology and sandwiching it into a trial is not a best practice. Wearables need to be viewed as a component of an overall patient-centric strategy rather than a solution in themselves. When creating a remote trial, sponsors shouldn't be simply shifting the burden to patients, requiring them to carry out an unsustainable number of tasks in an unsupported, uncontrolled environment.

Via wearables, we now have the capability of capturing real-life, continuous data streams that could unlock new insights into therapeutic responses, which are also meaningful to the patient, thereby creating a true patient-centric clinical trial. L

MARIE MCCARTHY is director of innovation at ICON. She has presented at a number of industry conferences on wearable technology, including the DIA Clinical Forum and the PRISME Forum.

How Patients Will Revolutionize Next-Generation Clinical Research

JAE CHUNG

Often when we think about inefficiencies in the clinical trial process, we focus on the role of the sponsor or CRO, a particular aspect of the value chain, or new technologies that promote data sharing and faster decision making. While these are critical aspects that drive day-to-day operations, there is another aspect of the value chain that we may be neglecting: the patient side.

In study startup, we talk about patient enrollment targets, recruiting strategies, and the like, often in abstract terms. We look at the data and consider aggregate numbers that drive decision making. But are we really thinking about this from a patient-centric perspective or more from a site-centric perspective? For example, with what we've learned as an industry about the struggles and concerns patients have with clinical trials, shouldn't we make it easier for prospective participants to engage with the study sponsor before, during, and after the study?

MATCHING PATIENTS AND CLINICAL TRIALS

Consider the case of a patient with an advanced cancer with a particular genotype that has been characterized. The patient's physician says there are two clinical studies for targeted therapies and another that offers an immunotherapy. There is also an FDA-approved medication, which may be available as an off-label option. The doctor is leaning towards the immunotherapy option that is in Phase 1 but gives the patient the final choice. So how does the patient go about making that decision? Are there other upcoming clinical trials that the physician does not know about? Where does the patient go next?

Aside from ClinicalTrials.gov, there are other sources emerging that are designed to match clinical trial participants to studies and address this major issue. For example, ClinicalConnection connects researchers and patients. It has a trial finder, and you can join the site and be notified when trials become available. Other options include the Cancer Research Institute, SmartPatients, and CureClick. Some of these even offer a helpline or specialist navigators who help patients through the process.

But what about the patient consulting with the study sponsor directly to get additional data such as if anyone has done comparative studies, even in animals? How does the sponsor benefit from such a patient-centric focus?

First, such websites take patient engagement to the next level, in which informed patients are highly engaged patients who are more likely to comply with requirements, such as completing patient reported outcome questionnaires and attending follow up visits. That leads to better data integrity. Not only that, it could improve the number and diversity of enrollees, which increasingly is seen as a major issue in clinical research. One notable example was recently published by researchers at Harvard Medical School, whose research showed that over the last decade, genetic testing may have disproportionately misdiagnosed hypertrophic cardiomyopathy (HCM) in black Americans due to lack of diversity in genetic studies. Recognizing the importance of the issue, the FDA has become a strong advocate for increased diversity in clinical research. In fact, 2016 was dubbed "The Year of Diversity in Clinical Trials" by the FDA.

Are there other potential up-sides? If a patient engages with a sponsor, even if they decide to forgo participation in that particular study, they may become a potential candidate for a future study — perhaps in a later phase or for an entirely different study. Beyond study startup, engaging the patient directly could have other benefits. What if you could invite patients to share their experiences with each other as part of the study via a closed, secure social media channel and also submit questions to the sponsor? This becomes another valuable data source and potential resource for mining trends that can be compared with endpoint information.

The end result? Turning our focus toward a true patient perspective gives us ways to think about innovative solutions for accelerating clinical research, at a time when the stakes are higher than ever for patients. And those patients may just hold the key to unlocking the next frontier in clinical research.

JAE CHUNG is president and founding visionary of goBalto. A startup evangelist, Chung wants to change the way pharma and CRO companies initiate clinical trials.

Getting Great =

Confidence + Willingness

CHRIS RUISI

CHRIS RUISI, is a nationally recognized executive coach and leadership expert, professional speaker, global talk radio show host, and author. He has 35+ years of corporate experience as a senior level executive.

All of us want to perform at a higher level than we are currently at. However, we let daily distractions, fear of trying something new, the fear of making a mistake, and unsolicited feedback from others get in the way of our efforts to "get great." We put ourselves in a "stuck-in-the-mud" position and lose sight of what we should do first.

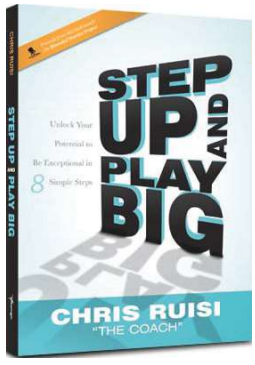
I believe the first thing we should do is build our self-confidence and willingness to take action. Many of us always talk about wanting more self-confidence but struggle with building and maintaining it in the face of our daily challenges.

When I talk about confidence, I frame it within the concept of your "personal willingness." For example, building self-confidence is your personal willingness to:

- Keep moving forward toward the achievement of your goals; your persistent and consistent actions will be key to your success. Far too often we let barriers and obstacles block our paths — there is usually a way forward.
- Put yourself out there for others to see and judge because you know what you're doing is the right thing. Hiding in the shadows does nothing for your growth or the growth of your organization.
- Take a risk — without risk taking, there is no way you can test your abilities. And, when you test them and succeed, your self-confidence grows.
- Never worry about what others think of you. It's none of your business. Stay focused on your vision and goals and do what is right for your organization.
- Question your status quo before you are forced to "react" to change. One of the biggest career and organization killers is complacency. When you allow yourself to become complacent, by the time you realize a change is needed, it is usually too late.
- Learn from your mistakes. Mistakes are a necessary part of the journey to becoming great, not perfect. They offer a great learning opportunity because you get to take new knowledge and try it again! Pursuing perfection is a meaningless and frustrating exercise and usually leads to procrastination and stagnation.
- Accept responsibility and accountability for your actions. The mantra that works best for me and my coaching clients is: You own it, fix it, learn from it, and move on.

As you can see, personal willingness involves taking *action*. Every time you take action you give yourself several opportunities. Some of these opportunities include accomplishing something, learning something, or setting new limits for your performance. The most important opportunity is that you build or increase your self-confidence.

To put yourself on the road to getting great, be confident, which means you're willing to act to first satisfy yourself (and no one else) that you did your very best – every time!



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