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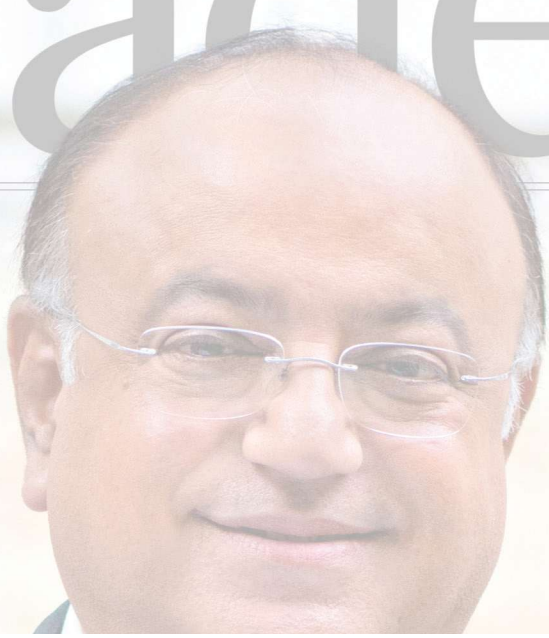

Weighing In On The Politics Of Drug Pricing

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Weighing In On The Politics Of Drug Pricing

p. 14

SURESH KUMAR
EVP Of External Affairs, Sanofi

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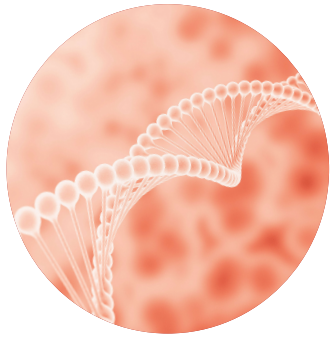

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If We Don't Police Ourselves, It Will Be Done For Us

ROB WRIGHT Chief Editor

It was over 23 years ago that I joined our industry in the role of a pharmaceutical sales representative. We called on doctors, not providers, and some of those physicians still referred to us in this noble profession as "detailers," not drug reps. Our job was to provide these medical practitioners with the "ethical details" for how, when, and where to use the drug we promoted, with messaging supported more by the use of approved clinical reprints and less by sales aids, or what doctors often liked to refer to as "Fifth-Avenue marketing slicks." Doctors actually took notes during these discussions, and not for the purpose of trying to help law enforcement try to catch a rep for promoting their product off label. But soon pharmaceutical companies embraced reach and frequency sales promotion models with such vigor that the number of reps working in the field more than doubled. Even for those of us who had built significant relationships with doctors, twice as many reps calling on about the same number of physicians resulted in less access.

It was around this time that my district manager suggested a new sales tactic — the dine-and-dash. The concept was simple. Because many physicians had become too busy to let you detail them in the office, why not provide them with a win-win opportunity where you could detail them outside the office? Reps would book a table at a local restaurant and invite physicians to swing by on their way home from work. Doctors would stop and place a "to-go" order to take home to their families. While the meals were being prepared, the rep would detail the physician. I was not a fan, as it didn't seem in keeping with our ethical promotional roots. But I did it anyway and watched the concept soon spin out of control (e.g., Christmas-tree-and-dash, pumpkin-and-dash, gas-and-dash, etc.). In January 2009, PhRMA tried to police itself with the introduction of "voluntary" guidelines on marketing to physicians. For many reps, to gift or not to gift was no longer a question. But the guidelines were voluntary, and from my perspective, arrived nearly 10 years too late. As a result of our inability to effectively police ourselves, we soon saw it done for us via the Sunshine Act.

I share this trip down memory lane as a teachable moment. Presidential candidates from both political parties have developed a taste for blasting the biopharmaceutical industry for its "high-priced" drugs. And though we can all agree that the Martin Shkrelis of the world are not reflective of our industry, mainstream media are happy to shape public perception to the contrary. History should have taught us that those who cannot remember the past are condemned to repeat it. Just as we were ineffective at policing ourselves during the days of the dine-and-dash, unless steps are taken to better self-police current drug pricing practices, it is likely we will soon have it done for us. Already we have seen the formation of the Health Transformation Alliance, a group of 20 of America's largest companies (e.g., American Express, Macy's, Verizon) that have banded together to use their collective resources to hold down the cost of providing worker healthcare benefits. Are government drug price controls just around the corner? We need to do more than preach the value our products provide while reciting how drugs make up only 10 percent of the U.S. healthcare bill. Isn't it obvious that America isn't listening? Perhaps it is time for biopharma to take the lead in driving for a "moon shot" approach to reducing U.S. healthcare costs. Otherwise, the industry may continue to be led to the public-pricing-perception slaughter. L

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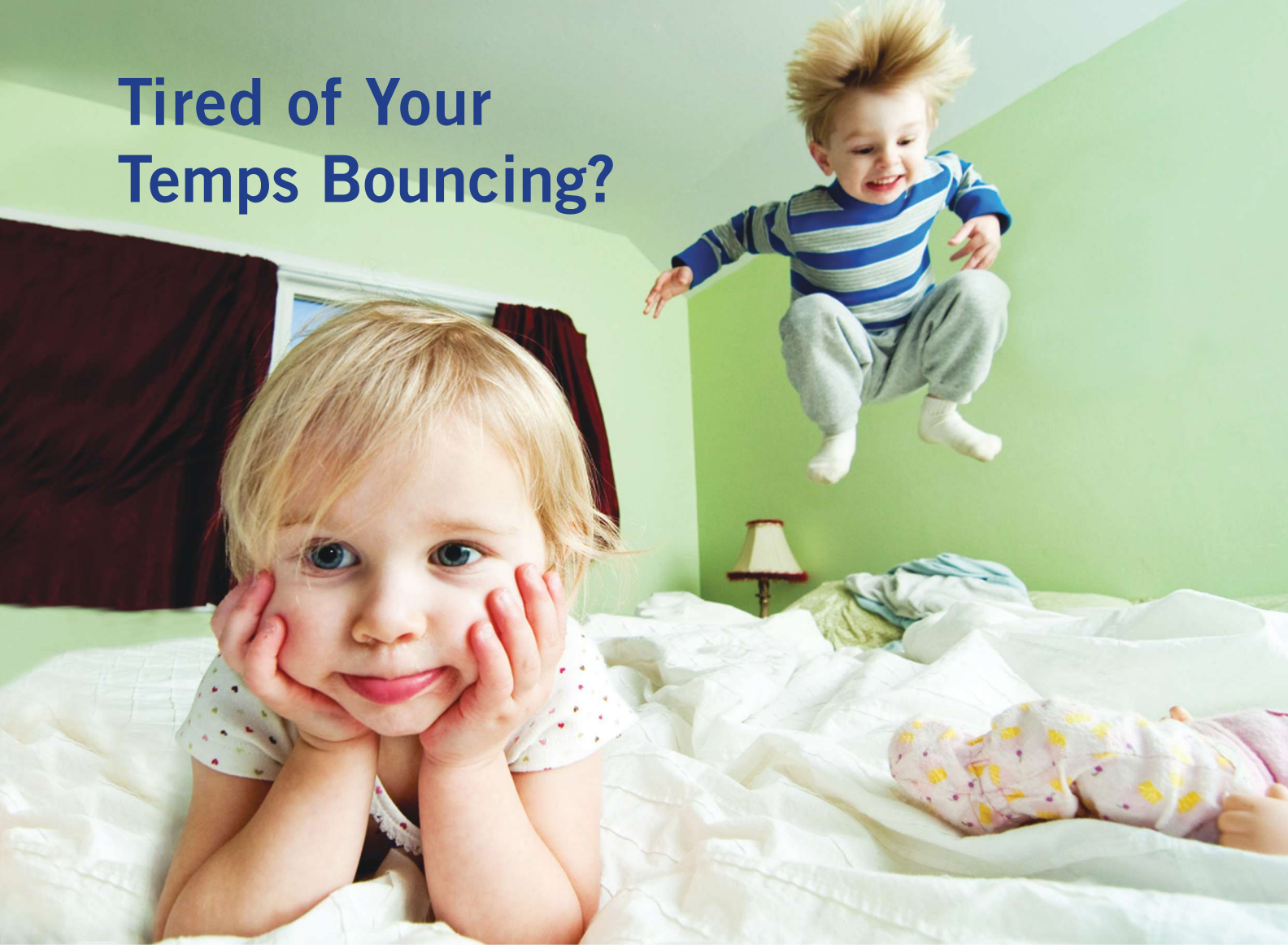

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Q What should be an area of focus for clinical trial executives?

A GIVEN THE POTENTIAL TO POSITIVELY IMPACT the quality and cost of clinical monitoring, the implementation of risk-based monitoring (RBM) with analytics and cloud-based approaches needs to be accelerated. But implementation is not simply retrofitting existing approaches, but a fundamental change to the process via QbD principles (e.g., development of monitoring plans that incorporate real-time data and analytics to trigger monitoring visits). What is required is industry change management, including extensive collaboration among regulators, sponsors, CROs, and clinical trials sites. If you are to disrupt the clinical trial process, you need to ensure there are no gaps in training, processes, or technologies that could negatively impact data quality or patient safety.

JOHN HUBBARD, PH.D.
is a member of the board of Agile Therapeutics and CEO of Bioclinica. He has over three decades of experience, including executive-level positions with Pfizer, ICON, PAREXEL, and Hoechst Marion Roussel Pharmaceuticals.

Q How do you address the FDA guidance on integrated summary of effectiveness (ISE)?

A IN THE AGE OF PRECISION MEDICINE, we are encouraged by regulators to focus on diversity. Achieving true diversity provides a field day for statisticians (e.g., give me six of these and six of those). Effectively requiring a quota system for patient entry might be achievable if there were enough research sites truly serving a diverse population. But in the age of specialization, this is not the reality. I can only reach all of the desired patient groups by significantly increasing the number of qualified research sites in the trial, and this brings its own set of issues described in another guidance document on the perils of working with small numbers. This brings me full circle to another of my old favorite solutions, the post-approval commitment – perhaps the only way to demonstrate which patients benefit.

MARY ROSE KELLER
is VP clinical operations at Heron Therapeutics. She has 30+ years of industry experience in clinical development strategy and execution of global Phase 1 to 4 clinical trials for drug, biologic, and diagnostic products.

Q What are your top books on leadership and why?

A Here are my nine "go to" resources.

Peter Drucker
- *Management Challenges for the 21st Century*
- *The Effective Executive*
- *Managing in Turbulent Times*

Nicholas Webb
- *Breakers: Leading by Destruction in the Innovation Economy*

John P. Kotter
- *Leading Change*

Daryl R. Conner
- *Managing at the Speed of Change*

David Cottrell
- *Monday Morning Leadership: 8 Mentoring Sessions You Can't Afford to Miss*

Michael Watkins
- *The First 90 Days: Proven Strategies for Getting Up to Speed Faster and Smarter*

Marshall Goldsmith
- *What Got You Here Won't Get You There*

All have a couple of common themes, beginning with change. What I like about all of these resources is they all go beyond analysis and encouragement to actual application. While visionary guides can be inspirational, toolkits are much more practical in equipping executives to lead (not manage) change.

MITCHELL KATZ, PH.D.
has 30 years of experience in the pharma and biotech industries, including preclinical research, pharma operations, and regulatory affairs. He is the head of medical research and drug safety operations at Purdue Pharma L.P.

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CMS's Radical Experiment On Pricing Of Part B Drugs

JOHN McMANUS The McManus Group

Capitalizing on the growing vitriol directed at the pharmaceutical industry, the Obama administration unveiled a far-reaching and aggressive "demonstration project" that would fundamentally change how physician-administered drugs are reimbursed by Medicare.

The administration proposes to scrap the current market-based "average sales price" (ASP) payment formula, which reimburses physicians and hospitals 106 percent of the ASP of a Part B drug (accounting for all discounts, rebates, and other price concessions).

To begin as soon as August 1, phase 1 would commence this fall and slash reimbursement to 102.5 percent of ASP plus $16.80. When the effects of the budget sequestration are accounted for, this scheme actually becomes 100.86 percent of ASP plus $13, putting many physician practices and hospitals under water when prescribing expensive Part B drugs.

Phase 2 could roll out as early as January 2017 — obviously before any meaningful evaluation can be made of phase 1 — and empower Medicare to establish value-based purchasing tools, including:

- **REFERENCE PRICING**, whereby drugs within a therapeutic class would be tied to the cheapest drug in that class or to an average price of those drugs in a therapeutic class or some other benchmark price. The CMS does not reveal what reference price it intends to use.

- **INDICATIONS-BASED PRICING**, whereby drugs would be paid for on their "varying clinical effectiveness for different indications." CMS explains that a drug could receive a higher price for cancer A than when used to treat cancer B.

- **OUTCOMES-BASED, RISK-SHARING ARRANGEMENTS**, whereby drugs would be paid for based on the health outcomes of the patients and adjusted down through rebates and discounts if the outcomes are not achieved.

- **EPISODE-BASED OR BUNDLED PRICING**, whereby a provider could be held accountable for a total cost of service across an episode of care to reduce the incentive to use more costly treatments.

Similar policies have been tried in Europe and resulted in patient access restrictions to important life-saving products.

The mandatory "demonstration" would be tested on patients in three-quarters of the country. Just one quarter of the country in zip codes, randomly assigned, constitutes the control group that would continue to receive drugs as required in the Medicare statute enacted by Congress. Oh ... and the experiment would also exempt the state of Maryland, home to 5,000 Baltimore-based CMS employees and their families. CMS argues that Maryland's all payer system could introduce "unobservable bias." How convenient!

In a rare joint statement by the three committees of jurisdiction, House Ways & Means Chairman Kevin Brady (R-TX), House Energy & Commerce Committee Chairman Fred Upton (R-MI), and Senate Finance Committee Chairman Orrin Hatch (R-UT) said the "model could ultimately result in seniors receiving different standards of care based solely on where they live in the country."

The cancer community has reacted with shock and outrage. The Community Oncology Alliance's scathing response stated, "What this experiment is saying is that CMS believes it knows better and intends to dictate the drug treatment choice rather than the patient's treating oncologist. This experiment is a misguided government intrusion into the treatment of seniors with cancer and is a very dangerous precedent severing the sacred physician-patient bond. And make no mistake about it — CMS has designed ... a blind experiment to force treatment to meet CMS's definition of value, not the best, most appropriate cancer treatment determined by oncologists in collaboration with patients."

What enabled CMS to override and effectively disregard long-standing Medicare statute? Obamacare established the Center for Medicare and Medicaid Innovation (CMMI) — a division within CMS — and empowered it to waive the entire Medicare statute in order to test demonstration models.

For years CMMI has been viewed as a backwater where policy wonks lavishly fund schemes to better coordinate

"If CMS wins this battle over physician-administered Part B drugs, it will be emboldened to pursue even more radical 'demonstrations' in Medicare Part D."

care and move Medicare from volume to "value." Obamacare provided CMMI with a staggering $10 billion (you read that right — billion) of funding per decade. CMMI has struggled to help mostly hospital-led accountable care organizations better coordinate care and contain costs, repeatedly relaxing its rules to retain participant interest in the program. ACOs (accountable care organizations) have fueled provider consolidation but have done little to save money.

Last year, CMMI sparked controversy when it imposed the mandatory Comprehensive Care for Joint Replacement (CCJR) demonstration in 67 metropolitan statistical areas to test bundled payments of hip and knee replacement surgeries. Orthopedic surgeons and a substantial number of members of Congress objected, and the start date was briefly delayed, but it rolls into effect April 1.

Perhaps emboldened by its success in swatting away objections to CCJR and observing the developing narrative on drug pricing, the Obama administration undertook this aggressive Part B demonstration, of the scope and reach that few in the policy and physician and drug communities could fathom. The Medicare Payment Advisory Committee (MedPAC) had opined that the 6 percent add-on payment to ASP could encourage physicians to prescribe more expensive drugs. But its role was merely to advise Congress, which then had to decide whether and how to act after hearing from stakeholders. Few could conceive that CMS would adopt nationwide, European-style reference-pricing regimes and sweeping schemes to tie reimbursement to subjective views of effectiveness. CMS's writing clinical support tools also has alarmed the physician community, which views that as their role.

Moreover, in refusing to engage stakeholders in the development of the demonstration model, the Obama administration has violated the very law that established CMMI. The Obamacare statute requires CMMI to "consult with clinical experts in medicine and health management and use open door forums or other mechanisms to seek input from interested parties."

Upon learning that CMS was about to release its proposal on Part B drug pricing, more than 100 patient and physician groups — ranging from the American Autoimmune Related Disease Association and Kidney Care Association to the American Society of Clinical Oncology and Society for Women's Health Research — quickly issued a strongly worded letter stating "This type of initiative, implemented without sufficient stakeholder input, will adversely affect the care and treatment of Medicare patients with complex conditions."

The lack of engagement stands in stark contrast to CMMI's own Oncology Care Model, which has been under development for more than two years with substantial interaction and dialogue with stakeholders. That voluntary alternative payment model will likely be overridden by this far-reaching and mandatory program.

Just as troubling, the administration ignores the CMMI statute's clear mandate to select a model that "addresses a defined population for which there are deficits in care leading to poor clinical outcomes or potentially avoidable expenditures." The "defined population" apparently means the entire country (except for CMS home base of Maryland.) CMS provides no evidence that Medicare beneficiaries are experiencing poor clinical outcomes based on the Part B drugs they are being prescribed. And moreover, in the panoply of academic and managed care literature, there is little to suggest the Part B payment structure has led to abuse.

Physician, patient, and industry groups are now mobilizing to at least delay the implementation of this demonstration project to the next administration. That will be a challenge, as there is no must-pass bill on the horizon. Yet a similar coalition successfully beat back a CMS attempt to remove protections to vulnerable patients taking drugs in one of the designated "6 protected classes" in the Medicare Part D outpatient drug benefit a couple years ago.

If CMS wins this battle over physician-administered Part B drugs, it will be emboldened to pursue even more radical "demonstrations" in Medicare Part D. It could effectively rewrite the Medicare program through executive fiat and without the people's representatives' input or consent. That is unacceptable.

Launch all ships and leave none in a harbor! 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.

Osel

Live biotherapeutics to restore microbiomes – in midstage development for vaginal and urinary conditions – with a special focus on women's health

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Osel is both a pioneer and a resurgent player in the microbiome space and in women's health, with two midstage clinical programs, Lactin-V for bacterial vaginosis and urinary tract infections and CBM588 for antibiotic-associated diarrhea. A third program in HIV prevention uses proprietary mucosal delivery of an engineered virus-fighting bacteria in the vagina. Osel's products are all "live biotherapeutics," blazing a new regulatory pathway toward FDA approval.

WHAT'S AT STAKE

Everyone talks about the microbiome — so it's good to see someone doing something about it. You might be forgiven for thinking it is all covered — nowadays, pharmacy and health-product shelves burst with probiotics, varying by their colorful packaging with who-knows-what inside, all promising a kind of liberation from suffering "down there." Osel, a longtime pioneer in the microbiome field, has brought science, clinical data, careful formulation, and delivery to the table. Through many years of big trials and small triumphs, Osel has designed and developed live biotherapeutics not only with the usual microbiomic focus on the gut but also on women's health — vaginal and urinary infection, and longer term in HIV prevention.

"There is a huge difference between our products and the previous probiotics, as you say, available over the counter," says CEO KT Moortgat. "Generally, they may not be harmful, but frequently they supply the wrong microbes to the wrong part of the body. All the products we are developing are FDA regulated; they go through clinical trials to demonstrate clinical safety and efficacy." A veteran academic-entrepreneur at the University of California, San Francisco (UCSF) and driver of the California Institute for Quantitative Biosciences (QB3-UCSF), Moortgat joined the company only months ago as the interim CEO. Her arrival followed a decade-long quiet period for Osel, which had started in 1999 based on research by its founder, Dr. Peter Lee, then at Stanford. Lee invented the novel mucosal delivery technology, MucoCept, the platform for Osel's HIV-prevention program, a descendant of his Stanford research. The two pipeline products, Lactin-V and CBM588, employ other unique formulation and delivery platforms, invented and refined at the company and each suited for its particular therapeutic environment. Lactin-V is a single strain of Lactobacillus identified in a healthy vaginal microbiome and female urinary tract, and has been demonstrated to lower common vaginal and urinary infections in previous trials. A proprietary applicator delivers the bacteria, now in U.S. Phase 2b trials for the two indications. CBM588 is a bacteria species taken orally to restore the natural, mutli-bacterial microbiome and reduce inflammation in the bowel. Its U.S. Phase 2 trial for treating antibiotic-associated diarrhea reflects its indication in Japan, where it has been sold for years. CBM588 is also in preclinical testing for inflammatory bowel disease.

"The gut and the urogenital tracts are very different," Moortgat explains. "In the gut, not only do you want a multitude of individual microbes, but you also want hundreds of different species to be present. When there's a low diversity, it causes gut problems. In the vaginal microbiome, it's the opposite — only a few beneficial species exist in the healthy vaginal tract, and high diversity is associated with a disrupted microbiome and infection." Native bacterial species maintain a healthy environment in their natural setting by colonizing and "antagonizing" harmful non-natives.

Besides formulation and delivery, Moortgat says the most important competitive factor for Osel and others in this space is the accuracy of measurement and selection of healthy microbiome constituents. "What species should each microbial environment contain, which strains are most protective, and how many of each kind?" How well Osel answers those critical questions will determine the ultimate success of its pioneering products. L

KT MOORTGAT
CEO

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10
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Global private investment, amounts not disclosed.

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SANOFI EVP WEIGHS IN ON THE POLITICS OF DRUG PRICING

By R. Wright

SURESH KUMAR
EVP of External Affairs of Sanofi

Sanofi EVP Weighs In On The

POLITICS *of* DRUG PRICING

ROB WRIGHT Chief Editor @RFWrightLSL

Is it plausible that biopharma is a victim of its own success? For example, since Richard Nixon first declared war on cancer in 1971, half of those diagnosed today will survive for at least 10 years — a point at which their chances of survival are pretty much assured. The HIV/AIDS epidemic that began in the late 1970s not only resulted in the advent of over 20 different disease-specific medications but also shifted an HIV positive diagnosis from a death sentence to a manageable chronic disease. Despite these and other incredible successes, the biopharmaceutical industry has descended from being *the most admired* business sector in the world to one that ranks barely above tobacco in honesty, ethics, and trustworthiness. As I watch politicians zero in on "high-priced" drugs as *the* big political issue for 2016, I have been brooding as to how we have allowed our industry to be reduced to no more than a populist cause capable of pulling voters across party lines. This is why I couldn't pass up the opportunity to interview Suresh Kumar, EVP of external affairs at Sanofi, about the politics of drug pricing. After all, Kumar's healthcare experience spans more than 30 years and includes stints in Big Pharma (e.g., J&J, Warner Lambert), big nonprofit (i.e., the Clinton Foundation), and big government (i.e., Assistant Secretary of Commerce and Director General of the U.S. and Foreign Commercial Service, spearheading global trade for the Obama administration). According to Kumar, "It is time for a constructive dialogue on drug pricing, but in the context of access, value, and overall healthcare costs." But where to begin?

Key Contributors To The Perceived Drug-Pricing Problem

Thus far, the rising negativity and focus on healthcare costs has primarily resulted in key industry players taking positions of isolation or attack. For example, in 2015 PhRMA moved from a two-day public conference to that of a "closed-door" event. Though PhRMA didn't disclose the specific rationale behind the decision, the perception created is one of an organization strategically circling the wagons against the rising barrage of drug-pricing attacks. At the 2015 American Society for Clinical Oncology (ASCO) meeting, Memorial Sloan Kettering Cancer Center oncologist Leonard Saltz, M.D., went on the offensive in his plenary speech saying, "These drugs cost too much." To date, at least six states (i.e., CA, MA, NC, NY, OR, and PA) have introduced prescription drug transparency legislation seeking to force companies not only to provide itemized drug R&D expenses, but also to reveal costs associated with manufacturing. (Let's keep in mind that collecting and organizing all of this information in order to comply will also involve an additional cost).

"Everyone would like [cost] transparency when it comes to healthcare," says Kumar. "For example, in 2013 there was a *Time* magazine article [*Bitter Pill: Why Medical Bills Are Killing Us*] that talks about the lack of transparency in hospital costs." Though many states have passed healthcare price transparency laws, most are doing a poor job when it comes to enforcement. Part of the problem is being heaped on payers and providers for functioning as barriers to successful enactment. However, another part of the problem might be the sheer number of moving parts (e.g., allocation of labor, systems, and supplies) involved in a typical patient's hospital visit. But according to Kumar, another problem is the back and forth finger pointing that takes place among various industries (e.g., payers, PBMs [pharmacy benefit managers], providers, and pharma) and government. (For more info, see sidebar "The Drug Pricing Transparency Versus Value Conundrum.")

Another problem is the preponderance of negative media coverage about anything related to drug pricing. "Most media coverage concerning drug pricing focuses on sensational headlines," Kumar attests. "I saw the disgusting testimony of Martin Shkreli before Congress. That is not the pharmaceutical industry." But because Shkreli pleaded the Fifth and said nothing, when combined with his smirking facial expressions and post-testimony tweets calling members of government "imbeciles," the result was a media frenzy that continued to try to position him as the poster boy of the entire pharma industry — obviously an unfair comparison that lacks context. "When we focus on only how much a drug price went up, as opposed to looking across the value chain of, for example, how much it costs to treat a person living with diabetes today versus yesterday without new products, versus the cost/benefit to treat a life tomorrow, you end up with just media soundbites," he shares. Consider the long-term out-

The Drug-Pricing Transparency Versus Value Conundrum

One of the problems currently preventing drug-pricing transparency is WAC — the wholesale acquisition cost. WAC is a manufacturer's list price of a drug when sold to the wholesaler (e.g., McKesson). "WAC has little bearing on the actual price to a patient," states Sanofi's EVP of External Affairs, Suresh Kumar. "If you look at the difference between the WAC price of a drug and the price negotiated with PBMs and insurance plans, you would see it is substantially discounted." According to Kumar, one of the roadblocks to achieving true drug-pricing transparency is pharmaceutical companies not being able to publically share the discounted price paid for a drug by a PBM or payer. "Why don't we provide it? Because, we are contractually barred from disclosing the level of discounts we provide," he explains. "That [WAC discount] savings has the opportunity to be passed along throughout the drug-distribution chain. But the savings provided by these pharmaceutical company discounts do not always find their way to the patient." To truly understand the price a patient pays for a drug requires looking at the entire system. What was the WAC price? What was the true price paid by a PBM or a payer? What was the price at which the patient got it, adding in their copay? While in a single-payer market this information would be much easier to find, in a market-driven situation like we have in the United States, these discounts are not transparent to the end user.

"How are we going to break through this conundrum?" asks Kumar. One way is moving to a collaborative effort among the various stakeholders and moving from fee-for-product to fee-for-performance. For example, consider Praluent (alirocumab), a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as an adjunct to diet for adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. "This is the first major innovation after lipid-lowering statins in 30 years and provides the appropriate patients up to a 50 percent reduction in LDL over their current regimen, including statins," Kumar explains. "With that level of innovation, we should certainly be able to do value-based pricing." According to Kumar, when Sanofi launches a new medicine, the company communicates with constituents the value the innovation represents. "We use multiple models that are very sophisticated, incorporating economic metrics and internal data derived from studies, as well as data from third parties to express a drug's value and definitively establish WAC prices that reflect that," he says. "Now, if we go through the exercise of demonstrating we have a therapy that reduces LDL by 50 percent, and your organization [payer/PBM] says it only wants to pay for value, then it is incumbent on the insurance company to have a system to be able to capture that value. You can't demand that you want to pay for only value and then turn around and say you don't know how to do it." Kumar says this is one of the challenges pharmaceutical companies encounter when broaching the subject with payers on developing or piloting value-based pricing models — the payer's inability or lack of systems to be able to capture the value a drug provides a patient.

> *"Most media coverage concerning drug pricing focuses on sensational headlines."*
>
> **SURESH KUMAR**
> EVP of External Affairs, Sanofi

comes associated with a drug everyone knows — Pfizer's cholesterol lowering agent Lipitor (atorvastatin calcium). "If you take the price of Lipitor at launch all the way through its life as a branded drug, you will arrive at some median price," he explains. However, that price does not adequately reflect its value to society. Since the development of statins (e.g., Lipitor), these drugs have become the standard of care, reducing LDL cholesterol levels and frequency of heart attacks. "In 2010, the price of 30 20mg Lipitor tablets was around $5.50 per pill," he continues. "Yet, today the price of a generic version is about $0.50 per pill." The reason generic statins can be priced so cheaply today is the direct result of investment by branded research-based pharmaceutical companies. That's the beauty of the market-based system, particularly in the U.S. Investment results in innovation and, eventually, lower prices, bringing about the new cures to those who so desperately need them. According to Kumar, though the concept is fairly simple to understand, when not communicated in its entirety, based on the present type of media coverage, public understanding is lost. "Solving big problems like this requires intelligent and substantive dialogues," Kumar contends. It also requires coalitions.

Solving Big Problems Requires Building Coalitions

Back in October 2015, Vice President Joe Biden called for a "Moonshot" in order to find a cure for cancer. "For a country that landed people on the moon, this may be the right approach in looking

Biopharmaceutical Companies Are Businesses, Not Charities

Suresh Kumar has worked for charitable foundations, so he knows that pharma companies do not fall into this category. Unfortunately, society often forgets what Kumar knows — that pharmaceutical companies are businesses. While all three require money to function, budgets to operate, and have a variety of expenses, they all receive their finances differently.

"It doesn't matter what industry you are in, any company must recoup its costs for the work it does," says Sanofi's EVP of External Affairs. "This is a responsibility we have to our shareholders." Anybody who owns healthcare stocks wants to earn a return on their investment, not to lose money, and not to just break even. Pharmaceutical companies take huge risks in discovery and developing innovative therapies that require significant financial commitments. "We have an ODYSSEY OUTCOMES (a collection of global Phase 3 clinical studies in the area of high cholesterol) study for Praluent (alirocumab) to see if the therapy stops or leads to a decline in frequency of heart attacks," he shares. "If it does, that's a major innovation." This is why prescription drug companies have been traditionally referred to as ethical pharmaceutical companies, because ethics preclude them from making any sort of product claim until it has been proven, which requires the design and execution of regulatory-approved clinical studies. Kumar notes that it's costly to conduct an 18,000-patient, strictly controlled, long-term clinical trial. There's the cost of discovery, manufacturing, and continuous product improvement, as well as many other expenses, including the cost of failure (i.e., attempts to develop cures that didn't work). "To either not understand all of that, or understand it and simply decide to ignore that pharmaceutical companies need to recover all of their costs, doesn't work," he shares. "I can't go back and tell my scientists, 'Oh, by the way, our drug didn't succeed, so I'm not going to pay your salary.'" Kumar says if we want to reduce the costs associated with drug development, we need to look for new paradigms that allow for forward-thinking (e.g., streamlining drug development) rules and regulations. However, if we want to reduce overall healthcare costs, we need to start thinking about how we can work together to remove costs from the entire system. "Drugs that impact big-ticket items, such as reducing the length of a hospital stay or eliminating the need for surgery, create significant and immediate savings," he reminds. "Simply saying that these drugs are too expensive without taking into account the value and long-term saving they bring to society is acting irresponsibly."

for the next cure for cancer," says Kumar. "I think we need to build on this concept (i.e., having a lofty target requiring a coalition to address) when it comes to tackling the rising global healthcare cost problem," Kumar attests. "There's no doubt the healthcare cost curve can be positively impacted by continuing to develop new medicines that more efficiently and effectively deal with disease. But this cannot be done in a vacuum." Perhaps what is required is the building of a healthcare moonshot type of coalition. But how?

"When I look at the current pricing debate and compare it to the failed attempt at universal healthcare from the past Clinton administration, it seems the challenge in tackling such big problems always starts with determining how far-reaching the coalition designated to solve those problems should be," he says. "Also, will you start with digestible bite sizes [of the problem] or take on the entire enchilada? Should you focus on the fastest-growing cost areas or the slowest growing areas?" As an example of the challenge of choosing what the best approach would be, he discusses Sanofi's dengue fever vaccine that has approval in four countries. It took nearly 20 years, an investment of more than 1.5 billion euros, and clinical studies across 15 countries involving 40,000 patients. Because dengue is primarily found in tropic and subtropical regions, the company first went to the countries where the disease is endemic, thereby not following the traditional approach of starting in the U.S., then on to Western Europe, and then rest of the world. "In January we announced our commitment to start looking for a cure for the Zika virus, a close cousin of dengue," says Kumar. "Given all the work we have done on mosquito-borne diseases, we have significant expertise and relationships to address this virus." And while he believes a coalition will be important to successfully solving the Zika problem, he asserts that the world doesn't have the luxury of time (i.e., 15 years) to invest billions to conduct clinical studies when the problem is now. "If you were to put together a coalition for the successful development of a Zika vaccine, obviously you would want it to be multifaceted, including organizations such as the CDC and WHO," he says. The coalition probably should also include funders, such as the World Bank or the Bill and Melinda Gates Foundation, or private companies willing to float corporate bonds. Another thing to consider is how to involve regulatory agencies (e.g., FDA) so they can become more adaptable during crisis situations (i.e., creating mutual acceptance processes among the various regulatory agencies involved in order to accelerate clinical studies and approval). "After that," Kumar continues, "since the delivery of all this will be in countries where Zika's a problem, those countries' governments need to be a part of the dialogue." But building a coalition also requires the oversight of a lead agency.

What It Takes To Execute A Healthcare Cost-Reducing Moonshot

Significant achievements such as putting a man on the moon or creating the Human Genome Project all required some kind of

agency overseeing the project (i.e., NASA, NIH). And while reducing U.S. healthcare costs might not seem as noble as landing on the moon or mapping the genome, it is easily as significant, if not more so. Achieving just a 1 percent cost reduction in U.S. healthcare spend equates to approximately $40 billion in savings — annually! To put this in perspective, that is $15 billion more than the cost of the *entire* Apollo program and $37.3 billion more than the *entire* Human Genome Project.

The question isn't whether the goal is worthy, but rather, what organization should take the lead? Further, where will the funding for such a bold project come from? Having personally gone through two senate confirmations, Kumar believes, given the polarizing world in which we live, such a healthcare cost-reduction project would fail if the White House decides to try to drive the process. But if we model such a coalition on our two previous examples, it is likely project funding will come from government, and as such, should involve a government agency with the clout capable of bringing key stakeholders to the table. Perhaps this is a job for the U.S. Department of Health & Human Services (HHS). "This past November, HHS convened a pharmaceutical forum on innovation, access, affordability, and better health," Kumar shares. "The day involved a number of presentations, but the real key was bringing together the varied components of a fragmented healthcare value chain, from discovery to delivery, well beyond just pharmaceuticals." For example, AARP, America's Health Insurance Plans (AHIP), *Consumer Reports*, the Generic Pharmaceutical Association (GPhA), Express Scripts, and state healthcare and employee retirement systems took part, to name just a few. Further, stakeholder participation hailed from the highest levels (e.g., Ken Frazier, CEO of Merck; Bernard Tyson, CEO of Kaiser Permanente; Marc Boutin, CEO of the National Health Council). "To build a healthcare cost-reduction coalition, while representatives from the pharmaceutical industry would need to be included, it would also have to include providers, payers, PBMs, patients, policymakers, regulators, and so on. That's the only way we're going to get this done," Kumar contends. He believes the HHS gathering was a great first step that created dialogue among all the key stakeholders. But to truly embark on a healthcare cost-reducing moonshot that focuses beyond just "high-priced" drugs, requires an agreed-upon common goal and an organization willing to take the lead and begin the process of creating a coalition. "Therein lies the essence," Kumar concludes. "What is it as a society we wish to do, and what role can each of us play to get there? Because having medicine, or access to healthcare, should not be a privilege."

MARK PERRIN
Chairman and CEO of InVivo

INVIVO THERAPEUTICS:
TAKING ON SPINAL-CORD INJURY

THE ENTERPRISERS

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

PUBLIC COMPANY

MARKET CAP: $191.5M (as of 1/6/16)

CASH: $22.1M (as of 9/30/15)

STARTUP DATE: 2005

NUMBER OF EMPLOYEES: Approximately 30

FOCUS: Novel investigational Neuro-Spinal Scaffold to promote recovery from spinal-cord injury

Not everyone knows someone with a spinal-cord injury. I did. We met as teenagers, shared a few years as friends but lost touch when I drifted to the opposite end of the country. Then, one day, I picked up the phone and heard through his girlfriend's sobs that he had broken his neck in a swimming accident and was paralyzed from the mid-chest down. When I later visited him and spent some nights on his couch, I could hear him crying out in the morning, "Why me?" But, tough as nails, he remained a great human being to the end, and after tripling his predicted lifespan, he died just two years ago, more than three decades after his accident.

Through all of that time, we looked for a significant breakthrough in preventing or restoring lost function due to spinal-cord injury (SCI). Once, for an article based on my friend's suggestion, I interviewed Chris Reeve at his home in New York and came away inspired with new hope. That was 16 years ago, and everyone who lives with such a condition is still waiting for the same breakthrough — that is, perhaps, until now.

It seems necessary to share all of the above as context for this article — the story of InVivo Therapeutics. It is not only because extraordinary claims require equal caution, but also because I have never seen such a bold and ambitious approach to treating, dare I say *healing*, one of the worst injuries anybody can sustain. InVivo's development of a tiny scaffold inserted into the injury site also takes me into new territory, because I have spent most of my career covering pharmaceuticals rather than devices. But the company's story merits attention in "The Enterprisers" both for its ambitious goal and its means for reaching it.

Spinal-cord injury is a rare condition — in the United States, it affects fewer than 300,000 total patients, or about one in every 1,000 people, with only about 12,500 new patients per year. Unless already wealthy or financially secure, SCI patients tend to live on the economic margins, with mercurial granting of Medicaid benefits and medical attention, except for the most severe cases. Countless discoveries, inventions, and treatment approaches for SCI have percolated out of various labs and institutions over the years, yet so far no company has succeeded in commercializing a transformative treatment. A near exception was a program for the neurogenesis agent Sygen (bovine-extracted monosialoganglioside), which had the sponsorship of the Italian company Fidia, but its clinical development stalled in the United States.

InVivo has followed the startup path, dedicating itself entirely to gaining FDA approval and practical adoption of its approach as the standard of care for U.S. patients. Its lead product, the Neuro-Spinal Scaffold, placed by an innovative surgical approach into the spinal cavity caused by the injury, may arrest further tissue death and create a "neuro-permissive" environment, friendly to nerve healing and regrowth. The FDA has given the product fast-track status as a Humanitarian Use Device (HUD) and allowed InVivo to convert a pilot study into a pivotal clinical trial. A second, related program still in the research stage at the company, Bioengineered Neural Trails, would add an infusion of neural stem cells in a biomaterial at the injury site.

The first 24 hours after an SCI event is a critical window for intervention. When vertebrae break, the shattered pieces push into the spinal cord and cause hemorrhaging, swelling, reduced blood flow, and ischemia necrosis. The trauma begins to kill and liquefy the innermost neurons or grey matter cells, which are surrounded by neural white matter cells inside the spine. Unimpeded, the necrosis will hollow out the entire area, creating a dead zone that thoroughly disconnects the spinal cord below the injury from the cord above.

To preserve as much of the connection as possible, the Neuro-Spinal Scaffold procedure must take place as early as possible after injury. In InVivo's first, five-patient study, researchers were encouraged to treat within the 24-hour window but in some cases found it practically impossible to do so. Nevertheless, one of the patients in the study who showed significant improvement received treatment at 80 hours, and if approved, the Neuro-Spinal Scaffold procedure could be used up to 96 hours post-injury.

In the procedure, the surgeon first siphons off the dead, liquefied cells, then inserts the highly porous biopolymer scaffold into the resulting cavity, where it gives support and protection for the remaining nerve tissue and allows natural regrowth, hopefully to restore basic functions such as bladder and bowel control. One of the polymers is PLGA (poly lactic-co-glycolic acid), a biodegradable structure for cell regrowth; the other is poly-L-lysine, to promote cell adhesion. The scaffold thus propels appositional healing, in which new neurons sprout and strengthen connections across the periphery of the injury by detouring around it.

With the aim of promoting extensive regrowth and even reconnection of nerve channels to the brain, Bioengineered Neural Trails would employ a patented device to make a longitudinal injection of stem cells incorporated into an injectable scaffold soft gel for the treatment of patients with chronic spinal cord injuries. Past stem-cell treatments have used multiple trans-spinal injections plagued by reflux and poor cell distribution. To avoid those faults, the longitudinal method leaves a clean line of cells along the path of healing.

FROM ACADEME TO ENTERPRISE

InVivo's technology originated in the laboratory of Robert Langer at MIT, which has been a prolific source of life sciences inventions and startups. "Bob has spawned about 30 companies out of his lab and holds more medical patents than anyone else in the world — and more patents generally than anyone except Thomas Edison," says Mark Perrin, InVivo's chairman and CEO.

When Perrin joined the company two years ago, it was trying to advance two main programs at once — hydrogel drug delivery and spinal injury. He soon came to see the dual focus as diluting company efforts and distracting it from the novel "sweet spot" in its portfolio: the Neuro-Spinal Scaffold. At the time, he says, the company's management was somewhat in disarray, with all the chief officers in only interim assignments. The situation gave him the opportunity to apply his business and commercial background — at Burroughs Wellcome, Lederle, and a number of smaller companies such as COR Therapeutics — to building his own team and steering InVivo in a new direction.

Perrin went after even more industry experience. He recruited Tom Ulich, M.D., former head of preclinical development at Amgen, as chief scientific officer; Lorianne Masuoka, M.D., formerly of Cubist, as chief medical officer; and Tamara Joseph, also from Cubist, as general counsel. He also terminated the drug-delivery program and concentrated the company's efforts on SCI. On a practical level, that meant raising enough cash to fund operations and accelerating clinical development of the Neuro-Spinal Scaffold.

At that point, the FDA had given the green light to the company's small pilot study in humans, a significant step following the extensive preclinical development in rodent and primate models. The study involved five patients with complete thoracic injury — total paralysis below the site of injury, in the thoracic region directly below the neck. Complete-injury patients have the highest rating, AIS A, on the American Spinal Injury Association's (ASIA) Impairment scale (AIS). Incomplete injury, where patients have some feeling or function below the injury site, carries the rating AIS B through AIS D, and AIS E represents normal function. Conversion from a higher to a lower score, as from AIS A to B or C, thus represents improvement in the paralysis.

Perrin says the FDA initially wanted InVivo to study patients sequentially — treating one patient at a time, waiting three months, and evaluating the results before treating the next. "But after completing the process with Patient 2, after we had established a good dialogue between the new members of our team and the FDA, the agency agreed to concurrent enrollment for Patients 3, 4, and 5. That probably took a good year off the early development program."

With the HUD designation, the scaffold is traveling the HDE (humanitarian device exemption) pathway. "HDE sounds like an orphan drug designation, and that is the comparable regulatory pathway for devices, but with a big difference — rather than running a placebo-controlled trial to show significance, all you need to do is show probable benefit," Perrin says. "So it's a classic risk-benefit analysis, and we must demonstrate a benefit outweighing the risk."

What InVivo needed was an agreement with the agency on an "objective performance criterion" to support its probable benefit claim. Fortunately, some relevant benchmarks already exist in the form of large historical patient databases: the European Multicenter Study about Spinal Cord Injury (EMSCI), the Spinal Cord Injury Model System (SCIMS), and the Sygen clinical trial. EMSCI showed a conversion rate of 15.6 percent at six months; SCIMS, 15.5 percent at 12 months; and the Sygen trial, 12.9 percent at six months. Thus, the estimated baseline recovery rate is between 12 to 15 percent.

Besides movement and feeling, including sexual function, the most critical losses in SCI are bladder and bowel control — the separate but related

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abilities to recognize and prepare for when the body needs to "go." Adapting and responding to the resulting incontinence can become almost a full-time preoccupation for patients. Fortunately, in the rare cases when SCI patients improve, bladder control and bowel control are often among the first functions to return. It appears conversion by treatment may follow the same pattern.

Among the first five patients treated with InVivo's scaffold, one converted to AIS C and another to AIS B at one month and a third to AIS B at six months. The first patient regained bowel and bladder function and has experienced ongoing, and one could say dramatic, return of sensation and movement below the injury. The second patient to convert continued to regain sensory function through month six. A fourth patient remained AIS A but showed significant recovery of bowel and bladder function through month 12.

"We have a video of the first patient's surgery and a video of the patient walking at 12 months," says Perrin. "He is walking with braces, but he's walking. Dr. Nick Theodore, one of the world's thought leaders in this field, did the surgery in October 2014 at the Barrow Neurological Institute in Phoenix, the largest neurological center in the United States. The patient was a young gentleman involved in a motocross accident, completely paralyzed from T11 down. At one month, he had improved to AIS C already, and at three months, he began to get recovery of function in his hips, and at six months, in his knees, and he was then able to lift his legs against gravity. At 12 months, in addition to walking up to a quarter mile with braces, he had regained function in his ankles and had complete bowel and bladder function."

TRIAL BY INSPIRE

Based on such results, the FDA granted the company's request to expand the pilot study to a 20-patient trial that would include the first five patients already tested, with a six-month primary endpoint of conversion from complete to incomplete injury status, or from AIS A to AIS B or better. Bending the normal bounds of acronyms somewhat, InVivo dubbed the trial INSPIRE (InVivo Study of the Probable Benefit of the Neuro-Spinal Scaffold for Safety and Neurologic Recovery in Subjects with Complete Thoracic AIS A Spinal Cord Injury). The objective performance criterion for the study is 25 percent or more of the patients in the study demonstrating an improvement of at least one ASIA Impairment Scale (AIS) grade by six months post-implantation. The conversion rate for the first five patients in the study was 60 percent.

Of course, this is thoracic, not cervical SCI. My friend's injury was low in the cervical region, so although he had total paralysis from the top of the chest down, he also had partial impairment of his arms and hands, and, most important in everyday life, he could not oppose his thumbs to achieve a firm grasp. Chris Reeve's injury was at the very top of the spine, so his paralysis extended all the way down from there. Generally speaking, in SCI, the higher in the spine, the more serious the injury — more and more nerve channels join the spinal cord as it approaches the brain. It is literally a simpler matter to show treatment benefits in the lower body than higher up, even though the upper-body gains may be more dramatic.

But InVivo seems ready to take on the next challenge. The company plans to initiate a second study with the Neuro-Spinal Scaffold in mid-2016, this time treating acute cervical SCIs in expanded populations — and again using the HDE path. It may also take the premarket approval (PMA) route for further expansion and acceleration of the scaffold program. A trial designed for PMA approval would allow the company to test the scaffold in all acute SCI patients, even those with incomplete injuries, and it could put the product on the FDA's Expedited Access Pathway (EAP) for devices, similar to the Breakthrough Therapy Designation on the drug side. With EAP, the FDA could grant a PMA for the device based on a two-phase study — one that meets certain criteria before approval and delivers confirmatory data post-approval.

"There is a big difference between cervical and thoracic injury," says Perrin. "If you can gain an inch in the thoracic spine, there's a lot of real estate there, so you may only get another area of feeling one level down. But, in the cervical spine, if you gain one level, it could make a huge difference, such as taking the patient off a ventilator or restoring the hand grasp. So the endpoints will be quite different in the cervical trial than in the thoracic trial, with ventilator dependency and hand grasp the two biggest additions."

At present, SCI patients receive the same initial treatment my friend experienced 36 years ago, decompression, or external stabilization of the spine with rods and bolts, which does not address the necrotic process in the spinal cord itself. "What was so attractive to me about InVivo was that, among all the therapeutic categories in which I had worked before, I had never seen another one like SCI, where patients have no good treatment options to improve their lives," Perrin says.

My friend loved to dream. When he slept and dreamt, he could walk and run and feel his entire self as most of us do. And when awake, he would dream about taking a trip in the space shuttle, where he would be free of the awful force of gravity on a paralyzed body. But most of all, he dreamed about a way to heal spinal-cord injury, even if it would only apply to the newly injured and not to himself. I believe he would share in the excitement over InVivo's approach as do the people at the Christopher & Dana Reeve Foundation. Where before there was only hope, the company may succeed in bringing progress.

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PART TWO OF THREE PARTS:
PARSING OUT PARKINSON'S

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

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

IRENE LITVAN, M.D.

Professor of Neurosciences

Director, Movement Disorders Clinic

UC San Diego Health Sciences

CINDY ZADIKOFF, M.D.

Associate Professor in Neurology

Ken and Ruth Davee Department of Neurology; Department of Medical Education

Northwestern University

Feinberg School of Medicine

ROBERT HAUSER, M.D., MBA

Professor of Neurology, Molecular Pharmacology and Physiology

Director, Parkinson's Disease and Movement Disorders Center

University of South Florida

National Parkinson Foundation Center of Excellence

The truth is, unlike oncology and even the related neurodegenerative disease Alzheimer's, the Parkinson's drug-development space still lacks any immediate prospects for disease modification. But new approaches to symptomatic relief have proliferated to fine-tune treatment regimens and exploit various mechanisms to address many other, often dramatic conditions that can affect Parkinson's patients.

Drug developers are targeting levodopa maintenance – augmenting and stabilizing the level of the neuron-signaling protein, dopamine, in the brain – as well as ancillary conditions, psychological and physical, that can greatly degrade patients' quality of life and lifespan. Longer-term, researchers are resolving a better picture of the causal mechanisms in Parkinson's, taking some leads from the works of their colleagues in the Alzheimer's field on misfolded, aggregated proteins. The top candidate in Parkinson's is alpha-synuclein, a structural component of neurons in the brain, that appears to follow a prion-like progression of misfolding that parallels advancement of the disease.

Here, in Part Two of our three-part series on new therapeutic mechanisms for neurodegenerative diseases, we compare the views of key scientific opinion leaders working with some of the companies developing new therapeutics for Parkinson's disease. (See Part One, "Aiming at Alzheimer's," in last month's edition, March 2016, and look for Part Three, "MS: Some Hopes in Sight," next month, May 2016.) In our "virtual roundtable," we stitch together the separate inputs of participants into one comprehensive discussion by a panel of disease experts — KOLs and scientists who are leading some of the most advanced research in their field. This month, we tap the thoughts of three KOLs in the Parkinson's area: Drs. Irene Litvan of UC San Diego Health Sciences; Cindy Zadikoff, Northwestern University Feinberg School of Medicine; and Robert Hauser, University of South Florida College of Medicine. (See KOLs on page 27.)

Separate cameos of selected companies suggest the range and variety of new-MOA (mechanism of action) and drug development in the Parkinson's space. As in the other parts of the series, our virtual panel discusses not only the scientific, regulatory, and other practical hurdles that lie before the new approaches, but also the issues that will affect any candidates that ultimately survive the development gauntlet and enter medical practice. Those include the possible use of therapeutic agents with different MOAs in combinations, the methods and authority for configuring combinations, and the challenges of clinical trial design, postmarket regulation, payer pushback, and patient education.

INTERNATIONAL STEM CELL CORPORATION

Entering Phase 1 with a proprietary class of stem cells to replace lost dopamine-producing neurons in Parkinson's patients

Russell Kern, Chief Scientific Officer: *We developed our own class of pluripotent cells, called parthenogenetic stem cells, which are made from unfertilized oocytes. They have the same differentiation and proliferation capabilities as embryonic stem cells, and they can provide immune-matching benefits like iPS [induced pluripotent stem] cells, though to millions of people instead of only one person, the donor. In choosing Parkinson's as our first therapeutic target, we considered two factors: how many types of cells must be transplanted, and where. Parkinson's is caused by the death of a single-cell type, dopamine-producing, or dopaminergic neurons, and the course of the disease is well localized in the substantia nigra pars compacta, or midbrain region; transplantation is thus relatively easy, and the stem cells stay in place. Our goal is to treat any stage of the disease. Instead of only replacing the dead neurons, we can replace just a small percentage of neurologic pathology and make the implanted neural cells to prevent other neurons from dying. We started enrollment in a Phase 1 trial in March of this year. [Announced enrollment 3/7/16.] Its design is to treat 12 patients who have had moderate to severe Parkinson's disease for more than four years. It is basically a dose-escalation study; the primary endpoint is safety, and secondary endpoint is clinical response, at 12 months.*

SYMPTOMS OVER CAUSES

Each of the members of our virtual-roundtable panel speaks from multiple perspectives — all of them treat patients, teach students, conduct research, and even run clinical trials. Tackling the first question in the discussion, they deliver useful details about emerging treatments for Parkinson's disease, including why major disease-modifying therapies may not enter the space for many years.

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

LITVAN: One of the most exciting new approaches for potential therapies for Parkinson's disease comes from our better understanding of how the disease may start and progress, which is based on pathologic and clinical studies. It is being proposed that Parkinson's disease may start in the GI system and/or olfactory bulb and following a prion-like progression, spread to the various brain structures. Aggregated, misfolded alpha-synuclein from affected cells acts as a template and converts normally configured alpha-synuclein from normal cells into the misfolded configuration, thereby spreading the disease. If protein misfolding causes disease progression, and aggregated protein leaves the cells when the cells die, then antibodies against the misfolded proteins may be

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ZADIKOFF: We can't really speak about just one mechanism for Parkinson's. We have to speak about mechanisms. There may not be a single target that you can attack to address all the symptoms of the disease, particularly both motor and nonmotor. Different people may not get to the same endpoint at the same time, and so where and when in the pathway should we intervene to have a reasonable shot of adjusting the disease course? From a symptomatic standpoint, there are interesting new approaches to dopamine delivery and nondopaminergic pathways in the pipeline. For disease-modification, the alpha-synuclein approaches are promising. But I hope we learn from the attempts to attack tau in Alzheimer's disease — it may not be as easy as expected to affect the course of Parkinson's by attacking misfolded alpha-synuclein.

HAUSER: Alpha-synuclein represents a huge change in our field during the past five to seven years. In the past, we made animal models for Parkinsonian slowness, stiffness, and tremor by killing dopamine neurons with various toxins and testing various agents to see whether they reduced symptoms or limited dopamine neuron loss. But people don't just get exposed to a dopamine neuron toxin and develop Parkinson's disease. It is a slowly progressive degenerative disorder.

Lewy bodies, large clumps of protein that occur in essentially all Parkinson's disease patients, are packed with alpha-synuclein. When we investigated fetal cell transplants as a potential Parkinson's therapy, two of our patients passed away about 14 years after transplant, and we saw the disease pathology had spread to the transplanted fetal dopamine cells; some of the transplanted cells had developed Lewy bodies. That got people thinking about Parkinson's disease traveling from neuron to neuron. Investigators also observed what appeared to be alpha-synuclein pathology starting at the bottom of the brain and spreading slowly up toward the top. Today we have gene-based animal models that look a lot like Parkinson's disease, so now agents are tested in conditions more similar to what happens in the disease.

But there is a lot of skepticism along with the optimism because we've been burned time and time again with agents that looked good preclinically and then failed in clinical trials. The lack of appropriate clinical biomarkers may be one reason for that. It is also frustrating we are still no closer to addressing a host of nonmotor symptoms and motor symptoms, including cognition, balance, gait, and speech in a Parkinson's-specific manner. In late stages of the disease, those symptoms are what most impact quality of life.

EARLY TO SEE, EARLY TO TREAT?

In Part One of this series, KOLs in the Alzheimer's field stressed the need for early-stage diagnosis and treatment with amyloid-plaque blockers. But, because disease-modifying therapies for Parkinson's lie much further in the

CYNAPSUS

In Phase 3 with an innovative sublingual delivery strip to improve tolerability and duration of a well-known bridging drug for patients in levodopa "off" periods

Anthony Giovinazzo, President & CEO: *Our novel and innovative approach is the sublingual delivery method we discovered and developed as opposed to a novel molecular mechanism of action. Apomorphine is the only approved drug in the U.S., Europe, Japan, Australia, and several other countries to treat "off" episodes in Parkinson's disease — the often long hours between when one levodopa dose wears off and the next one takes effect, when muscle rigidity sets in and other symptoms can resurge. For an idea of the seriousness of this aspect of the disease, I would note that a recent survey of 3,000 patients found that 90 percent suffer off episodes, 65 percent suffer at least 2 hours off daily, and 22 percent experience over 4 daily hours of off time, with some patients experiencing up to 6 hours total per day. It is not a narcotic or a scheduled compound, but a unique small molecule of the dopamine agonist class. Apomorphine is currently only available as a subcutaneous injection, which is inconvenient and uncomfortable because it is highly acidic. Our invention is a sublingual thin film strip, like a breath strip. Under the tongue, it dissolves in a few minutes and also neutralizes the acidity so the free-base drug can travel quickly through the mucosa into the bloodstream. It delivers the same amount of drug as the injection but doubles the duration to 1 to 2 hours. In 2014, we completed a Phase 2 study which demonstrated that our method of delivering the drug apomorphine on a sublingual film strip converts patients from off to fully on, rapidly, consistently, and reliably. We initiated the pivotal Phase 3 efficacy program in June 2015 and the Phase 3 safety study in September 2015.*

AMARANTUS

In Phase 2 with Eltoprazine for treating levadopa-induced dyskinesia; preparing for Phase 1 with MANF (mesencephalic-astrocyte-derived neurotrophic factor), for protecting dopaminergic neurons (and retinal cells) from misfolding and death

Gerald E. Commissiong, President & CEO: *We licensed in Eltoprazine, which was originally in Solvay's pipeline for aggression, but we believe it has great promise for dyskinesia induced in Parkinson's patients by levodopa therapy. Dyskinesia is a huge unmet need in the symptomatic side of the Parkinson's space. On the disease-modifying side, in preparation for Phase 1, our neurotrophic factor, MANF, will be several individual products with different dosing regimens and delivery mechanisms, but all around the same fundamental biology. The general mechanism of cell-stress protection has a lot of value because the underlying cause of cell stress might be different between an animal model than what's actually going on in the human body, but if this growth factor basically helps cells through stress, regardless of what that stress is, then we can still see a functional outcome that may translate from animals to humans. Parkinson's affects a discrete area of the brain, and the diagnosis is basically a response to drug. It is becoming increasingly simpler to target a specific brain area, and you can get a better sense of the drug's effects and benefits.*

future, our Part Two panel takes a more reserved view.

Is there a need for development of ways to diagnose and treat Parkinson's patients as early as possible in the disease course, before serious symptoms appear?

ZADIKOFF: Right now, early detection is actually unnecessary outside of research because, even if we detect Parkinson's early, we cannot treat it any differently. But at some point, the ability to identify this disease early will be necessary in practice, assuming we can learn to address its causes and have a means of disease modification

LITVAN: We need to find biomarkers that could help us diagnose patients at earlier stages, but we now have recently developed diagnostic criteria for prodromal Parkinson's disease based on age, potential risk factors, and symptoms. The criteria need to be validated, so they can be used to recruit patients at early stages in future therapeutic trials. We may be able to eventually include patients at earlier, preclinical stages when they have genetic markers and imaging with PET or DAT scans showing dopaminergic deficits. It will be ideal to include patients at preclinical stages and prevent progression to prodromal and symptomatic Parkinson's disease.

HAUSER: One thing Parkinson's shares with Alzheimer's disease — by the time physical symptoms appear, 90 percent of patients have decreased sense of smell. Screening tests incorporating smell might be a good way to identify individuals who should receive further testing for Alzheimer's and Parkinson's and potentially receive treatment to slow or stop either disease. The other tool we have is the DAT scan to discern whether patients have lost dopaminergic neurons. A DAT scan can also help differentiate between Parkinson's disease and other movement disorders, such as essential tremor. Identification of individuals with premotor Parkinson's disease will become critical once we have a proven disease-modifying therapy.

COMBINE TO CONQUER

As with Alzheimer's and complex diseases in other areas such as AIDS and cancer, the multiple mechanisms involved in Parkinson's will probably demand combination therapies, presenting similar challenges; our panel agrees.

How likely is it that some future drug therapies, each one hitting a different target, will prove complementary if used in combinations? Could combinations of new drugs pose medical, regulatory, or economic issues for treatment of Parkinson's?

ZADIKOFF: There are multiple pathways for the cascading effects of Parkinson's, and different individuals may go down different pathways or the same pathways in different orders, even though they all merge into one in the end. Maybe for one individual, we only have to attack a single pathway to prevent the disease from progressing to that final common end.

M3 BIOTECHNOLOGY

Coming out of preclinicals with high confidence in a disease-modifying small molecule mimetic of a neurotrophic factor to regenerate neurons in patients with Parkinson's and other neurodegenerative diseases

Leen Kawas, Cofounder, CEO & President: *Our technology is noninvasive – it will be an oral pill that passes the blood-brain barrier, and what it will do regionally is regenerate brain cells for neurodegenerative diseases. The ultimate outcome of those diseases is the death of neuron cells and the loss of the connections. At least in animal models, our compound recreates the lost connections by regenerating the brain cells, as well as improving memory, cognition, and ability to learn. We have done all of the preclinical work to support these claims.*

Many studies looking at the brains of Parkinson's and Alzheimer's patients postmortem have seen huge similarities. There is an overlap between the two diseases. Both kinds of patients at the end stages have cognition decline and marked motor dysfunctions, so the two diseases show similar clinical and pathological phenotypes. They are both degenerative diseases, sharing the same process of degeneration. We are working on a true disease-modifying treatment, and we expect our drug to help any kind of degeneration because it reverses the degenerative process.

Our drug is a small molecule and very inexpensive to manufacture, so it will be an affordable therapy, and we don't see a reimbursement issue. Our plans for a clinical trial have been supported by the FDA. In a novel clinical trial design, we're looking at patients, stratification, enrichment, and using a novel biomarker to detect an effective dosing for our drug by measuring function of the targeted brain regions.

But maybe once the disease is in motion, we have to attack multiple pathways all at once. For example, not all of the nonmotor symptoms of Parkinson's are caused by dopamine, so it seems naïve to think addressing only that pathway will resolve all problems.

LITVAN: There are many ways to think about how we might stabilize abnormal proteins or decrease their production or aggregation. Perhaps we will end up having therapies in the future like those in cancer, using more than one mechanism to slow or stop disease progression. There are several mechanisms proposed. Our study, STEADY-PD, is testing whether isradapine can slow disease progression by blocking specific calcium channels in very early Parkinson's patients. SURE-PD is studying if inosine can do the same by increasing uric acid levels. If these studies are positive, why not combine the two medicines? The idea that we could combine different therapeutic approaches using various mechanisms in the near future is encouraging, but it will be challenging to determine the synergistic effect of combining these different approaches. As there have been so many therapeutic failures, we must be sure that each new drug can slow disease progression on its own before we combine the various successful drugs. There are also a lot of needs in the Parkinson's area for which drug development needs to happen, such as cognitive deficits or other nonmotor symptoms where only recently therapeutic approaches have been attempted but beneficial drugs are still lacking.

HAUSER: We are still far enough away from having disease-modifying treatments that it is difficult to predict how our health systems will handle combinations of them. We already use drug combinations to manage Parkinson's symptoms, and they do present challenges in individual patient care, regulation, clinical trials, and reimbursement. Some payers these days refuse to pay for commonly used medications such as trihexyphenidyl, a standard drug for tremor. We are getting more and more denials from payers for approved medications, and it takes a lot of time and effort by doctors and staff to win payer approval. When we have a drug that slows disease progression, I believe third-party payers will be forced to pay for it. But it is up to us to provide convincing evidence that it is in fact disease-modifying.

DOWN TO BUSINESS

Better clinical trial design, regulatory guidance, and collaboration with academic researchers top the panelists' wish list for industry's role in the Parkinson's space.

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

HAUSER: Some companies have been shy about Parkinson's disease because of the uncertainty in the clinical and regulatory pathways for developing disease-modifying therapies. Everybody knows the pathway for getting a symptomatic medication approved. But what would it take to get a medication approved for slowing disease progression? No one knows the answer, and as an expert community, we don't really have a consensus on how to sufficiently demonstrate that a medication slows progression.

Before Parkinson's disease patients start symptomatic therapy, you can monitor clinical signs and symptoms as an index of disease severity. But patients can only go a year or so after diagnosis until they require symptomatic therapy. When symptomatic therapy is introduced, clinical status no longer reflects the underlying disease state. If your putative disease-modifying medication also has a symptomatic effect, you will get a false-positive result. This was the case for the first major trial attempting to show disease modification, DATATOP (Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's disease), which tested selegiline and tocopherol as potential disease-modifying agents. No benefit was seen for tocopherol. However, patients randomized to selegiline went a significantly longer time before they reached a level of disability that required treatment with levodopa. This was initially interpreted as an indication of disease slowing, but we know now that selegiline has a small effect in improving disease symptoms, so the study did not allow a reliable evaluation of disease progression.

One option is to perform disease-modifying studies in early, yet-to-be-treated patients, but then you are unsure if an agent will really delay the important long-term issues such as balance and cognitive decline that are only seen later. Another option is to identify individuals with the disease before motor symptoms appear with the use of olfaction

NEUROPHAGE

Going into Phase 1 to prove its GAIM (general amyloid interaction motif) has universal action against misfolded proteins, including alpha-synuclein in Parkinson's

Richard Fisher, Ph.D., Chief Scientific Officer: *Our lead disease-modifying compound uses GAIM to universally recognize and destroy misfolded proteins, including alpha-synuclein, as they assemble. A substantial chunk of Alzheimer's patients have Parkinson's pathology, and Parkinson's patients have Alzheimer's pathology. These diseases are characterized by multiple misfolded proteins, and one of the exciting aspects of our approach is we can target multiple misfolded proteins simultaneously. Our approach reduced multiple misfolded proteins in mice models; now we want to see whether it does the same in humans. In our Phase 1 trial, we will dose patients for six months, then image to measure two very consistent, well-researched biomarkers, amyloid and tau, to detect any reduction. If the trial is successful, we have proof the mechanism works, and it opens up a lot of possible indications.*

screening and DAT scans, and then determine if it's possible to delay the onset of classic motor features. Again, the ultimate long-term benefit would remain undetermined from such a study, and it is not clear if we can identify sufficient numbers of such individuals. Another option would be to start studying patients three to five years following diagnosis and monitor them clinically for about five years, possibly in combination with quantitative imaging. We have yet to determine the best design for these trials. At this point, we probably will need a combination of an early and a late study to convincingly demonstrate any disease-modifying benefit. This also explains why there is so much biomarker research under way.

ZADIKOFF: I see academic-industry interaction as a creative polarity. Academic and basic researchers know companies can see the theoretical, mechanistic aspect of drug discovery and development, but we understand companies may test drug candidates empirically at the same time. Empirical action may be necessary when we don't have all the data, biomarkers, and other tools to measure or define the mechanisms. Still, it is very expensive to go at a challenge like Parkinson's without good science and ways to measure outcomes accurately. Ultimately, mechanistic understanding and biomarkers will be extremely critical to the success of clinical trials in this field.

Closer collaboration between industry and academics would also be helpful, considering all of the mechanisms and approaches now under discussion. Getting industry and academic researchers and leaders literally to sit together around a big table — I don't know if that is feasible, but it would certainly help bring things forward. Typical interaction, mainly at conferences, is too random.

LITVAN: One way industry can promote progress in Parkinson's treatment is to better educate the patients and the general population, so people understand early on when they are having problems that are not normal. If we really want to get new treatments to patients at early stages, we need to diagnose them early. So patients need to recognize and report their first symptoms to their primary physicians, who need to know when to suspect Parkinson's and refer patients to movement disorder specialists. Education is important because we can improve the quality of life of Parkinson's patients by treating their symptoms, but education will be even more important once we have treatments that could slow disease progression. Unfortunately, most newly diagnosed Parkinson's patients have misconceptions about the disease and may see the diagnosis as a death sentence when it is not. In addition to pharmacologic approaches, there are multiple other therapies that can benefit patients with Parkinson's disease.

HAUSER: We need patients to get involved in clinical trials. Everybody wants better treatments, but we all have to do our parts. Besides physicians, investigators, pharmaceutical companies, and regulators, patients have to do their share, too. It would be very helpful, maybe across all fields and all diseases, if on TV every night we saw the message, "Get involved in clinical trials. This is the way we cure diseases."

LITVAN: There are many challenges to Parkinson's drug development, especially for disease-modifying therapies. The scientific challenges include further increasing our understanding of the true mechanisms for aggregation of key proteins in the brain, how the disease spreads, and which disease mechanisms we truly need to target. I believe we're getting there, and we're tackling all the different aspects of the disease in some way. So there has been some advancement, and I hope we can capitalize on all that progress and quickly move the new drugs through clinical trials and into the market.

CORE PARKINSON'S TREATMENT — BENEFITS WITH RISKS

At the center of the Parkinson's armamentarium for patients with motor symptoms is the levodopa/carbidopa combination (Sinemet). Levodopa converts to dopamine in the brain to augment the dopamine production curtailed by the progressive death of dopaminergic neurons; carbidopa does not cross the blood-brain barrier but prevents harmful conversion of levodopa to dopamine outside the brain. Still, levodopa maintenance poses a complex set of problems virtually unique and ever-changing in every patient, and much of the drug development in the Parkinson's space revolves around ways to ameliorate those challenges. Advanced patients suffer frequent "off" periods after one levodopa dose wears off and before another takes effect. Parkinson's patients may also experience strong physical, physiological, and psychological side effects from the drug itself.

One of the key opinion leaders on our virtual roundtable panel, **Dr. Robert Hauser, director, Parkinson's disease and movement disorders at the University of South Florida**, gives a practitioner's account of levodopa maintenance:

The most effective medication for Parkinson's disease with the fewest side effects, in use since the late 1960s, has been levodopa in combination with carbidopa, sold under various brand names, including Sinemet, and in generic forms. Sinemet only really lasts about 2 1/2 hours in the blood, but in early Parkinson's disease, when it reaches remaining dopaminergic neurons, it is converted to dopamine, and importantly, stored and then released over time. So neurologists commonly give it on a three-times-a-day schedule, and patients' slowness and stiffness are much improved throughout the day.

Tremor response to levodopa is a wild card. Tremor may or may not respond to dopamine medication, so that is an unmet need. It would be really nice to have good treatments for Parkinson's tremor.

As time goes by and people lose more dopaminergic neurons, that dopamine storage and release capacity is diminished. Levodopa may last about 4 hours and then wear off, and slowness and stiffness returns. Then we can move the levodopa doses closer together, which works pretty well for a time, but the levodopa effect keeps shortening, and ultimately, it reflects what's happening in the blood. It may take 40 minutes for the medication to have an effect, and the benefit may last about 2 1/2 hours, then wear off abruptly.

We can then add symptomatic medications such as the MAO-B [monoamine oxidase B] inhibitors, rasagiline (Azilect), and selegiline (Eldepryl, Zelapar), or dopamine agonists (such as ropninirole [Requip], pramipexole [Mirapex], or rotigotine [Neupro patch]) or COMT [catechol-O-methyl transferase] inhibitors, entacapone (Comtan) or tolcapone (Tasmar). Up to about four levodopa doses per day, plus an MAO-B inhibitor and maybe one other medication works reasonably well, but after that, it gets hard to take more medications more frequently.

One long-acting carbidopa/levodopa, Rytary from Impax Specialty Pharma, came out earlier this year, and it does last longer than the immediate-release form, so it helps some patients. But many still find they need to take Rytary up to five times a day, so we need to do better. Other long-acting levodopa preparations are in development, including Intec Pharmaceuticals' "accordion pill" – carbidopa/levodopa on a little film that is folded up like an accordion and put in a dissolving tablet. The product is being evaluated as a possible twice-a-day or a three-times-a-day levodopa.

There are two late-stage "bridging therapy" candidates for off periods: inhaled levodopa and sublingual apomorphine, a dopamine agonist. With the inhaled product, the levodopa goes into the lung, is absorbed into the bloodstream, and goes directly to the brain. Phase 2 data suggests the medication starts working in about 15 minutes and may last for about 90 minutes. The sublingual apomorphine could be used in place of the old injectable form, as the injectable form may be uncomfortable for some patients. Cynapsus has the sublingual product in early Phase 2, and it appears to take effect in about 15 minutes and to last about 90 minutes.

The newest levodopa product, already on the market, is a carbidopa-levodopa enteral suspension (CLES, Duopa) pump that moves the medication through the abdominal cavity, through the stomach, and down into the small intestine where it is absorbed. It is highly effective because it can deliver levodopa in a continuous fashion and maintains the response quite well. But it is invasive, and it is a mechanical device, so there is management involved, and you have to carry the pump around. Another promising product a little further back in development is the NeuroDerm pump patch, which delivers levodopa subcutaneously.

It would also be helpful to have a good medication for dyskinesia (impaired voluntary movement). There are two companies that are developing long-acting amantadine formulations. Amantadine (Symmetrel) is available currently in a standard or immediate-release form, and it's moderately effective for dyskinesia, but can induce confusion or hallucinations, especially in older individuals and those with cognitive deficits. The developers hope a long-acting formulation might avoid some of the peaks of pharmacokinetic activity and thus be better tolerated, but both companies are testing their formulations against placebo rather than standard amantadine, so they won't really have comparative data. We still have an unmet need for better antidyskinesia medications that would allow us to use levodopa more liberally and prevent one of its worst long-term complications.

Takeda CEO Mandate
Sets Off A Nano Reaction

LOUIS GARGUILO Chief Editor, Outsourced Pharma @louis_garguilo

When recently promoted Takeda CEO Christophe Weber announced in the spring of 2015 that his company was determined to become a global leader in gastroenterology (GI), John Puisis, just a few miles from Takeda's offices in Deerfield, IL, straightened up in his chair. As CEO of Cour Pharmaceutical Development Company, Inc., Puisis had already entered discussions with some pharma companies about Cour's nanotechnology platform aimed at a GI-related disease.

"It was a clear mandate from one of pharma's newest CEOs," recalls Puisis. He had just returned from an international conference in Prague, where his company presented clinical data on a model targeting currently incurable celiac disease. About a month later, in May, Takeda let Cour know they, too, were indeed interested in the technology. Senior-level discussions with Takeda quickly took precedence over the other pharma negotiations and led to "a very rigorous process of due diligence." That culminated in December with an announcement of the industry's newest pharma-nanotech partnership.

"You know what was interesting?" asks Puisis. "Their immunologists and particle experts just got what we were doing with our nanotechnology. There wasn't much of a learning curve." In fact, Takeda is one of a growing list of pharmaceutical companies more actively pursuing the application of nanotech to biology to develop nanomedicine for targeted diseases.

Vincent Ling, senior director for Takeda New Frontier Science (NFS), a group also formed as a part of CEO Weber's strategy to enter new therapeutic areas and pursue new scientific approaches, is tasked with finding technologies to enhance the company's innovation in drug discovery and development. Ling says, "While nanotech as applied to medicine is relatively new, and much of it still in the science mode, it's going to be fascinating to see where it leads us. I have a feeling that we will end up with applications we haven't dreamed of yet."

DREAMING BIG FOR CELIAC DISEASE PATIENTS

Actually, Ling's NFS didn't introduce Takeda to Cour ... for a very good reason. NFS is focused on emerging opportunities, but the Cour nano-application to celiac disease had already advanced sufficiently and, as such, was on the radar screen of Takeda's GI group. Of course it didn't hurt that Takeda has been a leader in micro-particle delivery of proteins, starting some 20 years ago with the blockbuster drug Lupron Depot. Puisis puts it this way: "The translation of the Cour technology to a product is real. This is not the kind of collaboration where we've been working with Takeda for a dozen years trying to come up with a product. We have a realistic, short, game plan. It's about making a product utilizing nanotechnology and getting it to patients."

Cour's technologies reveal the three paths of nano in drug development. The first — and current path — is using nano drug-delivery systems with often highly toxic drugs encapsulated in nanoparticles, or nano "cages." The second path, still somewhat in the future, is nanoparticles actually *becoming* the drug, or at least drug-like. The third path connects the first two and is the one we are steadily heading down, as the science increasingly reveals that

> *"When we talk about nanoparticles, I see such a wide variety of different structures, types of chemicals, and nanotechnology surfaces; it's almost broader than biotech."*
>
> **VINCENT LING**
> Senior Director,
> Takeda New Frontier Science

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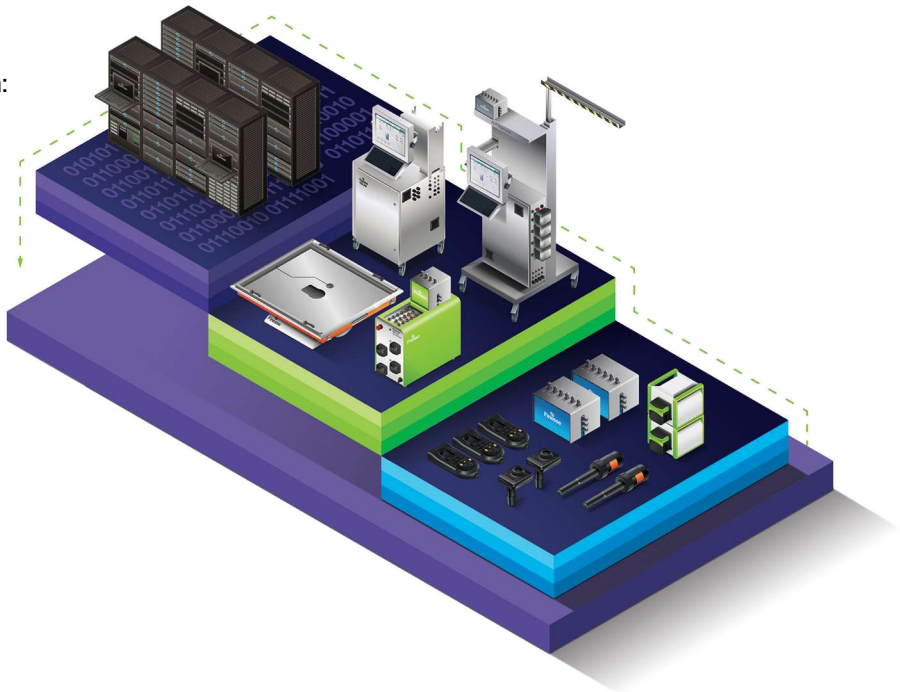

the nanoparticle itself has mechanically programmable *biological* effects in the human body. "I have to always be clear about what I am talking about," says Puisis, "because my scientists say, 'The nanoparticle can be more than a carrier ... it's an agent in and of itself.'"

To fight celiac disease, the Takeda-Cour approach starts with the straightforward use of a nano-carrier housing a protein. The disease is an autoimmune disorder of the small intestine, and it can occur in people of all ages, including infants. It can cause severe pain and discomfort in the digestive tract, chronic constipation and diarrhea, and other symptoms. Most commonly, celiac disease is caused by a reaction to gliadin, a gluten protein found in wheat. And the protein the Takeda-Cour nano-carrier encapsulates? That very same gliadin. But Cour has found "a back door into the immune system," and with it a method to stop the body — specifically our T-cells — from attacking the protein and causing the disease.

In short, a nanoparticle filled with gliadin hitches a ride to the spleen (the "back door") on monocytes circulating in the blood. Once there, the gliadin is released. Instead of attacking the protein there, the T-cells start to recognize it as part of the body. "This reprograms the immune system and the painful inflammatory response, in a very elegant way, and without using any immune suppression," says Puisis.

Pre-nano, and for decades now, the pharma industry has dealt with inflammation and immune responses with immune suppression attempts and particularly cortisol steroids. According to Puisis, for patients with an inflammatory flare-up or an adverse immune reaction, "It's this pretty old technology that usually stuffs and suppresses your immune system. Unfortunately, this comes with a slew of side effects, and in fact it's archaic." Puisis adds, "There's no cure for celiac disease nor good therapies. Doctors simply recommend a gluten-free diet, but that doesn't solve the issues around celiac disease. We're working so nanotechnology can help deliver the first therapeutic remedy for celiac disease patients."

CELL ENCAPSULATION CAPTURES ATTENTION

Takeda's Ling has had nanotechnology in his sights for years. He has a broad background in biotechnology, with experience in genetic engineering, medical biotech, embryonic stem cells, genomic sequencing, gene chips, and checkpoint inhibitors. "But what really changed my life," says Ling, "is work I did on cell encapsulation. It led me to understand it's not all about the drug. The delivery is a major part of the equation."

Ling recognized early that because cell encapsulation could protect us from our own immune systems, we could better utilize the newer science of converting recombinant cells into tiny bioreactors by implanting them directly at the site of a disease. "The question," says Ling, "was how could we best shield these cells from an immune attack? The answer is with transformative surfaces made with new biomaterials. That takes place at the nano scale and with the promise of nanotechnologies for immune evasion." In fact, says Ling, Takeda recently announced it was funding a "biotech" company — Providence, RI-based NsGene, Inc. — to continue to develop cell bioreactors with nano-surfaces allowing for drug elution and targeting Parkinson's disease.

The New Frontier Science group is headquartered in Takeda's offices in Cambridge, MA. Including Ling, it has a core of 10 entrepreneurial scientists dispersed around the world, particularly in the U.S. and Japan. I asked Ling if, with his company's background in micro-particles and the new relationships with Cour and NsGene, he believes Takeda is developing a specific nano-strategy. "I can say we're interested in any technology platforms that could mutually benefit our pipeline of chemicals in development. If a nano-application would be beneficial, we won't hesitate to take a look. However, at this point, I don't think we'd put nanotechnologies first and then try to fit a drug around that. Takeda is a drug discovery company first, and it's the molecule that drives the process." Having said that, though, he adds, "I think nanotechnologies will be very good for disease areas such as oncology — also a Takeda disease focus — where the nanoparticle structures can shield the chemotherapy agent from being too toxic and delivering it to a more precise location."

NANO IN TAKEDA'S DNA?

Takeda, although a global company, might also benefit from its Japanese roots when it comes to nanotechnology. Having spent over 30 years closely following technologies in Japan, I like many others, know the Japanese have advanced nanotechnology as much as any other country. For example, Ling tells me about a "hot-selling" cosmetic skin product (described as anti-aging care for the skin) in Japan called AstaLift from FUJIFILM Corp. "It's based on anti-oxidant nanoparticles. It's a semisolid gel that looks like a jelly, but is really a container of nanoparticles. I was blown away that even the Japanese cosmetic industry is using nanoparticles."

Is there nanotech in Takeda's DNA? Ling smiles at hearing the question, and says he believes, for example, Takeda's new Lupron Depot (six-month) formulation of microparticles (which are precursors to nanoparticles) is a step ahead of many others without these types of products.

So, does Ling foresee Takeda with a future nanotechnology division? He replies that it may not be so much about internalizing nanotechnology as letting it develop externally. "Takeda is devoting itself to the idea of spinning off companies based on new technologies, including those discovered outside. As a pharma designed for drug discovery, at times it's best to fund an alternate modality, so it can grow externally, before integrating it into our pipeline. I think that's a view of nanotechnology we can entertain for the future. When we talk about nanoparticles, I see such a wide variety of different structures, types of chemicals, and nanotechnology surfaces; it's almost broader than biotech."

Perhaps a few more CEOs of nanotechnology companies have just straightened up in their chairs. L

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Is Kyle Bass' IPR Crusade Reshaping Pharma Business?

ANNA ROSE WELCH Editor, Biosimilar Development @AnnaRoseWelch

Last February, Hayman Capital Management hedge fund director Kyle Bass took the pharma industry by surprise when he launched a newer form of patent challenge against Acorda Therapeutics. The Inter Partes Review (IPR) process, established in 2012 as part of the America Invents Act (AIA), was originally earmarked by Congress as a method for competitors or other biotech companies to clear bad patents out of the system.

It boasted a more-efficient, cheaper process for resolving patent challenges. However, according to two experts from the Biotechnology Innovation Organization (BIO), Kyle Bass is considered an atypical petitioner, as his efforts go against the Act's intentions for the IPR. While Bass' proclaimed goal has been to eliminate patents to clear the way for cheaper generic drugs, he also has used the IPR as a method to short-sell a company's stock for his own financial gain. Now, a year after launching his first IPR against Acorda's Ampyra, Bass has launched upwards of 35 IPRs on high-profile pharma and biopharma companies. Only seven of the 16 reviewed IPRs have been passed to trial, where final rulings are still pending. However, Bass does not show signs of quitting.

In his latest move, profiled by the *Financial Times*, Bass returned a majority of the $700 million he collected to fund his campaign. He says these funds were earmarked for short-selling pharma stocks. While returning $700 million to investors could appear a sign of defeat, Bass still has in his possession roughly $80 million, which he intends to use to continue his IPR crusade. "We have all the capital we need to pursue everything to its logical conclusion at the patent office," Bass said. "We are not stopping."

ARE BASS' IPRs STILL A CONCERN FOR PHARMA IN 2016?

According to BIO, Bass' efforts are just as alarming today as they were when they started — if not more so. As Tom DiLenge, BIO's general counsel and head of public policy, argues, Bass' efforts are a perversion of the system. Bass' attempts at eliminating bad patents for generics have also been used to bring financial gains for the hedge fund mastermind. How successful he's been financially is still unclear. DiLenge says, "There has been no transparency around what he is shorting, how much he is shorting, and when he's selling. We don't know all of those details, so it's unclear if he's making money. One would expect that he wouldn't continue to do this unless he believed it was financially advantageous to him."

His strategy is particularly upsetting to BIO and pharma because he does not need to be successful to be a threat. By launching these IPRs in the first place, Bass creates uncertainty over the value of the stocks, which ultimately affects a company's stock price. "We theorize that if someone was executing a short option, all you have to do is create uncertainty as to the value of the stock, and it will likely drop," says DiLenge.

THE IMPACT OF IPRs ON DRUG DEVELOPMENT

IPRs have been hailed as a time- and resource-saving procedure for patent litigation. But from a drug development standpoint, the procedure serves as a large stumbling block to innovation. According to Hans Sauer, BIO's deputy general counsel for intellectual property, companies faced with Bass' and similar entities' IPR challenges have to spend time and resources dealing with these challenges as opposed to creating cures for diseases.

For instance, a large company would need to reallocate resources and spend countless hours reviewing its patent portfolios. "Not only do they have to think about what that patent portfolio would look like in court under some kind of Hatch-Waxman type challenge after four or five years of market exclusivity, but now they need to worry about those patents being challenged at any time, either before development or immediately after approval of that product," says DiLenge. For smaller companies, these petitions can impact conversations with partner companies that might be tied to universities or receive investments from private equity.

"Adding uncertainty to IP rights can be

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highly leveraged in a business environment, where there's already a lot of other uncertainty," says Sauer. Especially in drug development, there are already many uncertainties (e.g., funding, competitors) when it comes to ushering experimental treatments to market. "When you stack all of these uncertainties on top of the likelihood of losing your patents in a new proceeding, the whole thing can come to a tipping point," Sauer argues.

HOW IS PHARMA APPROACHING IPRs TODAY?

Now that a year has passed, companies that have been faced with Bass' petitions are arguably better prepared than they were at the start of his rise to IPR fame. According to Sauer, companies have become better versed in conveying potential consequences to investors and stakeholders. Similarly, investors are becoming more familiar with this process and, therefore, are more skilled at evaluating the impact of these challenges. "At the same time, we are seeing the same high level of concern over where this is going to go, because it is not stopping," says Sauer.

In fact, Bass' efforts have inspired other organizations to launch IPRs against innovator patents. According to Sauer, an increasing number of BIO members have come forth voicing concerns. Sauer goes on to list several of these threatening organizations by name, including Neptune Generics, Complex Innovation, and Lower Drug Prices for Consumers. "When you look into these organizations, you see that they are, for the most part, backed by hedge funds or other financial ventures," he says.

Despite the fact that Bass' questionable use of the IPR process is becoming popular, there has not been any action to stop him or similar parties. The issue lies with the way IPRs are being reviewed by the Patent Trial and Appeal Board (PTAB), which has been delegated authority for handling IPRs by the director of the U.S. Patent & Trademark Office (PTO). The PTO has the power to put its foot down on Bass' challenges. However, the PTAB has been hesitant to take a stand against these proceedings, potentially because of the PTAB's sole focus on the technical merits of the IPR rather than broader policy implications of allowing abusive IPR challenges.

For example, the experts point to a case in which one BIO member company succeeded in upholding a patent in the district court. However, when brought before the PTAB, this same company saw the patent struck down on almost identical grounds. The PTO supported this decision by saying that it has "a lower burden of proof and a different standard of evidence, with no presumption of validity."

However, as DiLenge emphasizes, when it comes to Bass' seemingly endless pattern of petitioning, it's the PTO's responsibility to protect the integrity of the patent system. "This behavior is going to keep going until the PTO stops it," says DiLenge. "The PTO has the power to do it, and BIO keeps encouraging them to do that. But I think Congress is going to need to step in and give clearer direction to the PTO on how to stand up against this type of abusive behavior."

WHAT IMPACT WILL IPRs HAVE ON THE DRUG IP REGULATORY LANDSCAPE?

Pharma IPRs are launched against drug patents protecting chemical structure, formulations, methods of dosing or administration, or drug combinations. However, when reviewing IPR challenges, Sauer and DiLenge say there are few commonalities that jump out between the patents that have been passed on for a final PTAB decision. "It's not that one specific type of drug patent is challenged or instituted more often than the other. IPRs seem to cover and run the gamut," Sauer states.

But the rise of IPRs against pharma patents also signals a change in the balance of the court system. The PTAB is becoming the preferred method of getting patents invalidated in many different industries, not just the biotech realm. (The IPR process has been termed the "patent-killer," after all.) As previously mentioned, the PTAB can trump a decision by the district court. Patents that have been upheld in the district court can be found invalid by the PTAB, and Sauer claims that BIO has been seeing the PTAB's decisions taking primacy over the district courts more frequently. "When the patent office strikes down these patents, that always trumps whatever the district court decides," says Sauer. The court system, not the PTO, used to be the prime driver of patent law development in the U.S. "This really does change the balance of power," Sauer explains.

The prevalence of the IPR process could also stifle pharma's willingness to innovate. Drug development becomes

"I think Congress is going to need to step in and give clearer direction to the PTO on how to stand up against this type of abusive behavior."

TOM DILENGE
General Counsel And Head Of Public Policy, BIO

more complex every year, and patent litigation is evolving into a bigger concern for both large and small drug companies. If the increasing frequency of Bass-like IPR petitions is left unchallenged by the PTAB, pharma could become more risk-averse over time. This would lead the industry down a dangerous path, as drug development could become dictated by the strength of the patent rather than medical need. "Companies over time will attach more importance to IP risks. In turn, they will be more motivated to develop drugs that have the strongest substance patents, rather than the drugs that offer the most value to patients," Sauer warns.

Similarly, DiLenge stresses the negative impact that the IPR process — as it's being handled today — could have on society. There are already a large number of drugs shelved because of patent protection uncertainty. "We don't want to do anything that increases this number," says DiLenge. "We want to make sure that we are developing the drugs that offer the most value to society."

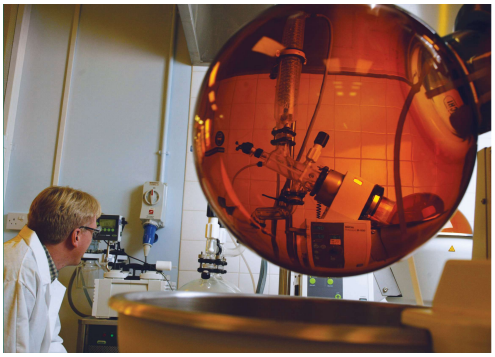
> *"Adding uncertainty to IP rights can be highly leveraged in a business environment, where there's already a lot of other uncertainty."*
>
> **HANS SAUER**
> Deputy General Counsel For IP, BIO

In order to ensure that business remains focused on this goal, Sauer and DiLenge urge pharma and biotech CEOs to become much more involved in this issue. CEOs need to direct energy toward engaging with Congress and the PTO to emphasize how the IPR process is impacting investments and drug development. As DiLenge says, "Policy makers need to be made aware of how companies' experiences with IPRs are reshaping business. Only CEOs can really do that."

GW Pharmaceuticals Changes Its Focus To Rare Diseases

SUZANNE ELVIDGE Contributing Writer

Building a pharmaceutical company based on cannabis may have seemed like an "out there" idea back in the 1990s, but in 2016, with a listing on NASDAQ and AIM (the London Stock Exchange's international market for smaller growing companies) and a lead drug, Sativex, approved in 28 countries, the idea behind GW Pharmaceuticals now looks pretty mainstream.



This success hasn't stopped the company looking at its model and making some major changes, switching its R&D from larger indications to smaller and more challenging areas within orphan diseases.

Patients have self-medicated with cannabis for many years, using it to relieve pain and help with symptoms of MS, psychiatric disorders (e.g., depression, anxiety), nausea and vomiting (including chemotherapy-induced nausea), glaucoma, diabetes, and wasting caused by cancer and AIDS. As a response to calls in the UK from physicians, patients, and regulators to find a way to make a standardized cannabis pharmaceutical, Dr. Geoffrey Guy and Dr. Brian Whittle formed GW Pharmaceuticals in 1998 to create standardized and testable therapeutics from the plant sources, in a story told in *Life Science Leader* in October of 2007. At that time, GW Pharmaceuticals' focus was on the use of cannabis to relieve spasticity from MS, leading to the development of its first product, Sativex (nabiximols), from a *Cannabis sativa* whole plant extract.

Sativex is an oromucosal spray containing THC (delta-9-tetrahydrocannabinol), cannabidiol (CBD), and a number of other naturally occurring cannabinoids and was the first cannabis-derived prescription product available on the market. Sativex is now available in 15 countries, including the UK, Spain, Italy, and Germany.

A SHIFT FROM PAIN TO ORPHAN INDICATIONS

What is interesting about GW Pharmaceuticals is how it has changed its approach since the 2007 article. Fast-forwarding almost 20 years from 1998 to 2016, research at GW Pharmaceuticals, while still looking into drugs derived from cannabis, is taking a rather different focus. In a step away from large indications like cancer pain, MS, metabolic syndrome, and inflammatory conditions, GW Pharmaceuticals is moving its spotlight to rare and orphan indications, where there are limited or no other treatment options. Working in rare diseases is challenging because of lack of recognized outcome measures, small markets, and for the rarer diseases, difficulties in finding sufficient patients for clinical trials. However, Stephen Schultz, VP of investor relations for GW Pharmaceuticals, is convinced that the company is making the right move.

"These are areas where there are few or no therapeutic drugs approved, so there is a high level of unmet need and a significant demand for new treatments," says Schultz. "Though the population for the marketed drug will be smaller, the clinical studies are likely to be smaller and shorter as well. The regulatory authorities also provide companies with incentives to develop drugs for these small populations, for example Fast Track designation to speed approval and orphan exclusivity to protect the drug from competition after launch."

The initial focus will be on the development of a treatment for Lennox-Gastaut syndrome and Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI). These are both rare and difficult-to-treat forms of childhood-onset epilepsy. Other potential indications

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"Though the population for the marketed drug will be smaller, the clinical studies are likely to be smaller and shorter as well."

STEPHEN SCHULTZ, VP Of Investor Relations, GW Pharmaceuticals

are expected to include tuberous sclerosis complex, a rare genetic condition that causes epilepsy following on from the growth of benign tumors in the brain, and also intractable childhood epilepsy. In this form of childhood epilepsy, the repeated seizures can lead to brain damage, and the disease is very hard to treat successfully.

"The current drugs are not working in rare epilepsy disorders and treatment-resistant epilepsy, so these untreated conditions can lead to significant long-term health challenges that have a major impact on the families and, in many cases, lead to hospitalization. If the use of new drugs can reduce the length of an expensive hospital stay, even if they are higher cost than existing treatments, they should offer value to the payers," says Schultz.

THE EPIDIOLEX STORY

There have been anecdotal reports of cannabis helping people with epilepsy over the last 150 years. In the U.S., where CBD-enriched cannabis oils can be accessed from certain dispensaries, parents have tried to use these to control their children's seizures with varying levels of success. However, these so called "artisanal"' preparations are only available in some states, and the active ingredients are often not as described. According to Schultz, the FDA tested 18 artisanal CBD oils and found that around a third contained no cannabinoids at all, and others contained high levels of THC, which can act as a proconvulsant. Schultz added that the parents of children with treatment-resistant disease were reading papers and publications about the use of GW's CBD in epilepsy.

"We had been working on Epidiolex, a liquid formulation of pure, plant-derived CBD, in preclinical studies and had gained orphan drug designation for the treatment of Dravet syndrome and Lennox-Gastaut syndrome, along with Fast Track designation for Dravet syndrome. The parents of a boy with intractable epilepsy found out that GW Pharmaceuticals was behind the science, and they and their son's physician approached us about getting the drug for the boy, even though it was still in early development. This initial patient led to a compassionate access program and helped us move into clinical trials."

Epidiolex has been made available under expanded access investigational new drug (INDs) applications in patients with Dravet syndrome, Lennox Gastaut syndrome, and 14 other types of severe epilepsy including tuberous sclerosis complex, Aicardi syndrome, and Doose syndrome. The results from the expanded access program, which involves around 450 children and is still ongoing, showed that Epidiolex reduced seizure frequency and was generally well-tolerated.

Epidiolex is also in Phase 3 clinical trials with two safety and efficacy studies in Lennox Gastaut syndrome and two in Dravet syndrome. Initial data is expected in the first quarter of 2016, with a submission for approval planned for both indications in the fourth quarter of 2016.

"The dispensary-based cannabis tinctures, oils, and pills can be highly variable and are not supported by data," says Schultz. "We are dealing with treatment-resistant children who are highly sensitive to changes in their medications, so giving them uncharacterized products can be challenging. While dispensary-based medical cannabis may continue to be used, forms approved by the regulatory authorities should be well-received, as they demonstrate safety and efficacy in controlled clinical environment and meet a true medical need."

EXPANDING THE EPILEPSY PORTFOLIO

GW Pharmaceuticals is developing another epilepsy therapeutic, GWP42006, a formulation of the nonpsychoactive cannabinoid cannabidivarin (CBDV). This was well-tolerated in a Phase 1 trial and is now in a Phase 2 trial with 130 patients who have inadequately controlled focal seizures. CBDV may also have potential in other epilepsy-related conditions.

After signing a memorandum of understanding, GW Pharmaceuticals is working with the government of New South Wales in Australia to carry out research in severe, drug-resistant childhood epilepsy with Epidiolex and GWP42006, including the first Phase 2 trial of GWP42006 worldwide in children, compassionate access for Epidiolex in Lennox Gastaut and Dravet syndromes, and additional Phase 3 trials and a Phase 4 trial in children with treatment-resistant epilepsy.

Other products for orphan indications in GW Pharmaceuticals' pipeline include GWP42003, an IV therapeutic for neonatal hypoxic ischemic encephalopathy (NHIE) that has a Phase 1 trial expected to begin in the second half of 2016, and a cannabinoid combination of GWP42002 and GWP42003, currently in Phase 2 clinical trials in recurrent glioblastoma multiforme. Clinical trials are also under way in the larger indications of type 2 diabetes (GWP42004) and schizophrenia (GWP42003).

"Our development platform allows us to evaluate cannabinoids rapidly alone or in combination against different therapeutic targets," says Schultz. "There is significant scientific evidence for cannabis-derived drugs for a wide variety of different diseases, and as research advances, I expect to see more opportunities opening up for GW Pharmaceuticals."

CHANGING THE REGULATORS' PERSPECTIVE ON CANNABINOIDS

While an increasing number of states

are legalizing medical cannabis, and others are decriminalizing and even legalizing recreational forms of the drug, the legalization of marijuana is still controversial in the U.S. While GW Pharmaceuticals products in the U.S. have yet to be approved for use, Schultz has seen his company used as an example by the FDA of how cannabinoids should be handled in clinical trials.

"We are still one of only a few pharmaceutical companies working on drugs derived from cannabis. When we started, there was less of a known pathway for cannabinoid-based drugs. Since then, we have become better at creating reproducible and fully characterized pharmaceutical medicines, designing clinical trials, and navigating the regulatory pathways. We have seen the EMA's (European Medicines Agency) and FDA's perspectives on cannabinoids change, and we are confident that we have been part of this evolution. They now have more confidence in the ability of companies to develop therapeutics from botanical sources, creating consistent products that meet or exceed the regulatory authorities' requirements. It's still challenging to test scheduled drugs, and we are bound by specific requirements related to handling, storage, and accounting by the DEA, as is each clinical site and all the physicians involved in the studies," says Schultz. "But it is possible, and it has actually become a core competency of the company, to be able to navigate these regulations."

Sativex, which contains THC, is a Schedule 4 Part 1 drug in the UK, which means that it is a prescription-only medicine (POM) and does not have to be recorded in controlled drug registers. Before April 2014, it was categorized as a Schedule 1 controlled drug, requiring specific reporting and recording requirements. Even though Epidiolex only contains CBD, it is still likely to have restrictions.

"Although GW has been developing cannabis-based medicines longer than any other company in the world, working in cannabis isn't really what makes us different — it just happens to be the area of our focus. What makes us different is that we have a very well-described process, strong regulatory expertise, a world-leading understanding of cannabinoid science, GMP manufacturing expertise, and a proven record to execute clinical trials and secure regulatory approvals. We have evolved a lot over almost 20 years. We started off with large therapeutic areas and have focused down to identifying therapeutic targets in rare diseases with areas of significant unmet need where cannabinoids offer promise. We are expecting results from eight different placebo-controlled clinical trials over the next year. These are exciting times!" concludes Schultz.

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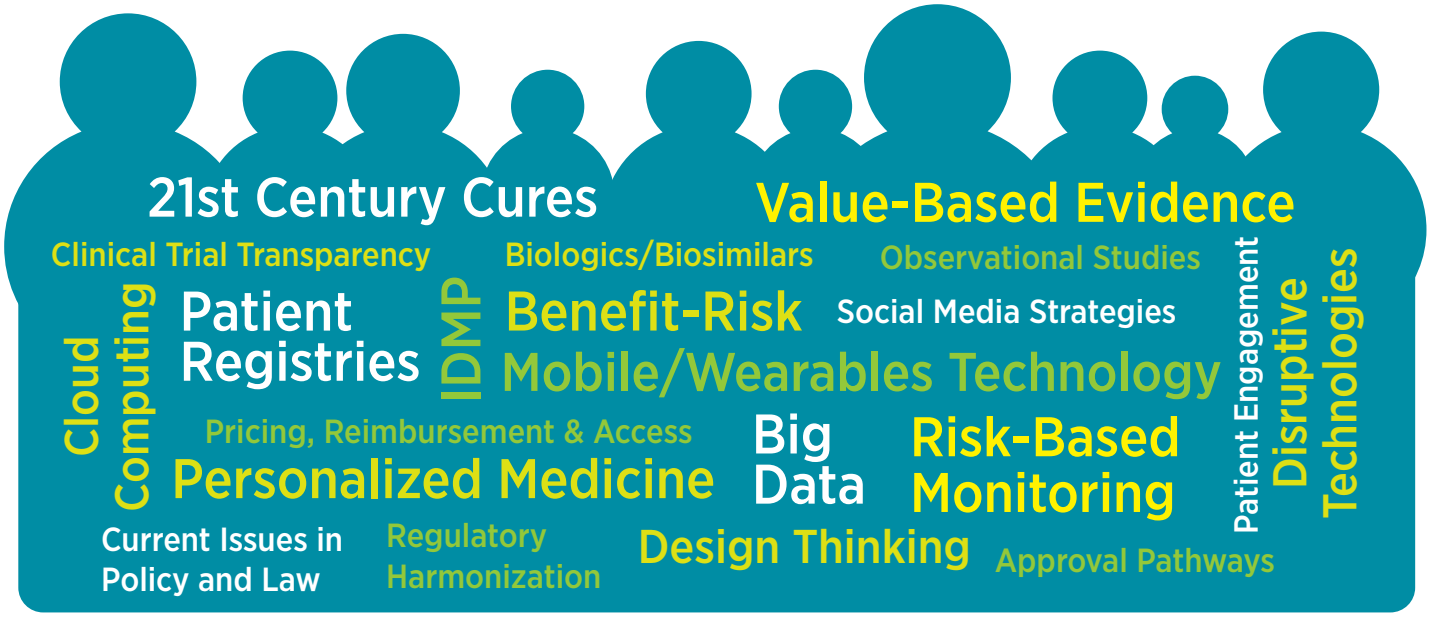

How Acting With Integrity Improves Business Results

CHRIS HITCH, PH.D.

Chris Hitch, Ph.D., is program director of executive development at the University of North Carolina's Kenan-Flagler Business School. He has over 25 years of leadership and management experience.

"Is cutting corners and hoping to not get caught simply the cost of doing business today?" This question came from one of our participants during a strategic leadership program. Simply put, absolutely not! While the news is filled with ethical lapses and corporate scandals, acting ethically and with integrity provides greater profitability to the corporation

WHAT IS INTEGRITY?

In simple terms, integrity is doing the right thing toward direct reports, colleagues, and your various stakeholders, both internally and externally. On the surface, acting with integrity would seem relatively easy — stick to one's values, be honest, and sleep well at night. Few people wake up one morning and decide to go against every value they were taught. The few who do are generally called psychopaths.

ETHICAL LAPSES ARE NOT DUE TO BAD MORAL CHARACTER

In reality, though, acting with integrity is more difficult, especially in organizations where leaders put profit above integrity by cutting little corners here and there. Dr. Alison Fragale and Dr. Michael Christian at University of North Carolina's Kenan-Flagler Business School note that most people think of themselves as moral, ethical people. They found that lapses of integrity may start out small and may seem innocuous, but tend to grow over time — because once started, people tend to continue to rationalize small unethical behaviors, leading them to continue to behave unethically to cover previous lapses.

WHY INTEGRITY PAYS OFF

Lack of integrity can place an organization's future at risk. These costs, however, occur *after* the lack of integrity has gone public. Yet many studies show that organizations with high levels of integrity actually perform better than organizations with low levels. Interestingly, one study found that an organization's proclaimed values were less important than the employee's perceptions of the CEO and senior leaders as trustworthy and ethical. In fact, some proclaimed values like those found in mission statements and other organizational communications may actually impede integrity, particularly if they are at odds with a CEO's and senior leaders' perceived trustworthiness.

HOW YOU CAN REINFORCE INTEGRITY

You can't inoculate people to act with integrity. You can, however, reinforce the tenets of integrity, just like you focus on other key performance indicators. Reinforce the probability of consistent ethical behavior by applying the "safety tips" below from Fragale's and Christian's research. You should also be aware of the psychology of decision making and biases.

HONESTY AND MORAL COURAGE

Honesty means telling the whole truth, even when it is uncomfortable. This is increasingly important when encouraging people to have the moral courage to speak "truth to power."

CONSISTENCY

Ensure your beliefs, words, and actions are consistently aligned with the ethical lens. Periodically meet with your team to analyze recent business decisions through that ethical lens.

VIGILANCE

Quickly address small "everybody does it" types of possible ethical lapses. Small lapses can translate to larger ones.

SELFLESSNESS

Great leaders emphasize "we" with organizational successes while using "I" with issues and problems. They respect and listen to their team at all levels, especially when their employees are speaking up about possible ethical and issues of integrity.

NUDGE

Great leaders at all levels provide "nudges" to help employees consider ethical implications when making business decisions. Help your team recognize and self-correct in possible issues of integrity.

By investing in integrity and ethical conduct, you and your company can reap the financial and nonfinancial rewards, including improved employee loyalty and retention, and more satisfied customers and stakeholders. That's truly ROI (Return on Integrity).

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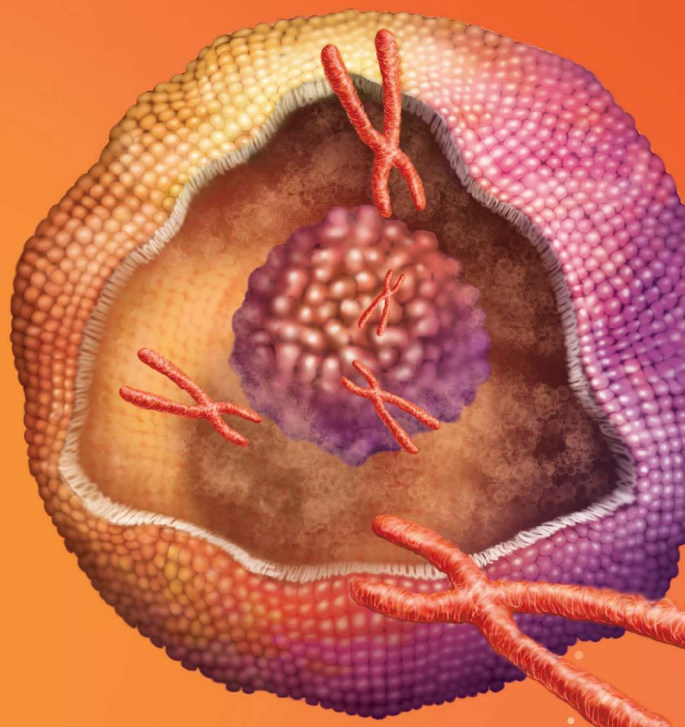

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