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CHRISTOPHE WEBER
President and CEO, Takeda

Supply Chain **22**
How To Achieve Excellence In A Biopharma Supply Chain

Drug Development **26**
Experts Discuss New Opportunities For MS

Clinical Trials **44**
How Agile Therapeutics Got Through A Critical Phase 3 Trial

Capitol Perspectives **10**
CEO Corner **12**
Science & Business **36**
Biopharma **40**

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CONTENTS

Welcome to

Life Science Leader

JUNE 2016 VOL. 8 NO. 6

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6 Editor's Note

8 Editorial Advisory Board / Ask The Board

Columns:

10 Capitol Perspectives

12 CEO Corner

Insights:

36 SCIENCE & BUSINESS
Pursuing Drug Development Against Investors' Advice

40 STARTUPS
Alios BioPharma: From Startup To Big Pharma

44 CLINICAL TRIALS
How Agile Therapeutics Got Through A Critical Phase 3 Trial

50 LEADERSHIP LESSONS
Tackling Transformations In Highly Regulated Industries

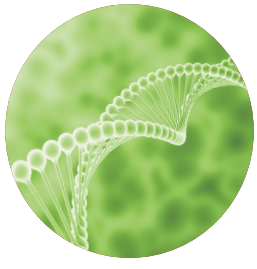
16 Cover Story: TAKEDA

Takeda's president and CEO Shares New Plans For Worldwide Growth

Features:

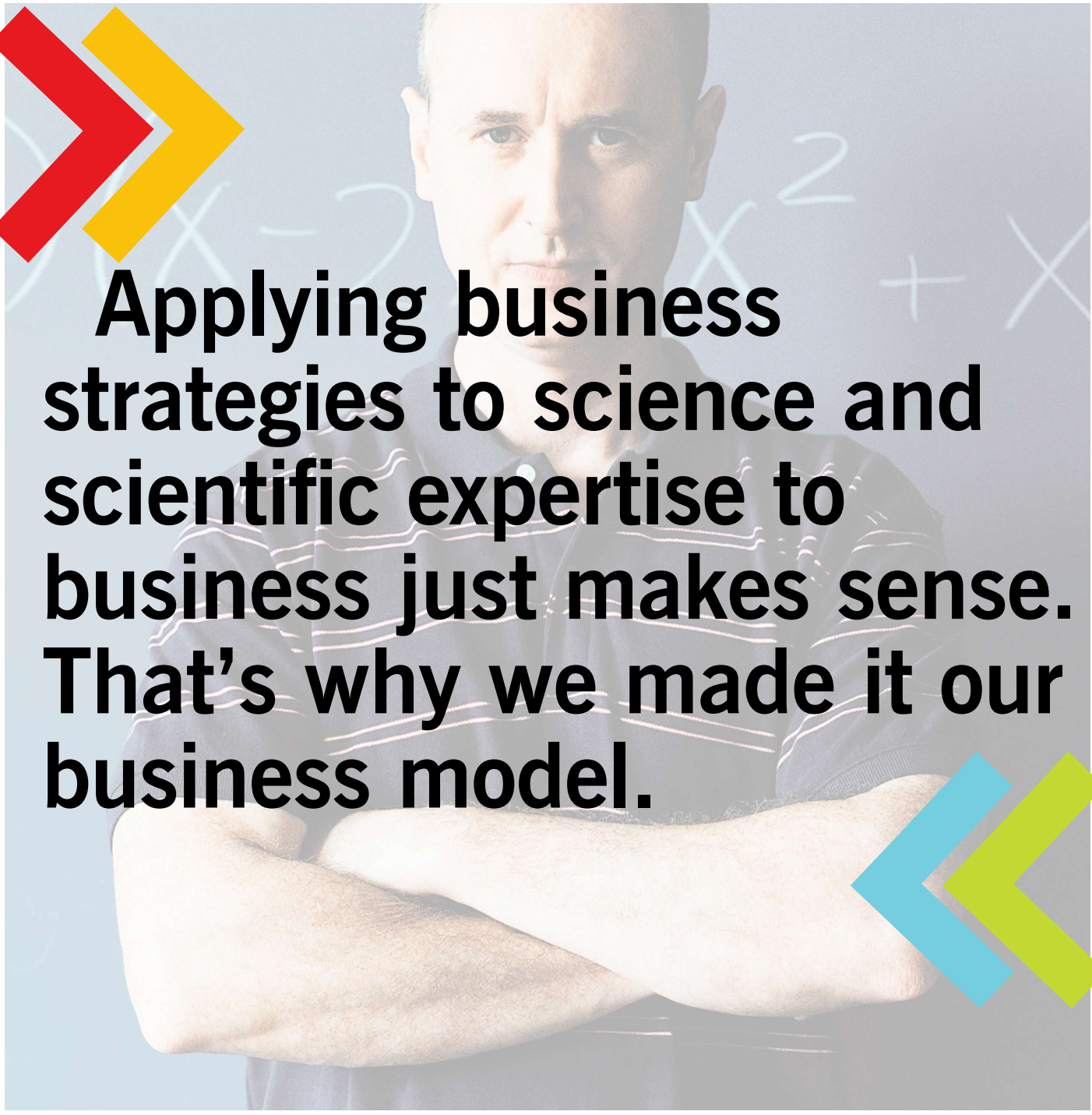
22
How To Achieve Excellence In A Biopharma Supply Chain
Experts give insight into what biopharma companies can do to be better customers and consequently, achieve better supply chain integrity.

26
Growth Opportunities
Part 3 of our Neurodegenerative Diseases series focuses on developing new therapeutics for progressive MS.



CORRECTION: *In our May issue, the article* The Value Of A Dual-Track Process For Raising Capital *had the wrong photo for author Alex Castelli of CohnReznick LLP. This is the photo that should have run.*

LIFE SCIENCE LEADER (ISSN: 21610800) Vol. 8, No. 6 is published monthly by Jameson Publishing, Inc. at Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. Phone (814) 897-9000, Fax (814) 899-5580. Periodical postage paid at Erie, PA 16510 and additional mailing offices. **SUBSCRIPTION RATES** For U.S. based subscribers, $295 for one year. If your mailing address is outside the U.S. the subscription price is $445 for one year. **POSTMASTER:** Send address corrections (Form 3579) to Life Science Leader, Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. **PUBLICATIONS AGREEMENT:** No. 40722524 c/o AIM, 7289 Torbram Road, Mississauga, ON L4T 1G8.



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Who Will Move Biopharma Beyond The Cutting Edge?

ROB WRIGHT Chief Editor

When you think of companies that revolutionized the way business is done, it is important to consider the attributes of their founders. Often they had gained life experience from working in businesses that could best be described as tangential to those they eventually disrupted. As a result, these "outsiders" not only brought different perspectives toward tackling problems in these industries, but their wisdom in doing things differently than in the past resulted in ideas that forever changed the world. For example, Ray Kroc was a traveling food-processing equipment salesman before spawning the fast food industry via the franchising of McDonald's. Apple's founder, Steve Jobs, not only played a significant role in bringing personal computing to the masses, resulting in the obsolescence of the typewriter, but he also helped transform both the music and cellular communications industries. There are countless other examples of outsiders having a transformative impact beyond the industry in which they got their start, and it makes me wonder — who or what, from the periphery, will eventually alter the way biopharma business is presently done?

Though this is a subject I have pondered for a while, it has been more top-of-mind of late as I prepare for one of our industry's biggest annual events — the 2016 BIO International Convention in San Francisco this June. You see, I have the honor of moderating a super session titled Beyond the Cutting Edge: How to Enable Life Science Organizations Today for the Societal Challenges of Tomorrow. When putting together the panel, our goal was to make this BIO session unlike any that had ever previously been done, with a bent toward bringing in a variety of very different perspectives. For example, the lone biopharmaceutical industry representative, Kemal Malik, comes from Bayer AG. A board of management member with responsibility for innovation, and the Latin America region, Malik has spent 21 years at a company that seems to quietly go about its business, yet consistently finds itself ranked among the likes of Apple and Google as a company that has changed the world. Interestingly, of the top-20 largest biopharmas in the world, only Bayer (ranking #13) has business units spanning agricultural, animal, and human sciences.

In December 2015, Alphabet, Google's holding company, revealed a new name for the company's Life Sciences division: Verily. In an unprecedented coup, the Beyond The Cutting Edge super session will be the first in BIO's history to have an executive panelist hailing from Verily, Chief Medical Officer, Jessica Mega, M.D. Ever wondered how Google might approach conducting a clinical trial? Perhaps now we might find out. Other panelists include:

- **Noubar Afeyan, Ph.D.,** senior managing partner and CEO of Flagship Ventures. He is responsible for having cofounded over 30 life science and technology startups.
- **Matthew Meyerson, M.D., Ph.D.,** currently serving in multiple research and teaching roles at the Dana-Farber Cancer Institute, Harvard Medical School, and the Broad Institute of Harvard and MIT
- **John Nosta,** founder of the digital think tank NOSTALAB, member of the Google Health Advisory Board and author of articles for Forbes Health Critical, a top global health and technology blog.

Given the terrible diseases being tackled by biopharmaceutical companies today, there can be little doubt that it is an industry at the forefront of working on the cutting edge. But other biopharma challenges, such as developing innovative therapeutics at a price and cost we can all afford, might benefit from an outsider's perspective — especially if we ever hope to push our industry to a point somewhere beyond the cutting edge.

Life Science Leader
JUNE 2016 VOL. 8 NO. 6

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Q What nonbiopharma company do you anticipate as being the biggest disruptor to our industry?

A IT IS A TOSS-UP BETWEEN SAMSUNG AND APPLE. Reason: digital health is upon us and promises to transform drug R&D and its economics. But to enable it, one needs mobile computing/storage, wireless transmission, and the cloud. Several companies offer that, including Google, Microsoft, and Qualcomm, but Samsung and Apple clearly dominate the market with a joint market share of 70 percent of smartphones in the U.S. In addition, they are in this to sell devices, while Google and Microsoft's business models rely on reselling user data to all comers. With health data, that's a big problem since consumers are more concerned about privacy and more likely to embrace providers that will protect their data, as Apple has done. Samsung and Apple also offer manufacturing know-how to device innovators, resulting in richer, more robust, and better-integrated platforms.

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

Q What do you think will be the end result of the bullying of biopharma?

A THOSE OF US WHO SPEND OUR LIVES IMMERSED IN THE MINUTIA of drug development find ourselves embattled … on all sides. On the one hand, we're chastised for the time it takes to get new drugs to the market (people are dying!). On the other hand, we're excoriated for moving our drugs too fast (what about safety?). And then there are the pricing issues popular in the press today. Innovation and saving lives does not happen cheaply: 15 years of nonstop effort per drug, and hundreds of millions of USD. If we cannot recover the cost of developing our drugs and achieve a revenue stream that enables second-generation drugs that are even better, we will be forced to abandon innovation entirely. Activists, politicians, patient advocates, and tax payers can all complain now, but when there are no drugs to save the lives of their loved ones, cost will become irrelevant.

CAROL NACY, PH.D.
is CEO of Sequella, Inc., a private company that develops new anti-infective drugs. She was formerly CSO at Anergen and EVP/CSO at EntreMed. Prior to her business experience, she directed research in tropical infectious diseases at Walter Reed Army Institute of Research, Washington, D.C.

Q What are your top leadership books to read, and why?

A WHILE ANYONE CAN GET A GENERIC TOP-10 LEADERSHIP books list from Amazon or any business magazine, I am going to focus on the books that defined leadership to me. For me, leadership is about inspiration, authenticity, vision, and execution. To begin with, I learned about the nuts and bolts of leading in an organization and getting the job done from *The Feiner Points of Leadership* taught by my Columbia Business School professor Michael Feiner. My other favorites, covering everything from innovation to inspiration, include *The Innovator's Dilemma*, *The Art Of War*, *Seven Habits Of Highly Effective People*, and *Never Give In!: The Best of Winston Churchill's Speeches*. It is always valuable to get leadership exposure earlier in life, and my favorite gift to college graduates is Katie Couric's *The Best Advice I Ever Got: Lessons from Extraordinary Lives*.

CHANDRA RAMANATHAN, PH.D.
is the VP and head of Bayer's U.S. East Coast Innovation Center. His 20 years of industry experience include positions at Bayer, Pfizer, and Bristol-Myers Squibb.

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Congress Rebukes CMS On Part B Demo

JOHN McMANUS The McManus Group

After issuing a far-reaching proposal to "test" the impact of payment cuts to all physician-administered Part B drugs on three-quarters of the population in a compulsory five-year demonstration program, CMS has received dramatic and overwhelming rejection from Congress and stakeholders demanding the proposal be withdrawn or substantially modified.

The proposal would effectively rewrite the payment formula Congress enacted in the Medicare Modernization Act, which reimburses physicians for drugs they administer at average sales price (ASP) plus 6 percent. Phase one would reduce that to ASP+2.5 percent and a flat fee of $16.80, which after the 2 percent sequester cut pegs reimbursement to less than ASP+1 percent. Phase two of the demonstration, which could commence as early as January 2017 and before the phase one payment cut could even be evaluated, would test "value-based purchasing" including reference pricing and indication-based pricing schemes.

The first fusillade came from a united House Republican caucus, which amassed 242 signatures (including four Democrats) on a letter led by former physicians Reps. Price (R-GA) and Boustany (R-LA) as well as Rep. Shimkus (R-IL) that demanded a full withdrawal of the proposal.

That letter stated, "CMS' proposed Medicare drug experiment would lead physicians to refer patients to a hospital outpatient department. Driving more care to an often less convenient, more costly setting makes it more challenging for beneficiaries to access needed care and increases overall Medicare costs. This will lead to further consolidation and less choice for seniors."

Then every member of the Senate finance committee, which has jurisdiction over Medicare, weighed in against the proposal. Ranking member Wyden (D-OR) and his 12 Democratic colleagues demanded that CMS resolve several important concerns before moving forward:

- **BENEFICIARY ACCESS TO PART B DRUGS**, including implementation of real-time monitoring to rapidly detect beneficiary quality and access issues.
- **IMPACT OF SITE-OF-SERVICE**, particularly on rural and smaller physician practices.
- **INTERACTION WITH EXISTING DELIVERY AND PAYMENT MODELS**, such as the oncology care model and alternative payment models.
- **GREATER ENGAGEMENT WITH STAKEHOLDERS.**

The Republican finance letter led by Chairman Hatch (R-UT) admonished the administration for using the Center for Medicare and Medicaid Innovation (CMMI) to rewrite other programs: "We caution against invoking a similar unilateral effort to make changes to the successful Part D program through a flawed overreaching read of the CMMI authority ... We sincerely hope that you will withdraw this proposed rule and work with the Congress on a bipartisan approach."

OPPOSITION INCREASES

But even more dramatic were the rank and file Democratic letters — eventually totaling two-thirds of the Democrats in both the House and Senate — voicing opposition to their own administration's proposal to address drug pricing. Rep. Richie Neal (D-MA) collected 57 Democratic signatures on his letter, the Congressional Black Caucus amassed 23 signatures, and Senator Heidi Heitkamp (D-ND) recruited Senate moderates to oppose the demonstration project.

Democratic support for the administration's demonstration was minimized to fewer than a dozen senators and fewer than 20 members in the House, despite much of the caucus begging the administration for a solution to high drug prices.

Why did Congress overwhelmingly rebuke the administration that had seized on the populist issue of drug pricing? The answer is an overwhelming stakeholder — patient, physician, and industry — grassroots outreach to every member of Congress expressing their deep concern on the clinical ramifications and the policy implications. It started with a letter signed by more than 300 patient, physician, and industry organizations. It culminated with thousands of phone calls, emails, and meetings with senators, representatives, and their staffs urging them to contact the administration and express their concerns and opposition to the experiment.

CMS is now wading through a plethora

of officially filed comments that take issue with the very premise of the demonstration project — that the percentage add-on payment incentivizes physicians to choose more expensive and not necessarily clinically superior drugs.

The American Medical Association (AMA) slapped down that suggestion. "Phase 1 is based on a specious premise — i.e., that physicians may choose their patients' drug therapy based on the drug with the highest reimbursement to the physician. Although the agency primarily relies upon a June 2015 Medicare Payment Advisory Commission (MedPAC) report to Congress to support this assertion, the reality is that MedPAC looked at that question and concluded that there is little evidence to support this claim."

Indeed, CMS provided no evidence whatsoever that physician prescribing behavior is driven by reimbursement rather than appropriate therapeutic treatment for patients.

The Large Urology Group Practice Association (LUGPA), representing free-standing urology practices, noted the bizarre distortions created by the proposal. "The proposed model will simply cut reimbursement for critical therapies — such as those used to treat patients with advanced prostate cancer — while creating windfalls for drugs either incident to care (such as narcotic opioids used for anesthetic purposes and perioperative intravenous fluids) or for benign conditions, such as testosterone treatments used to treat loss of sexual function. ... (Moreover) There are no generic alternatives available for any of the Part B advanced prostate cancer medications that represent the largest component of urology Part B drug spending. Yet, the phase one methodology proposed by CMS would levy its largest cuts on this category of drugs."

The math on this is simple: expensive drugs, often used as a last resort, are cut the most. Cheap drugs receive massive bonuses because the $16.80 flat payment bears no relation to, and in many cases dwarfs, the underlying cost of the drug.

Congress is now holding hearings to provide greater insight on the implications of the proposal. The Immune Deficiency Foundation, the national group dedicated to advocacy and research of immunodeficiency diseases, testified at the Energy & Commerce Committee on May 17 : "What this proposal lacks — and what other CMMI demonstrations have included very explicitly — is outcome measures."

Dr. Debra Patt, testifying on behalf of the American Society of Clinical Oncology, the Community Oncology Alliance, and the U.S. Oncology Network, said, "Seven of the top 10 drugs that account for 48 percent of Part B spending are used to treat and cure cancer. Limiting an oncologist's ability to provide current, cutting-edge treatments, as will occur if the 'Part B Drug Payment Model' is implemented, will likely result in inferior outcomes for Medicare beneficiaries with cancer."

Dr. Patt went on to contrast the surprise release of the sweeping Part B drug experiment with the three-year collaborative and transparent effort between CMMI and the oncology community to develop the Oncology Care Model, an episode payment model aimed at improving coordination, appropriateness of treatment, and access to care for Medicare beneficiaries. "Unfortunately, CMS took the opposite approach in crafting and announcing the Part B Drug Model. It was introduced to the oncology community for the first time when it was released March 11, 2016. Oncologists' patients and others had absolutely no input on the proposed model."

ALLIES EXPRESS CONCERN

While the Obama administration is touting support from groups on the left, including the Center for American Progress, the Committee to Preserve Medicare and Social Security, and AARP, key allies appear to be questioning or abandoning the cause. Chris Jennings, an adviser to Democratic presidential front runner Hillary Clinton, recently declined to say whether a Clinton administration would seek to implement the proposal.

Chip Kahn, president of the Federation of American Hospitals, whose hospitals may actually benefit should care migrate to the hospital outpatient setting, expressed concern. "This is not a demonstration," Kahn said, pointing to the scope CMS' proposal. "I have concern for the precedent of moving national."

Perhaps he is wondering if CMMI can unilaterally rewrite deliberately negotiated statutory law regarding drug reimbursement, what is to prevent it from rewriting hospital reimbursement under the guise of a new demonstration?

As anxious stakeholders await CMS' final rule, Congress is gearing up to legislatively halt the demonstration. Rep. Larry Bucshon (R-IN) has introduced legislation to block the Part B drug rule. A big bipartisan vote for that bill on the House floor may compel the Obama administration to scrap or substantially scale back the proposal. And bipartisan support for fundamentally altering or delaying the proposal by the Senate Finance Committee can grease the skids for action in that chamber if the administration refuses to bow to the mounting pressure.

The pharmaceutical industry understands that this battle is a key test to even bigger changes the left would like to undertake to Medicare's outpatient drug benefit through Obamacare's empowerment of CMMI, as well as the pending Independent Payment Advisory Board (IPAB) that is waiting in the wings. (IPAB is an unelected board empowered to rewrite Medicare law to achieve savings if Medicare spending exceeds arbitrary levels written in the Obamacare statute.)

The larger healthcare industry and patient community are now beginning to appreciate just how much power has been transferred from the people's representatives to unaccountable bureaucrats. 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.

In A Political Year, We Need To Remember The Value Of Pharma/Bio

RACHEL KING CEO GlycoMimetics

It seems that in nearly every political debate this election season, someone attacks our industry. Some politicians, in their angry criticisms of corporate America, echo many complaints about drug companies, and a few have even linked "big oil, big tobacco, and Big Pharma" in one breath, as if the industries are the same! The drug pricing debate has been particularly challenging for our industry, and, with the presidential election coming up, I can't help feeling that the attacks will only get worse.

As the CEO of a biotech company, there have been times I wanted to believe that we in biotechnology could skate by this debate and leave it to Big Pharma to deal with political criticism. After all, many biotech companies still don't have products on the market. So as far as drug pricing goes, the criticisms don't apply to us directly — at least not yet.

But we are all part of the same community, the same economic ecosystem. Small biotech needs Big Pharma, and vice versa, and when Big Pharma is dragged through nasty political debates, it hurts us all. We are in this together. This year's criticism has made me ponder the value of biotech and big drugmakers and what we really do bring to our society. This value can be measured in new treatments delivered, patient quality of life, financial value, and, yes, even political value.

We know that it takes many years and millions of dollars to get to the point of generating data that determines if a drug works. We also know that more often than not, drugs fail. At small companies like ours, the very survival of the company can hinge on key clinical results. Living through that kind of data read-out makes us appreciate the huge investment risks taken in drug development.

We lived through that at GlycoMimetics several years ago when we were waiting for data from our Phase 2 clinical trial in sickle cell crisis, the extreme pain caused by cell blockage of blood vessels. This pain is felt by just about everyone with sickle cell disease and can last from hours to days, even requiring a hospital stay. The study on our drug candidate Rivipansel, which could reduce the duration of sickle cell crisis, had taken longer and cost more than we had planned. We had spent several years and millions of dollars completing the enrollment in our study. As we waited for the unblinded data, we were running out of money. The survival of the company literally depended on positive data. While the final data analysis was being done, our management team had to plan both for the opportunities that a successful outcome would bring, as well as the downside that would come with a study failure. I can't think of another industry where after so much time and money, so much hangs in the balance depending on a single set of data. In this case, the Rivipansel study was a success, and we are now in partnership with Pfizer, which has taken over further development of the compound. To our whole team, it was a huge relief!

When I think of what we go through to get to a successful drug and how much our industry needs good public policies to support our work, I have wondered why society doesn't place more value on what we do. Why don't policy makers and the public understand and support us?

WHY THE POLITICAL DEBATE FOCUSES ON US

But recently I've realized that the reason we are at the center of so much political debate these days is precisely *because* society places so much value on what we do. It's because we have been successful in developing drugs that prolong life and improve quality of life that we are under the microscope of political debate. Policy makers and politicians realize what we are capable of, many patients and their families have experienced the benefits of what our industry can deliver, and people do profoundly value the outcome of our work. That is exactly why our industry does not get a free pass.

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"I've realized that the reason we are at the center of so much political debate these days is precisely because society places so much value on what we do."

It is also striking to think that members of Congress, much maligned for Washington dysfunction, are focusing so much on improving our ability to discover and develop new drugs — and are actually making progress. One of the very few areas where a bipartisan consensus is emerging this year is around the work we do. The 21st Century Cures Act in the House and companion bills in the Senate all embody a set of policies that many people believe will help improve our ability to get innovative drugs developed and approved. These include making it easier to accelerate development of compounds for serious unmet medical needs, supporting the development of "precision medicine" drugs, and better incorporating the patient voice into drug development.

Many different interest groups representing patients, industry, and regulators have come together to provide ideas and momentum. In the midst of one of the most contentious political climates ever, a major piece of bipartisan legislation focused on drug development could very well get passed. If it doesn't, there was at least an encouraging moment of possibility, and I don't think the fact that the bill dealt with our industry was a coincidence. It really does speak to the widely accepted importance of what we do.

There are still ongoing key policy debates. I generally feel that policy makers understand what is at stake, though there is often intense disagreement about how to achieve our goals. We have much work to do to ensure policy changes will support and not impede new drug development. It will be hard to continue making the case for our industry, and it can be especially difficult and discouraging to face the criticism that comes as part of that debate — even when some criticism may be deserved. When I think of how uncomfortable the political bullseye can be, I remind myself how satisfying and important it is to do the kind of work we do with the potential impact we have in biotechnology.

TAKE A LONG-TERM VIEW

I know that many in our industry often think about the potential impact on the lives of individual patients and feel especially grateful to have a role to play. I experience this often in the context of our clinical trials at GlycoMimetics. One of our drug candidates is currently being tested in a clinical trial for Acute Myelogenous Leukemia, or AML, for which currently available treatments are not particularly effective and where cancer cell resistance to chemotherapy is a problem. The trial is a so-called open label study, meaning that everyone in the study will be receiving our drug, in addition to the standard of care. Testing is still in its early days, so we know when each patient is enrolled. We don't know personal details, of course, but we hear general background, usually the age and sex of the person and a top line summary of their disease status. So we might hear, for example, that a 35-year-old man with poor cytogenetic risk factors has been enrolled, or perhaps a 76-year-old woman with relapsed disease. I can't help feeling invested in each patient's progress. I know when their treatment ends, and if their disease has cleared. I am rooting for them. I feel disappointed and sad if their disease progresses, and if we see signs of improvement, it makes my day. I may be a bit overinvested, but I know from others who work in our industry that many people feel the same way. We do care — for our companies' sake, but also for the human impact. It is a wonderful feeling to know that if our work is successful, the benefits to individual people can be so profound.

And it's that value — the real possibility to impact people's health — that is the reason we are at the center of the political debate. It is easy to get defensive when we feel attacked and easy also to feel disappointed when the markets turn downward as they have at the beginning of this year, but we need to take a long-term view to remember how critical our work is. We need to remember the patients who benefit if we are successful. Much is at stake for the patients with disease, for our companies, and for our nation, which continues to lead worldwide in innovative drug discovery and development.

So let's welcome and engage in the political debate that recognizes the potential impact of what we do. Let's appreciate the opportunities we have to be part of this incredible time of creativity and innovation in human health. And most of all, let's remember what we are trying to accomplish. Because after the long years, the risk, and the dollars invested, if all that works out and new drugs are discovered and developed and human life lengthened, and if the quality of patients' lives can be improved, we will know that the politics are worth the struggle, and we can feel proud to have persevered. L

RACHEL KING has nearly 30 years of experience in various management roles in the biotech and pharmaceutical industries. In 2003 she cofounded and became CEO of GlycoMimetics, Inc., a publically traded biotechnology company in Maryland.


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TAKEDA'S CEO SHARES NEW PLANS FOR WORLDWIDE GROWTH | By W. Koberstein

CHRISTOPHE WEBER
President and CEO of Takeda

TAKEDA'S CEO SHARES NEW PLANS FOR *Worldwide Growth*

Christophe Weber says a historic push to globalization enlarges the company's culture.

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

Christophe Weber, the current and still nascent CEO of Takeda, is also an unavoidable symbol of the company's current transformation into a global organization as the first non-Japanese person to head a Japan-based pharma company. I spoke with Weber by phone with a 17-hour time gap between us — from late evening in my New York hotel room to the following afternoon in his Tokyo office. As I adjusted my equipment and sometimes strained to hear Dr. Weber on the other end, it felt something like the old short-wave communications, simultaneously evoking a sense of vast distance and immediacy. The effect amplified the theme of our exchange; if you want a tangible impression of globalization, try wrapping a conversation around two-thirds of the planet.

French-born, in Strasbourg, Weber is a PharmD from a family of physicians, among them his parents and sister. His own interest in medicine led him to earn a doctorate of pharmacy, but he soon discovered he had more of a penchant for business than research in pharmaceuticals. He joined GSK in 1991 as a product manager in Australia and stayed with the company most of his career as he took on positions of ever-greater responsibility around the world. His last position at GSK was head of its vaccine business, virtually the CEO of a fully integrated organization.

When Weber joined Takeda, the largest pharma company in Japan, as its chief operating officer in April 2014, the board and management had obviously decided to make a big break from the traditional isolation and centrism of Japan-based companies. Takeda allowed him to restructure and recruit his own management team to affect a leap forward on the global path. Weber created new positions on his team for some executives, two of whom I also interviewed for this story. (See "Bruno Villetelle: Chief Digital Officer" and "Jocelyn Trokenheim: Driving Takeda's Global Development.")

TURNED TOWARD GLOBAL

To say the current initiative by Takeda is a leap forward in globalization is not to ignore its previous global intentions or its global leadership among Japanese

companies. Takeda was the first company in Japan to form a U.S. joint venture — with Abbott, TAP Pharmaceuticals, later integrated into Takeda. It similarly absorbed Millennium, acquired in 2008, and Nycomed, acquired in 2011. And in many other ways, Takeda led the pack of home companies in growth initiatives outside of Japan. Weber's job is to build on previous moves to make Takeda more independent of its home market and to remake the company as global in culture as well as strategy and organization.

As he notes, 10 years ago, Japan held about 20 percent of the global pharmaceutical market; now its share is down to less than half of that. Like most other pharma companies in Japan, the industry faces even further setbacks in its home market as Japan recovers from a cluster of natural and technical disasters, deals with a sluggish economy, and places ever more restrictive policies on industry revenue and profits.

Like other companies inside or outside of Japan, Takeda has also found it a challenge to integrate its large acquisitions, and it sees globalization as the only way to do so. One of the largest effects of the mergers was geographic, increasing the company's presence in 70 countries. "I came at the time when it had become necessary to organize the company into a fully global company, integrate all of the different businesses and functions, and move to the next page," Weber says.

BRUNO VILLETELLE
CHIEF DIGITAL OFFICER

It's not about IT — it's about culture. New digital technologies and applications change how people obtain medical care, how doctors and patients relate, how biopharma companies interact with customers and regulators, and how a fast-grown company such as Takeda undergoes a sweeping transformation and stiches together its global organization. Bruno Villetelle, Takeda's chief digital officer, thinks big. With a newly created title to fit his job, Villetelle has the charge to explore every avenue where digital technologies may improve Takeda's business and operations.

"We are very committed to make digital a driver of our transformation. Health and medicine have become information technologies. Our ambition is to become a digital health leader by 2025. We decided to approach digitization in a way that supported our transformation objectives and our company values."

Villetelle refers specifically to the company aphorism: "patients first." He says the company wants to use digital tools to empower patients, "to help patients become the CEOs of their own health." Beyond websites and mobile apps, he notes, digital technology now includes point-of-care tools, diagnostics, artificial intelligence, robotics, and many other platforms, in a constantly growing list of items outside Takeda's own capabilities. So the company is reaching out, he says: "We have entered into this space where the pharma industry and the consumer technology industries are meeting up, and we clearly need to partner with the suppliers in this space to succeed."

Inside Takeda, Villetelle's mission is to build an inclusive, global system for all operations and levels of the company. "We don't want to create a digital realm at Takeda that is just a privilege of the few," he says. "Digital technology now permeates everything, so we don't see it as something that could become controlled by a certain group of people in the company. We want it to become part of everyone's job at Takeda, one way or another."

Taking the democratic approach to digitization is also key to fulfilling the "33,000-person startup" of President and CEO Christophe Weber, says Villetelle. "The digital space is entrepreneurial; it is fueled and inspired by what startups are doing. So we are trying to disseminate this startup spirit in our organization. We are encouraging and educating our people, whether they are on the field or in our research centers, to see the importance of digital tools and to work through barriers that some people might have with the new technologies — and then to come up with their own ideas and suggestions for applying the tools in their area of work." Like potential partners, employees can even submit their ideas to the company's VC fund, which vets the suggestions and selects some of them for further testing and, if results are positive, scale-up to wider application in the company. Separate tracks handle incremental and "exponential" changes, Villetelle says.

Company culture was his first priority, as it remains, and to begin moving the culture toward a more global state, he turned to listening as his primary tool. Weber spent the first few months understanding the dichotomy of tradition and transformation at work in the company.

"On one side, the company's culture is very strong because it was established in 1781, so there is a very long foundation," he says. "But on the other side, the culture is really new because of these acquisitions. Seventy percent of Takeda's employees are outside of Japan, and they are very new to the company. So we had to create a common picture, building on the blended history and traditions of the company." Besides increasing geographic spread, the mergers also greatly expanded its worker base — in one case, the number of employees doubled. "Each time the company would make a merger, always with a company outside of Japan, it was a cultural shock," he says.

After conducting focus groups with employees in various parts of the world, Weber had a clear agenda about "what to change and what to integrate" in the company, which guided a sweeping reorganization in 2014. So far, he reports, employee feedback has been good in all parts of the company, new and old. "We made sure we are still loyal to strong values that have existed in the company for a very long time. We aim to bring this company to a new next level, recognizing that we are now a truly global company, yet still be loyal to the foundation and values of the company, which are based on integrity and focus on innovation."

RETURN TO CHANGE

Takeda's master strategy for the next 10 years is to achieve industry leadership in three therapeutic areas where it sees its strongest global assets: gastroenterology, oncology, and CNS, plus specialty cardiovascular and an initiative in vaccines. According to Weber, the company's selection of those areas reflects where it has the greatest strengths on both the R&D and commercial sides of its global

organization. GI and oncology promise to be the biggest drivers of Takeda's business, he says, showing an awareness of the challenge and risk, as well as the potential for drug development in those areas.

"We define ourselves as an R&D-driven, innovative company. This is our business model, delivering innovative medicines in our areas of focus. We don't want to go into the generics business. That is how a traditional Japanese company looked in the past. But we decided to be much more focused in our business model and in our therapeutic areas."

At the same time Takeda creates more global R&D and commercial functions, Weber says, it strives to maintain enough flexibility to adapt to regional and local markets. "We believe every region or country is unique because medical practice is always local. So we gave a lot of empowerment and agility to our organization in each region to adapt as needed for the local conditions."

But accountability must balance agility, Weber adds. Here, the Japanese tradition of near-perfect diligence may serve the company well; that is, if the organization can keep moving at optimum speed. This will be one area of Takeda to monitor over time, as the first-ever challenge by a Japan-based company gone global: Will its decision making and implementation tend toward a more traditional pace as it holds its operations to high ethical and technical standards, or will it find a way to have accountability and nimbleness, too?

TEAMING UP FOR WORLD CLASS

Nothing in Takeda seems to have changed more than its top management. Although the Japanese board and chairman, Yasuchika Hasegawa, remains in place, the corporate executive team has become quite varied on Weber's watch. More than half of the Takeda executive team members have joined the company, and almost everyone has a new job, since his arrival. The executive team contains seven different nationalities, and more than half of the team resides outside of Japan. One-third of the team is U.S.-based, including the head of research, Dr. Andrew Plump, and the head of oncology, Dr. Christophe Bianchi, both in Boston.

Global goals require world-class performance as a business. One immediate challenge the team will have to face together is the company's legacy of relatively low profits and generic-eroded sales. Takeda has already shown its commitment to cutting costs with manufacturing consolidation and plant closures, cash-flow management, and other measures, but Weber emphasizes its other main approach to boosting profitability: increasing the top line. How? By doing something it had not usually done before — launch its own new, innovative products, globally.

"Before we launched our new product Entyvio [vedolizumab] when I joined the company two years ago, Takeda never had a global marketing/commercialized plan for a single global product. For the first time in our history, we are launching globally innovative products with global marketing strategies, and these products will drive the growth of the company. We are organized now as a global company to launch these new products at the global stage, which we did not have before."

Considering Weber's statement on innovation, people who chiefly focus on company ledgers will notice a seemingly contradictory downturn in Takeda's 2016 R&D spending. He explains the drop as a temporary one caused by the "pipeline evolution," with a swell of later-stage products requiring more conservative early-stage investment.

"For a while, we will be extremely stringent in our partnering prioritization to select only the most innovative candidates," he says. "It's just good top-line and good bottom-line management, and it also leverages our efficiency. One year ago, we created our first procurement organization so now we can negotiate with our suppliers at the global level, yielding a lot of savings. We are always looking for more efficiency as well."

Takeda also has created a single manufacturing organization for the first time. It previously had four separate organizations, independent of each other. "We have closed a few sites that unfortunately we couldn't keep, but at the same time we just bought a site in Minnesota to produce biologics so this is an ongoing situation to optimize our network," says Weber.

He says the company is open-minded about outsourcing, which it does on a case-by-case basis, factoring in market proximity, efficiency, and risk. For strategic products, the company employs dual sourcing, often combining insourcing and outsourcing. Takeda has traditionally used outsourcing partners extensively in its clinical trial operations and continues to do so.

VALUE FROM VALUES

A company that has existed for 235 years will have traditions that endure along with the ones that fall behind the times. And sometimes, during historic shifts, it becomes necessary for a company to define its values in new terms. Weber recounts how Takeda greeted the 21st century by declaring "Takeda-isms," or aphorisms that translate into English as integrity, honesty, fairness, and perseverance.

"We want to further ask ourselves, based on these values, how do we want to conduct our activities at Takeda? And our answer, in simple logic, was patient first, trust, reputation, business. We want to do the right thing for the patient, for

JOCELYN TROKENHEIM
DRIVING TAKEDA'S GLOBAL DEVELOPMENT

As the executive VP of corporate development, the responsibilities of Jocelyn Trokenheim concentrate mainly on global mergers and acquisitions (M&As) and business development. Her work focuses chiefly on the company's three main therapeutic areas: oncology, gastrointestinal, and central nervous system. She also oversees academic research collaborations from very early discovery all the way to late-stage compounds or commercial products.

Were your position and responsibility created as a result of Takeda's globalization or has it always existed but perhaps had a different agenda?

TROKENHEIM: The position has existed before, but the corporate development role now reinforces the company's current focus on continuing the transformation and driving growth through external opportunities.

What are some of the transactions you have done since you arrived last April?

Actually, the biggest was the divestment of our respiratory portfolio, which we completed just before the holidays last December. The whole objective was to help Takeda focus on our current areas. Divesting the entire respiratory portfolio will help us optimize our resources to focus on those three key areas. There were also a few recent GI-related deals, one with enGene Research Laboratories, a gene therapy company, at an extremely early stage. It is a research collaboration; we will support the development, the clinical design, and other related activities.

Gene Therapy Is Challenging. Would You Say It Is Risky?

It is difficult, but it is the kind of innovation in which Takeda would like to be involved and contribute to. We see its potential as high science and its innovative nature in how it could help the patients down the road, and so we're very interested in that.

So, is that part of the globalization — to expand how you do discovery and perhaps take on more risk in certain areas?

Yes, the way we're trying to globally transform Takeda is to focus on our resources, corporate strategy, and corporate direction, and, we are very open to exploring anything that fits within that framework.

What does that mean culturally for the company?

I've been with the company for 13 years now, and I've seen a lot of changes, not just from a business perspective but from a cultural perspective. Christophe Weber being the first non-Japanese person to lead Takeda has been very positive. I believe people feel very positive and energized by the sharp focus and energy he has brought in.

increasing trust between Takeda and society, for Takeda's reputation, and for our business — in that order. Our people know these are the company's formative values; they are our compass, to guide everyone in the company, wherever they are, to make the right decisions."

To drive those general principles home and make sure the company applies them to actual circumstances, Weber's team has been holding a series of internal leadership conferences and "progressively transforming the company." He gives an example: "When we launched our new oncology drug in the United States, we had to decide on the price, and we really followed this line of patient, trust, reputation, business. What is the right price that will reinforce a trust that we have with, for example, oncologists, and improve the reputation of the company? And we followed the same process in our approach to the other markets."

Considering the range of pricing practices among companies in the biopharma industry, Takeda's approach may stand as a model for those that wish to avoid the extremes. Subjective, human-level responses play a central role alongside attained wisdom in the tradition of the great Japanese poets — a traditional principle, perhaps, but one with universal, global appeal.

HOW TO ACHIEVE *Excellence* IN A BIOPHARMA SUPPLY CHAIN

ROB WRIGHT Chief Editor @RFWrightLSL

When Walt Kelly put the quote "WE HAVE MET THE ENEMY AND HE IS US" on the first Earth Day poster in 1970, it is doubtful he envisioned it applying to the biopharmaceutical industry. Yet, for David Lowndes, SVP of supply chain management at Shire Pharmaceuticals, the quote is pertinent to how his company approaches working with supply chain partners. He says it all started with a paradigm shift related to how Shire maintained the integrity of supply for its wholly outsourced, 100 percent virtual small molecule drug business. "We had seen the Heparin disaster of 2008, and I think we [as an industry] all knew there was a huge gap in our supply chain capabilities," Lowndes shares. "In 2012, Xavier [University, through its PharmaLink conference] initiated the integrity of supply initiative, with the idea being to increase product confidence."

The 42-member team working on that initiative represented a wide variety of industry stakeholders (e.g., pharmaceutical, biotech, food, medical device, suppliers, regulatory, and academia), and the team embarked on a structured research process (e.g., gap, cause and effect matrix, and Pareto methods of analyses) to tackle the problem. "The data came back saying we should really be looking more at ourselves than our suppliers," Lowndes concedes. "Supplier surveys and focus group sessions corroborated those findings." What emerged were three key areas that biopharmaceutical companies (i.e., customers of suppliers) needed to focus on. "Those three areas were our understanding of our products and processes, our supply chain management capabilities, and finally our behaviors within that system," he states. When faced with the reality that the enemy of supply chain integrity was most often the customer, Shire embraced the opportunity to become a better customer. In that same spirit, Lowndes invited two members of Shire's supply chain network to share their insights on what biopharmaceutical companies can do to be better customers, and consequently achieve better supply chain integrity.

Andy Polywacz, VP, quality & regulatory affairs at West Pharmaceutical Services, Inc., and Harry Gill, SVP of quality and continuous improvement at Patheon, have a combined 55 years of industry quality and plant operations experience that include stints at Baxter, Catalent, Cardinal Health, and Wyeth (now Pfizer). "These two have a multitude of customer relationships and, therefore, a very broad set of experiences to draw on," Lowndes states.

DAVID LOWNDES
SVP of supply chain management, Shire Pharmaceuticals

ANDY POLYWACZ
VP, quality & regulatory affairs, West Pharmaceutical Services, Inc.

HARRY GILL
SVP of quality and continuous improvement, Patheon

What Six Issues Impede The Building Of Strategic Partnerships With Suppliers?

Issue No. 1

ALIGNED SPECIFICATIONS ≠ ALIGNED EXPECTATIONS

ANDY POLYWACZ: The first issue that jumps to mind is a misalignment of expectations between the supplier and the customer. In my experience, we typically come to alignment on specifications fairly quickly. But a specification is just the start. Where we often end up getting tripped up is with the expectation. For example, let's say West is working with your company's supplier quality group regarding stoppers going into your facility. You tell us this is the stopper specification you need, and we all sign our agreement. However, what if this doesn't align with what you need at the end of your fill line? All of a sudden we've got this disconnect and can't release a drug product lot. Despite the "spec" having made it through your incoming quality checks, and West having not done anything wrong, we still end up interrupting the supply chain, and patients aren't getting their drugs. That's a big problem and an example of misalignment of an expectation.

Where we are trying to be more collaborative with our customers is beginning the conversation by asking, "What do you need this to do? Let's talk about what the drug is. What is the delivery method? How is it getting to the patient? How is the patient going to use it?" From there we can walk back through the supply chain and look at things like the types of filling systems you already have. Do you have vision inspection? As we keep walking backward, we can now build a specification that meets the expectations of the supply chain, not just getting it past incoming quality. While those conversations have a lot of value, they require taking more time up front. However, the value those conversations have on the overall integrity of your overall supply chain pays off exponentially.

Issue No. 2

DOES SUCCESSFUL TECH TRANSFER = PRODUCT AND PROCESS ROBUSTNESS?

HARRY GILL: One of the issues we identified is a lack of product and process robustness after the development or tech transfer is complete. Let's say we go through everything and it looks really good. But when we go into production, we start to see deviations. The No. 1 issue that causes us, as a CMO, to miss on our on-time delivery is process deviations. As a client you are understandably upset when a CMO is late on delivery because you can bet that this type of situation usually happens when your demand for your product is going up in the market. What do you think about when trying to mitigate stability problems or deviations that lead to the need to file field alerts or taking regulatory agency actions? As your CMO, the first thing we want to be able to turn to is your product's chemistry, manufacturing, and control (CMC) section and development reports, inclusive of all the things you've done to create your design space.

You would think this is common sense, right? After all, you want us to make something for you. As such, you would think that giving us the rules that you filed with the agency would be useful in order to make it correctly. Two years ago we had a PAI [pre-approval inspection] in one of our European facilities. About two days into the inspection the investigator asked us if they could see our packaging validation and visit the packaging line. We were a little stunned. Why? Because we thought we were just going to provide bulk drug tablets for packaging later by someone else in the client's network. But because the client had put us in the dossier as a packager for this particular product, we ended up getting a 483 [a notice of the need for corrective action], the PAI failed, and the client ended up taking us out of the dossier completely. The end result was both sides lost (i.e., they lost their U.S. market risk mitigation strategy, and we lost a business opportunity for which we had actually set up capacity just to manufacture that product). During a more recent negotiation, a client balked at our quality agreement because it stated that they had to give us their CMC section. They were concerned with protecting IP, stating that the IP was in the API, and since all we were doing was putting it into an oral-solid dose in a traditional solid-dose manufacturing process, we didn't need the CMC. Eventually the client capitulated, signed the deal, and everybody was happy. But it shouldn't get to the point where we feel like we are forcing you to give us the information necessary to successfully make your product. Besides, if manufacturing in Europe, even if not for EU distribution, the Medicines & Healthcare products Regulatory Agency's (MHRA) Annex 16 specifies that a medicinal manufacturing facility is required to be certified by a Qualified Person (QP) against the CMC. Similarly, FDA guidance also specifies that the customer has to share the CMC section with their CMO.

Issue No. 3

HOW MUCH TRANSPARENCY DO YOU REALLY WANT?

POLYWACZ: We talk about transparency in many different ways. For example, transparency from a raw materials standpoint could be what happens when we need to make a raw material change. In the supplier-customer relationship we need to agree on what transparency specifically means. It may sound like a silly question of what it means to define transparency, but the reality is that transparency has a lot of different legs. One thing customers need to consider is that when your supplier is transparent and shares information with you, please appreciate that trust. The agreement as to what levels of transparency are going to be in place between supply chain partners goes both ways. For example, when we ask, "Where is this drug product going to be marketed?" and you say, "We can't tell you that," you've greatly hindered our ability to help you. Let's say you are trying to get a drug product into Japan, but it's getting bounced out for a particulate. If we had that conversation up front we could have built in the appropriate "spec" for entry into that particular market. Unless you agree on the level of transparency up front, communication will often end up with a lot of back and forth and with more angst around issues when they arise. If you want your supplier to be transparent, you as the customer should consider reciprocal transparency.

Issue No. 4

WHAT IS THE IMPACT OF A MISSED FORECAST?

GILL: Another customer issue involves client forecasting, in particular for

new product launches. Here is an interesting statistic. During DCAT Week 2016, results from research conducted by ORC International were published as a white paper. ORC interviewed 50 pharmaceutical company executives and found that 65 percent of all product launches miss forecasts by more than 25 percent, either high or low. Now, this is pretty logical. As a manufacturer, when you're trying to decide what your supply chain will look like for a new product, you have to make decisions three to four years ahead of time. And while we can joke that the one thing that will be right with every forecast is that it will be wrong, customers need to consider the impact of a missed forecast. When you miss by forecasting too high, that's an impact to our business because as a CMO we may have been counting on that particular volume. When you miss low, that impacts the patient.

Recovering from a missed forecast of 30 to 50 percent can be very difficult. However, we've had a client miss a forecast on the low side by 500 percent. When you haven't planned for this type of demand, it becomes very difficult for your CMO to react in order to supply, in some cases, lifesaving drugs. To try to mitigate that risk we do our own market research. Even if it's an orphan drug, we will identify the population for that particular disease. If it is a new drug that is being released, we'll look at the market for similar products and work with customers to develop some risk-mitigation strategies (i.e., suggest they consider doing an alternative train in the same facility, an alternate site, either in or outside of our supply chain). Everybody knows that forecasting of new products can be difficult. However, we should be much better at the forecasting of established products. Many forecasts have variability within the first three to six months and then flatline. If a CMO has to change capacity to meet increased volume needs, unless they are sitting on idle capacity, it can be very difficult for them to help. We work best when integrated into the client's S&OP [sales and operations planning] process and can see all the markets they are in. If we know where a client's supply is in every single market, we can work together to help mitigate issues when forecasts are missed.

Issue No. 5

HOW DO YOU ENGAGE WITH SUPPLIERS WHEN THINGS GO WRONG?

POLYWACZ: The fifth issue I will refer to as the lack of rules of engagement. I'm not just talking about a quality agreement, which can be great unless it is just a battle of templates (i.e., "I need a quality agreement." "OK, here's our template." "No, we can't use yours, so here is ours."). What does defining rules of engagement really look like in real-world collaborations? Simple, define and resolve issues when something goes wrong (and trust me something is always going to happen). Don't just keep escalating the issue because often all that does is bring things to a head. What we want to try to do is resolve issues proactively. Neither of us wants to have an issue that puts us at a standstill. So how can we prevent such situations?

One solution can be to have a third party empowered to make a ruling on issues, and we have agreed that we are willing to live with whatever the third party decides, whether it be a testing lab or another entity. In a strategic partnership there should be "noisy" dialogue. Because if we are heading to a point where we are seeking to protect our own mutual interests, we aren't going to find the solution by throwing our quality agreement forms at one another. Think about building rules of engagement into a quality agreement so that the quality agreements actually work. If you have had the conversations you need to have on how you want to deal with issues when they do arise, you already know how to go about resolving those issues.

Issue No. 6

STRATEGIC PARTNERSHIPS CAN'T BE DONE TRANSACTIONALLY

GILL: What is the relationship you have with your CDMO (contract development and manufacturing organization)? We probably don't have a single client that doesn't want to be our strategic partner. However, like any good relationship, a strategic partnership requires work. The term strategic partner can sound really good when spoken in the higher echelons of an organization. However, when you get down in the trenches and the procurement teams get involved, that's where you tend to get into a transactional relationship. Problems that arise in transactional relationships tend to be much more difficult to solve. If you're in a problem-solving mode and one of the parties starts quoting the quality or manufacturing services agreement, it is much less likely that any problem resolution is going to end up satisfactory for anyone. Once the focus becomes "what is" and "is not" in the documents, you're done because at that point you are no longer solving problems but trying to mitigate your own risk.

To prevent these situations from occurring, you need robust governance models, and these require a great deal of time to construct collaboratively. Governance models work best when they work where the work is being done (i.e., the sites) and among the people working most closely together. The people at these levels should be able and empowered to solve 90 percent or more of the problems. Having the customer put a person directly in a plant also can help with creating strategic partnerships. As a matter of fact, if we follow some rules of engagement, it actually is better for us because we have somebody we can talk to every day about any issue. Clear escalation process models of who to talk to next when problems can't be solved at a particular level are helpful. Quarterly or semiannual face-to-face meetings between the right people who can talk about the strategic relationship is another consideration. When you try these approaches you are much more likely to have success because the reality is — it's always easier to have a relationship with somebody if you can look them in the eye versus trading emails. L

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A VIRTUAL ROUNDTABLE

PART THREE OF THREE PARTS:

PROGRESSIVE MS – SOME HOPES IN SIGHT

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

The following KOLs participated in this virtual roundtable on new therapeutic approaches in development for MS.

Each of the members of our virtual-roundtable panel speak from multiple perspectives – treating patients, teaching students, conducting research, and even running clinical trials. Tackling the first question in the discussion, they deliver useful details about emerging treatments for progressive MS, including why major disease-modifying therapies may not enter the space for many years.

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This is the concluding installment of our three-part series on new therapeutic mechanisms for neurodegenerative diseases. Here, as in the first two parts, we have brought together a "virtual roundtable" comparing the views of key scientific opinion leaders with some of the companies developing new therapeutics for progressive MS. (See Part One, "Aiming at Alzheimer's," March 2016, and Part Two, "Parsing Out Parkinson's," April 2016.)

First, it is important to understand MS comes in more than one form. Relapsing/remitting and progressive MS are the two primary disease types, with the latter dividing into the primary progressive and secondary progressive forms. Relapsing/remitting MS initially affects about 85 percent of patients, with the remainder suffering primary progressive MS; secondary progressive MS normally follows in refractory patients 20 to 30 years after initial diagnosis of relapsing disease. So the typical MS patient experiences periodic episodes of lost neural function for decades, then the episodes end and, instead, the condition gradually worsens until death. All the MS forms have this in common – the disease destroys myelin, the protective sheath around nerve channels, and what follows is incremental impairment of movement, cognition, and perception.

All but a few current drug therapies for MS treat the relapsing/remitting types, and almost all belong to the broad class of anti-inflammatories. Although the leading medicines are expensive, they do a good job of staving off disease symptoms and relapses for patients unless they develop progressive MS. Thus, the greatest unmet need and opportunity for innovation in this space is with progressive disease types. (See the sidebar, "Disputed Causes, United Cause.")

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 MS area. (See "KOL Panelists.")

Separate cameos of selected companies suggest some new avenues for MOA (mechanism of action) and drug development in the MS 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 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.

DISPUTED CAUSES, UNITED CAUSE

Strictly speaking, MS is not classified as a neurodegenerative disease but as an inflammatory one. Inflammation has been the center of drug R&D in the MS space because it is so obviously present at the sites where the disease has destroyed myelin. But no absolute consensus on that point has ever existed and, as the scientific opinion leaders in our virtual roundtable note and discuss, a central question has sustained doubt about the inflammation hypothesis: Why do the anti-inflammatories that work so well in relapsing patients fail so utterly in progressive ones? Some argue that inflammation may present at the disease sites only because of some other pathology. Competing explanations include neurodegeneration similar to the kind observed in Alzheimer's and Parkinson's, perhaps due to mitochondrial disease, rogue T-cells, genetic disorder, or some other hard-to-observe factor.

Most of the actual research and development of new approaches in the progressive MS space now happens in university and hospital settings, often funded by the public, not industry. The larger companies that now dominate the relapsing market have mainly tried, without much success, to apply their existing or next-generation anti-inflammatory drugs to the progressive form. A smattering of small companies, where the line between academia and industry often blurs, are working on novel approaches for progressive MS, and we feature some of them here, in Part 3 of Hot New Therapeutic MOAs Versus Neurodegenerative Diseases.

What are the most promising therapeutic targets/mechanisms for progressive multiple sclerosis?

COETZEE: We've seen a lot of progress addressing inflammatory stages of MS, although there are still opportunities to develop more specific therapies that can bypass adverse events such as opportunistic infection. There's high potential for developing therapeutics that target neuroprotection and the multiple mechanisms that appear to drive disease progression, including CNS-based innate immunity, mitochondrial failure, and signals within lesions that stall or stop oligodendrocyte precursor cells from maturing into fully functional oligodendrocytes capable of mediating remyelination.

There are likely multiple targets for stimulating endogenous myelin repair, both antagonists to "stop" signals and agonists for "go" signals. There's also potential for developing stem-cell therapies; however this approach has some commercial challenges. Moreover, as more and more is understood about the gut microbiome, there's potential for developing probiotics as immunomodulators.

The recent clinical findings with ocrelizumab, targeting B cells, are remarkable. The MS community has known for decades that B cells play a role in the disease, yet most therapeutic approaches either have targeted inflammatory cells of the immune system or are broadly active agents that limit the influx of many types of immune cells into the CNS. We expect more therapeutic progress to be made by directly targeting B cells and by understanding their role in the promotion and maintenance of disease progression.

FOX: We need to develop new approaches to treating progressive MS that are not anti-inflammatories. We must find a biomarker for progressive MS equivalent to the new lesions on MRI that we use in Phase 2 trials for relapsing MS. My colleagues and I are helping to lead an NIH-funded study comparing five different imaging metrics head-to-head in a 255-patient Phase 2 trial. One of the goals is to test the drug, and if it works, that would be wonderful. But the more important contribution of the trial will be comparing the imaging metrics and selecting the best biomarker for progressive MS Phase 2 trials.

Research scientists are doing whatever they can to understand the basic biology, develop animal models and high throughput screening assays, evaluate therapeutic approaches, create Phase 2 trial models to help test new therapies efficiently and effectively, and identify better clinical outcome metrics of

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MEDDAY PHARMACEUTICALS

In Phase 3 with MD-1003 (biotin), which targets neuron metabolism and may help myelin repair, for treatment of primary and secondary progressive MS

Frederic Sedel, M.D., Ph.D., CEO: *Progressive MS is a consequence of ongoing inflammation, chronic demyelination, and axonal neurodegeneration. Although immunosuppressive and immunomodulatory drugs may delay progression in patients who have ongoing inflammatory activity ("active" progressive MS), these drugs are relatively ineffective in patients who have no inflammatory activity but who continue to progress ("not active" progressive MS). The axonal degeneration in progressive MS is thought to arise from an increased energy demand in chronically demyelinated axons, which, together with some mitochondria dysfunction, create a virtual hypoxia phenomenon culminating in progressive axonal loss.*

Mega-doses of pharmaceutical grade biotin have a unique mechanism of action which is specifically suitable to target neurodegeneration (and not inflammation). Biotin is a co-enzyme for several "carboxylases," or catalysts critical for energy synthesis in the mitochondria and is also a coenzyme for the acetyl CoA carboxylase (ACC) which is expressed by myelin-forming cells (the oligodendrocytes). Thus, biotin potentially acts on two targets related to progressive MS: (1) it activates energy production that protects against axonal degeneration, and (2) it potentially activates the synthesis of fatty acids required for some myelin repair.

On the other hand, since biotin is not expected to have any beneficial impact on inflammation, it is not expected to be suitable to decrease the relapse rate or to decrease the inflammatory part of progressive MS, especially in patients with active progressive MS. As a consequence, if approved, it is expected that high-dose biotin would be the treatment of choice in patients with not active progressive disease. In the active progressive disease form, it is expected to be used in combination with other immune system targeting drugs to be certain that patients remain without superimposed inflammation. The fact that neurodegeneration is expected to occur in all patients with progressive MS suggests that biotin should be suitable for all patients with or without additional immunosuppressive treatments.

disability for use in Phase 3 trials. Still, I believe the problem is not that we can't show a therapy is effective — it is that we don't have a therapy. We don't have a molecule.

GREEN: The most promising area for new therapies, to my mind, relates to myelin regeneration and repair. There is an endogenous, preexisting pool of stem cells in the brain that are precursors for the oligodendrocytes damaged by the disease. It has been a mystery for several decades, since those precursors were first detected in the brains of MS patients and even within their lesions, exactly why these cells cease to function as they should. The other areas mentioned are all potentially promising, and it's possible that all play an important role in the degeneration. I feel some of the most exciting data on therapeutic efficacy in people suggests the myelin regenerative capacity could be harnessed for treating MS.

I believe inflammation is almost certainly the initiator of the disease process, and degeneration is a subsequent development that arises because of the early inflammation. We are doing a remarkably good job and an increasingly better job of addressing the initial inflammation, but there may be persistent inflammation that gets trapped within the brain where it is not directly addressed by most of our therapies. By the time someone gets diagnosed, there are already substantial amounts of brain injury, and unless we reverse the damage, degeneration may continue. Despite our extremely potent anti-inflammatory therapies, at best we are only delaying the degenerative, progressive phase of the disease. So I don't believe the progressive form of the disease is really separate; it just occurs at a different time. Besides the oligos, restoration of mitochondrial function may be equally beneficial and also shows promise for protection from neurodegeneration at-large, not limited to MS.

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

COETZEE: In MS, we've seen real progress in immunotherapies which, when taken early enough, could change the trajectory of the disease. We need, though, to hit MS earlier, before the damage is done, and so we need much better diagnostic biomarkers. There's also a lot of progress being made, thanks to the large-scale GWAS [Genome-Wide Association Study] and other "omics," toward understanding who is at risk and how MS is triggered. This may lead to early detection and prevention.

FOX: The positive outcomes of the ocrelizumab primary progressive trial do highlight that if we can catch progressive MS early enough in patients with active inflammation, an anti-inflammatory may still be helpful, so that's good. But we lack the biomarkers needed for early diagnosis of the progressive form of MS.

GREEN: Unfortunately, delayed diagnosis is almost written into our diagnostic criteria, because when we diagnose someone, there are two basic criteria —

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OPEXA

Nearing first data from a Phase 2b study of Tcelna, a T cell therapy, for secondary progressive MS

Neil Warma, President, CEO, Director: *Our approach with Tcelna is about influencing the immune system as a way to mediate disease, which starts with restoring the function of the body's immune system. We prime or boost or reboot the body's immune system to allow the body to fight the disease itself. We want to eventually apply our T cell approach to a number of autoimmune diseases, but the one the company has focused on from its inception is multiple sclerosis. We have run a half-dozen clinical trials treating early stage, relapsing MS and progressive MS patients with an autologous cell therapy, where the side effects are minimal. In the case of MS therapies, that is a huge advantage.*

We see MS as an autoimmune disease; a small number of T cells turn rogue and attack the body's own cells, and in the case of MS, they attack and destroy not only the insulating myelin sheath around neurons in the brain, but also the oligodendroglial cells that produce myelin, over the course of years. We clone each patient's own rogue T cells, attenuating them with radiation, and present a large number of the cloned cells to the body's immune system through subcutaneous injection, where T regs are exposed to them and go off to destroy the rogue cells throughout the CNS. This prevents further destruction of myelin sheath and of the oligo cells. In theory, some sort of repair and improvement should then take place, and we actually saw that in one of our clinical studies. It showed a reversal in disability, a first for any MS therapy. Typically, the aim is merely to slow down the rate of progression. Rarely do you stabilize, and never have we seen the condition actually reverse, indicating some sort of neuroprotection or improvement.

We are now reaching the end of a Phase 2b clinical study in secondary progressive MS. The trial has 190 patients in 35 centers across the U.S. and Canada, with brain atrophy and disease progression the key endpoints in the two-year, placebo-controlled, randomized study. We're expecting results from the trial early fourth quarter of 2016. We could potentially commercialize Tcelna with Merck/Serono, but we have developed the manufacturing and distribution solutions for this cell-based therapy in-house.

dissemination in time and dissemination in space. There has to be evidence that the disease has spread, even by the time of its initial diagnosis. As a consequence, when we first diagnose people, there's already damage, and often extensive damage.

We need better biomarkers to detect disease early — but biomarkers alone won't get us there. We understand the pathophysiology of MS far better than we understand the pathophysiology of any other neurodegenerative disease. We have a much better sense of the factors that initiate the disease process and then allow the ongoing inflammatory injury at the early disease phase. However, we need to understand the biological processes underlying degeneration better to develop both drugs and biomarkers.

We already have the only biomarker that has been predictive of clinical success and useful in Phase 2 clinical programs in clinical neuroscience: new lesions detected by MRI. That is one of the main reasons all the anti-inflammatory drugs exist in MS, and the space attracts continued interest from industry and investors. The development of additional biomarkers has also marched ahead, though it still needs a significant amount of validating work. Some of the most promising are measurements of atrophy in the nervous system — whole-brain atrophy on MRI and atrophy as measured on Optical Coherent Tomography — and functional assessments such as electrophysiology. One form of electrophysiology, evoked potentials [measuring cortical responses to a repetitive electrical stimulus], are making a resurgence because they likely measure myelin injury and processes that drive some of the degeneration.

How likely is it that some future drug therapies, each one hitting a different target, will prove complementary if used in combinations?

COETZEE: It's fair to say that in MS there are powerful immunotherapeutics available to quell the adaptive immune responses thought to drive much of the neuropathology. It's likely that if a successful endogenous or exogenous reparative therapy is developed, it would need to be given in tandem or staged with an immunomodulator to prevent destruction of the newly repaired tissues. Effort is under way to advance therapeutic development of compounds with repair or remyelinating activity in the absence of effect on the adaptive immune system.

FOX: Combinations are inevitable because, for the progressive MS patients who still have active inflammation, we will need to use an anti-inflammatory in addition to something that stops the progression. In the past, we asked whether a patient had relapsing MS or secondary progressive MS. We have now reconceptualized the disease, and we ask: Does the patient have active inflammation — yes or no? Does the patient have gradual progression — yes or no? If the first answer is yes, then we use an anti-inflammatory. In the future, if the second answer is yes, we will use a therapy developed for progressive MS. In the trial that I'm leading, the Phase 2 trial of ibudilast in secondary and primary

progressive MS, we allow patients currently on some of the anti-inflammatory therapies to remain on them. In the past, patients had to stop those therapies to go into a secondary progressive MS trial.

GREEN: When we do have better treatments for progressive forms of MS, patients might need multiple treatments because of different disease processes that all need to be tackled. This may not wait until patients become progressive because there is an overlap between refractory and progressive states. We also don't know for sure whether specific biomarkers will be tightly tied to specific mechanisms. If a particular therapeutic agent helped with mitochondrial survival, you might measure the response to therapy in a different way than you would for a remyelinating therapy.

There likely will be significant overlap between the meaningful biomarkers. Will predictive biomarkers that work with one mechanism of action work with others? In the case of the anti-inflammatories, the answer has been, yes, the anti-inflammatories that work on a variety of MOAs all seem to align with the same set of biomarkers from MRI. But even though MRI has been hugely important in the development of MS drugs to date, we should not presuppose MRI will be the meaningful biomarker for antidegenerative or neuroreparative therapies. New techniques will be developed in conjunction with new therapies. Oftentimes, biomarkers and therapies develop in tandem, because we must test out effective therapies to assess whether a biomarker has a meaningful result and then use the biomarker to assess effect. It is an iterative process.

Could combinations of new drugs pose medical, regulatory, or economic issues for treatment of MS?

COETZEE: Based on what we know today, it is difficult to predict if the cost of an expensive single treatment or combination of treatments would pose a treatment crisis. It is critical that patients with MS have affordable access to the medication that is most likely to produce the best outcome, support adherence, and maintain quality of life. The other challenge with MS is establishing a value framework for these treatments. Unfortunately, this is an area that is still in its infancy for MS.

FOX: On the access question, I've not found an insurance plan that denies coverage of MS therapies in general. It does come down to a question of which therapies are covered and what patients have to try first and either fail or not tolerate in order to move on to the next therapy. MS docs have been a little bit spoiled in past years, in that we've been able to use any MS drug we wanted, and the insurance would approve it. It's not surprising to see the situation change considering the list prices of these drugs are around $50,000 a year, though with the manufacturers' rebates, they may cost the health plan around $40,000 a year. Cost will be a significant issue in the development of progressive MS drugs, especially if used in combination with anti-inflammatory drugs.

GREEN: MS patients constitute 0.1 percent of the total population, and yet currently MS care consumes somewhere between 3 and 5 percent of the healthcare budget in the United States. In part that is a reflection of success; it means we're spending money as a society and as a healthcare system because we're being successful. But on the other hand, those treatment costs are probably outsized, especially when considering the limited efficacy of some of the agents. That raises many important questions that will take engagement from many different stakeholders, from MS patients, to providers, to healthcare systems, to the rest of society. Treatment reduces costs for care, and it reduces lost productivity in a way that may more than offset those costs. I am someone who wants to see us develop therapies that make a major difference, but the biggest challenge will be properly pricing them so they reflect all the time and resources pharmaceutical companies, the government, and academic institutions and research teams have invested, yet at the same time, recognize the limitations on healthcare resources.

FOX: One issue might make a big difference in cost. A typical MS patient will be

diagnosed at about the age of 32. Then they go on an MS drug, and we have no idea when to stop the drug, though they may live another 50 years. So they may be on a $40,000 drug for years, and then if they evolve into progressive MS, another expensive therapy may be added. But what we don't know about the initial, anti-inflammatory MS therapy is when it can be stopped. Dr. John Corboy at the University of Colorado is leading a randomized trial aimed at when to stop MS therapies. It won't give us all the answers, of course, but it'll start answering whether and when patients no longer need their anti-inflammatory therapy.

GREEN: We don't know enough about whether, with long-term treatment, the immunology of the disease process turns off. Inflammation may not be important late in the disease because the inflammatory process has caused so much damage to the nervous system that now the prevailing and operative process becomes degeneration. It might be we need some degree of ongoing and persistent dial-down on the inflammatory process. But maybe if we turn off the inflammatory phase of the disease for 30, 20, 10 years, or maybe even less, it will turn off permanently. Some recent data from use of the drug alemtuzumab suggests turning off the disease for as little as five years might have a significant effect. These are challenging questions, and they require long-term follow-up on patients, which is a huge practical and logistical undertaking and hugely expensive. It could only be done with support by federal government, large advocacy groups like the National MS Society, and potentially by single-payer health systems in countries that are smaller than ours.

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

COETZEE: It's very likely that some later-stage pathways, such as degenerative mechanisms, are similar across a spectrum

INNATE IMMUNOTHERAPEUTICS

In a Phase 2b trial with a novel drug (MIS416) for patients with secondary progressive MS

Simon Wilkinson, Managing Director, CEO: *MIS416 is an immune modulating microparticle of bacterial origin developed and manufactured by our company. Our current Australian and New Zealand-based Phase 2b trial has enrolled 93 subjects with relapse-free active disease and is on schedule to report in Q3 2017. The reported improvements in a range of MS-related signs and symptoms arising from previous open-label studies, together with an ongoing compassionate use program, have helped inform the design of our current 2b trial.*

In contrast to the acute peripherally driven autoimmune pathology, which is the predominant feature of relapsing remitting phase MS, we view secondary progressive MS (SPMS) as a neurodegenerative disease where inflammation is still significantly involved in disease pathology, but the nature of that inflammation has fundamentally changed. In large part, this shift in the type, location, and duration of inflammation in progressive MS accounts for why the present autoimmune blocking RRMS drug strategies have failed to achieve a sustained and meaningful effect in progressive disease.

Instead of targeting adaptive immune cells such as autoreactive T cells, our drug candidate modulates the myeloid-derived innate immune cells, which play an important role limiting inflammation and promoting tissue repair inside the CNS. This last point is pivotal. We are directly modulating specific innate cells that are either resident in the CNS, can be licensed to access the CNS, or can exercise an effect inside the CNS. As a result, the chronic CNS resident inflammation, which is a hallmark of SPMS, can be down-regulated, while at the same time myelin repair can be supported by improved clearance of myelin debris. Modulating these same cells can also up-regulate the secretion of important tropic factors that can directly promote neuronal survival and axon regeneration.

By adopting this strategy of taking advantage of inherent myeloid cell plasticity, it becomes possible to trigger multiple therapeutic modalities, which in turn might help in the treatment of other CNS disorders. We think MIS416 has the potential to be the CNS anti-inflammatory tool in the toolbox approach to treating many CNS disorders or injuries. While CNS resident inflammation won't be the cause of disorders such as refractory epilepsy or Alzheimer's disease, its presence is unhelpful, to say the least. If we can safely and effectively manage the inflammatory component of these conditions, then it may help clear the way for other drugs, which might be specifically targeted to the underlying disease mechanism, to work more effectively.

of NDs. But from what we know right now, early stages of most NDs are distinct and driven by different causes. Therefore each ND will likely require individualized approaches to stop the primary assault early enough to preserve function. That said, there are clearly similarities between MS and Alzheimer's disease. For example, both display mitochondrial dysfunction, a link to oxidative stress, and both show signs of inflammation. In MS, the importance of controlling inflammation is well-established and is the mechanism of several approved therapeutics. However, the role of inflammation in Alzheimer's has yet to be firmly established, even though signs of inflammation are evident. Early life exposure to environmental factors such as smoking and Epstein-Barr can drive both conditions, the difference being the genetics of the response to those stimuli. Also, we don't fully understand the role of activated microglia in initiating and/or promoting inflammation, but this is clearly a component of several NDs.

FOX: We're better off when we understand what's going on in different fields. In Alzheimer's, there has been a major focus for years on developing inhibitors of the amyloid precursor protein and more recently the BACE-1 protein that clears the amyloid precursor protein. Is that the right thing? I don't know, but there are other potential mechanisms in Alzheimer's such as dystrophic neurites in the tubular endoplasmic reticulum, which have nothing to do with amyloid precursor protein cleavage or BACE-1. So, until we figure out what causes those other diseases, it will be hard to know specifically how relevant MS mechanisms might be to other NDs.

GREEN: There is no question better understanding of the MS mechanisms might have spillover effect on understanding of other neurodegenerative disease areas, for two big reasons: shared mechanisms and a head of steam, or momentum for continued progress in clinical neuroscience. When people in the drug development or business side of the pharmaceutical and biotech industry look at the neurodegenerative space now, they see mostly failure with all the tested therapeutic candidates. But even small successes really help drive the field forward because they show it is not a lost cause. We just have to find the right drugs, the right times to administer the drugs, and the right ways to measure the drugs' effectiveness. It is a tall order, but it's not out of range. Step by step, we will make inroads and progress that shift the paradigm.

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

COETZEE: The industry's focus needs to be on progressive aspects of MS and stopping neurodegeneration. We're in need of reliable and robust biomarkers for early diagnosis and response to therapy, and better regulator-approved clinical outcome measures that will reduce the time and numbers of patients it will take to show benefit in both proof-of-concept and registration trials. Because of the considerable failure rate for clinical trials in MS and other NDs, pharma needs incentives to stay in the field. NDs pose considerable clinical development challenges related to duration of study, cost, and enrollment. Although the markets addressed by NDs are considerable, there is added risk for the clinical indications, so some concessions or incentives might promote more development in the space.

The pricing of new treatments for all NDs will be an ongoing and significant issue. We understand the need to maintain an environment that encourages research and investment by pharma. At the same time, people need access to new therapies, and access includes affordability and insurance coverage. Identifying and confirming credible connections between various NDs might stimulate clinical R&D. For MS, we need to gain a better understanding of the pathophysiology of progression before we can identify meaningful new therapeutic targets.

FOX: Progressive MS is neglected in that we have no effective therapies, not in the sense there were no trials done. We've done many, many trials; it's just that they were negative. They didn't work, I believe in part, because we kept throwing one anti-inflammatory drug or another at a disease state that's not driven by inflammation. Whether it is an errant inflammatory response to the degeneration or degeneration in response to inflammation, no one knows for sure.

We now have a very nice paradigm in relapsing MS: Do a six-month, Phase 2 trial with about 150 patients. If you show that your drug reduces new lesions in MRI, you proceed to your Phase 3 trial to look for reduction in clinical relapses, which will be the basis of FDA approval. Almost invariably the drug shows benefit and gets approved, unless there's a safety signal. But in progressive MS, we have a couple of challenges. One, we are not really sure what the pathophysiology is. What is really going on that is causing these patients to have a gradual, little by little decline in their function? We don't know. Two, we have no Phase 2 outcome metric; progressive patients get few or no new lesions in MRI. Although sponsors have tried a few drugs in progressive MS, it's been in trials of 1,000+ patients followed over two years.

What industry companies have been doing over the last 10, 15 years is taking their success in relapsing, remitting MS and just slapping it on progressive MS, hoping that it'll work, and unfortunately it hasn't. But I believe industry has now gotten the message to stop and break out of the old pattern.

GREEN: Industry will be well-served to associate itself and support research that comes out of smaller biotech companies. Those companies have the potential to be nimble, responsive, and innovative in a way that's very hard for huge corporate organizations. Some of those companies will grow out of the research done by academics within the university laboratories. Can academic institutions figure out a way to cultivate and support that kind of research? The jury is partially out on that. There are challenges for both types of very large institutions because many people consider themselves stakeholders in that process, yet some may not have adequate knowledge of what needs to get done, and some may be too focused on bureaucratic processes rather than accomplishment. We learned from the IT industry that small-company qualities such as nimbleness, responsiveness, innovation, and idea-fermentation are all crucial elements to success in science-based fields.

Pursuing Drug Development Against Investors' Advice

ED MISETA Chief Editor, Clinical Leader @EdClinical

There are probably few CEOs in the pharma industry who have as much insight into one of their products, as well as its patients, as Seth Lederman, M.D. Lederman is the CEO of Tonix Pharmaceuticals, but did not travel the usual route in getting to that position. He started the company, provided the vision for it, and also supplied the molecule currently in its pipeline; cyclobenzaprine, a drug being developed to address the sleep issue associated with fibromyalgia.

He is also in the unique position of having worked as a scientist in academia (at Columbia University) and as a physician treating patients, prior to starting the company. This experience gives him the perspective of having worked with fibromyalgia patients before setting out to find an effective treatment for them.

"Everybody knew the existence of patients with chronic, widespread pain was a common problem, but for a variety of reasons doctors didn't want to deal with fibromyalgia," he says. "In my experience working with these patients, I was reminded of my early days in medicine trying to treat patients who had been infected with HIV."

Lederman has made quite a transition in this journey of going from physician, to scientist, to CEO. Even when he was working as a bench scientist developing new drugs, he felt the natural place for him was in a large pharmaceutical company. In 1989, he even spent four months performing a short sabbatical with Merck, where he served as part of an industry-leading group developing therapeutic monoclonal antibodies.

"We were trying to engineer a monoclonal antibody as an HIV treatment," says Lederman. "This was also at a time when monoclonal antibodies were out of favor as therapeutics. Merck had a leading team in that area, but at some point, decided they didn't want to be in therapeutic antibodies and shut down the group. Ironically, today one of their biggest products is KEYTRUDA, which is a therapeutic antibody. Once they shut down their internal group, they had to purchase Schering-Plough to get an antibody."

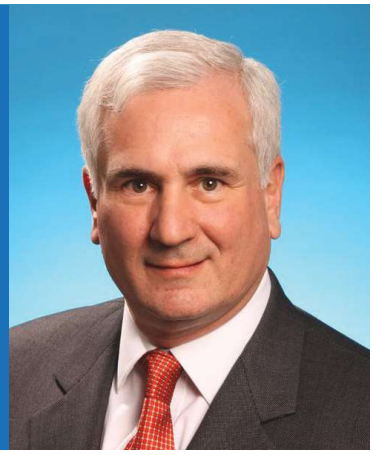
But shortly thereafter, he sensed he had changed — or the industry changed beneath him. He felt many of the large pharmaceutical companies were shifting their focus from research to marketing organizations. Today he believes much of the innovation in the industry is coming from smaller companies. "In that old era, Big Pharma business development groups consisted of a couple of people. Today those departments might have 100 employees. That is a huge change for the industry, and in retrospect, I'm not surprised I ended up working for a smaller company."

WHEN INVESTORS ARE SKEPTICAL

The first company Lederman formed to work on cyclobenzaprine was called Vela Pharmaceuticals, which received some investor funding and performed a small study. Unfortunately, the company's investors decided fibromyalgia was too challenging for a VC-backed firm, so they stopped working on the molecule. That changed the entire direction of Vela.

According to Lederman, those VCs called a lot of experts in the field and were told that fibromyalgia didn't exist or was not a real medical condition. At one point, a

> *"Once there was an approved drug on the market, naysayers could no longer say the condition didn't exist, or that the FDA would never approve a drug for it."*
>
> **SETH LEDERMAN, M.D.**
> CEO, Tonix Pharmaceuticals



senior consultant with a lot of experience in the industry told them the FDA would never approve a product for fibromyalgia. After hearing those types of comments, pursuing low-dose cyclobenzaprine before bedtime for fibromyalgia just seemed like too risky a proposition.

"Ultimately, you do have to go to the FDA for approval, and the FDA listens to those same experts in the field," says Lederman. "At that time, there were too many experts who didn't believe fibromyalgia was a real condition. Unfortunately, I never had the opportunity to be on any of those calls and never had the opportunity to debate those opinions. But even during that time, which I call the dark days of fibromyalgia, there were other names that were applied to the condition, such as chronic widespread pain. If you knew any of these patients, you knew the condition was real. It's almost as if experts simply didn't like the name. In retrospect, it's interesting to have lived through the period where the entire mindset on this has changed."

FRUSTRATION LEADS TO NEW COMPANY, BUT NO VCs

Lederman knows that it is not unusual for VCs to change the focus of a company. Since professional managers are often put in place by the investors, the control and vision of the founder can often be pushed aside. "It was a little frustrating for me, because you feel like your ideas and IP are tied up in the company," he says. "It did slow me down for a few years, and I was not able to regain control of that IP until 2006, when they finally acknowledged they were no longer pursuing the molecule."

The beliefs of the consultants and investors did not sway Lederman's convictions, and he remained committed to finding a new treatment for those patients he spent so much time treating. After he was able to retain the rights for the drug from Vela, he found a partner who was equally passionate about finding a treatment. In 2007, the two of them founded a company called Krele, which later changed its name to Tonix.

Lederman admits that VC investors can bring a lot more than just money to a company. They can help find directors and can locate consultants to use for clinical development. In fact, he says at Vela it benefitted having VC investors on board.

But by the time he formed Krele, it was 10 years later, and he had formed his own network of potential board members and investors, which is why he opted to forgo seeking VC investment. "We funded it

on our own and then recruited board members who were interested in the fibromyalgia program and were able to invest some of their own money. My time with Vela was a learning experience, and it was a little frustrating, but what I learned from it definitely helped me down the road."

While Lederman liked the name Krele, he notes Tonix is derived from the word tonic, which in the past was defined as a gentle, soothing medicine. Putting an X at the end simply gave it a more modern look and sound. It also ties in with his goal, which has been to find a fibromyalgia medicine that is well-tolerated by patients.

THE SEARCH FOR A PHARMACEUTICAL PARTNER

As he started to again develop cyclobenzaprine for patients, Lederman felt it would be good to have a pharma company working with him as a partner. "I approached large pharmaceutical companies and proposed that they either partner with us or purchase the technology," he says. "I also cast a very wide net — going to big, medium, and small companies. I focused my search on those companies that were working on disorders of the central nervous system or had a candidate in their pipeline dealing with sleep disorders or pain."

There were two principal ways he made contact with potential partners. The first was through the Licensing Executives Society (LES), an association for IP, technology, and business development professionals. The goal of LES is to help facilitate global IP commerce through education, networking, best practices, and mentoring. Although the organization is not 100 percent pharma, Lederman was able to use their directory to reach out to business development professionals in the industry. The other method he used was connections made at pharmaceutical research and investor conferences.

Most of his contacts started with either an email or a phone call. Once a confidential disclosure agreement was signed, information was exchanged, followed by a face-to-face meeting. Lederman feels that if you can get to three meetings, that's generally a good sign. He believes by the third meeting companies are lining up experts and taking a close look at the molecule. Although he was able to secure a third meeting with a couple of companies, that was as far as he got in the process.

"I think the main problem was the reaction of potential partners that we did not possess enough data, which posed an increased level of risk for them to invest time and money," notes Lederman. "Today the trend seems to be that companies are willing to pay more for a program that is sufficiently de-risked, as opposed to paying less for a molecule but having to absorb the risk of taking it to the next level. They also may have had some of the same concerns as our VC funders at Vela, but if so, those concerns were not expressed as candidly."

Although Tonix had already completed one Phase 2 study, several companies told him they might be interested after a second larger and more comprehensive study was performed. But during that time, another critical event occurred: The FDA approved Pfizer's Lyrica for use in patients with fibromyalgia.

"That was really a watershed moment for the industry," says Lederman. "Once there was an approved drug on the market, naysayers could no longer say the condition didn't exist, or that the FDA would never approve a drug for it. All of those concerns just seemed to dissipate.

FIND A CRO AND DO IT YOURSELF

At that point, Lederman decided the best way for the industry to realize the significance of the molecule was to take it through to clinical testing himself. Tonix conducted a second Phase 2b study, which enrolled more than 200 patients and seemed to successfully demonstrate its tolerability and activity. Tonix is currently conducting the first of two Phase 3 trials. Dosing started in May 2015, with results expected to be known by the third quarter of 2016. The current Phase 3 trial has targeted 500 patients in the U.S.

At this time, it appears Lederman's transition from scientist to CEO is nearly complete. The final step will hopefully involve an approval from the FDA for cyclobenzaprine and speeding the drug to patients in need, something he has looked forward to for more than 10 years. "I think the main reason I became a CEO is that I was more passionate about the project than anyone else," he adds. "That passion to help patients is what continues to drive my search for new medicines and new relief for patients." L

HOW TONIX RECRUITED FOR ITS PHASE 2B CLINICAL TRIAL

To recruit the 200 patients for Tonix's Phase 2b study, CEO Seth Lederman, M.D., secured the services of a CRO, which then reached out to sites and investigators. There were also two forms of advertising used to attract patients – a central campaign and a localized campaign that individual sites were able to perform with funds provided to them. The centralized campaign has a website and attempts to reach potential patients via both the internet and social media. Both efforts are overseen by the CRO.

Since the study is attempting to improve the level of pain via better sleep, each night patients will complete a telephone diary consisting of a series of questions answered via keypad. Patients will register a score between 0 and 10, indicating the level of pain experienced in the last 24 hours. Lederman is hopeful for the benefits new technologies may bring and notes future studies may even incorporate validated wearable devices that would track the amount and quality of sleep for patients.

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Alios BioPharma: From Startup To Big Pharma

SCOTT WESTCOTT Contributing Editor

If you had told Lawrence Blatt a decade ago that he and his team from then-fledging startup Alios BioPharma would today be working under the Big Pharma umbrella of Johnson & Johnson, he'd likely have written you off as delusional.

After all, to do so required navigating a range of potential obstacles and setbacks. For starters, Blatt and his cofounder, Leo Beigelman, did not start the company with the intentions of ever selling it. Then there was the matter of having to repeatedly secure funding in the midst of a historic recession in order to continue to develop the portfolio of potential therapeutics for viral infections. And finally, a buyer would have to craft a unique proposal that offered compelling selling points beyond a $1.75 billion price tag to convince Blatt and his cofounder to sell.

Yet, that's pretty much what transpired. The acquisition closed in November 2014, with Alios becoming part of the infectious disease therapeutic area of Janssen Pharmaceutical Companies of Johnson & Johnson. The acquisition included Alios' portfolio of potential therapeutics for viral infections with the promising compound AL-8176, an orally administered antiviral therapy for the treatment of infants with respiratory syncytial virus (RSV). RSV is the last of the major pediatric diseases that currently has no effective therapy — a fact that makes any potential treatment extremely valuable. The acquisition included two early-stage compounds for hepatitis C (HCV) that have the potential to augment Janssen's existing HCV portfolio as well. The deal also featured the unexpected aspect of J&J welcoming the Alios team to fully integrate with Janssen and offering them nearly unprecedented autonomy as well as ample support and resources to continue pursuing their promising work without significant interference.

Today — well over a year after being acquired — Alios seems to have integrated smoothly with Janssen in what appears to be one of those rare instances in which an acquisition plays out much like it was outlined in the corporate press release announcing the deal. Blatt serves as global therapeutic area head infectious diseases and vaccines, Janssen Research and Development, and the entire team from Alios remains intact.

"If you come to our building, it still says Alios on the sign, and we are moving forward with our dream of building a world-class portfolio," Blatt says. "It's under the J&J flag, but it's the same team and vision, just with a lot more power and resources.

"No doubt, we've had an outstanding outcome. A big part of our success had to do with the quality of the science and the quality of the data that really drove it. And there certainly was luck involved as well."

Luck perhaps. But a closer look at the Alios story reveals it's the sort of luck identified in that familiar old adage, "Luck is what happens when preparation meets opportunity." Blatt and Beigelman launched into their venture with ample preparation and experience and took the steps to ensure they met frequently with opportunity — despite operating in an overall environment in which that opportunity was often in short supply. It's also a story that affirms those other two factors highlighted by Blatt — good data and solid science — are fundamental must-haves for startups that aim to succeed on their own or ultimately attract the interest of potential buyers.

BIG IDEAS WORTH PURSUING

The Alios journey began in 2006 with the core mission of developing a portfolio of antiviral therapeutics based on nucleoside analogues that can prevent viral replication in infected cells. In addition to their shared research interests, Blatt and Beigelman had history together, having worked together at pharmaceutical companies including another Bay Area company, InterMune.

"Leo and I had worked together for more than a decade and had a number of big ideas that we wanted to pursue, but we wanted to pursue them in our own shop," Blatt says.

They started Alios with their own money as well as funding from a small group of investors made up of friends and associates. The firm operated virtually for the first two years, with no significant dedicated office or lab space. From the start, the partners were focused on growing a company that could take promising drugs from R&D to product launch.

"Was it our intention to start a company and sell it five years later? Absolutely not," Blatt says. "Our philosophy was you just don't do that. Instead, you build the company unless or until it makes sense for someone to acquire it. I think if you don't have the attitude that you are going to build the business to stand on its own, you are going to skimp. I've seen other businesses do that, and it typically doesn't work out. So we were fully prepared, if needed, to take this thing all the way to product launch."

By early 2008 they had developed some compelling science and had accumulated enough supporting data to turn their attention to raising Series A funding. They felt confident they were well-positioned to generate serious interest. Yet, what they couldn't control was the unfortunate timing. By the late summer of 2008, the financial crisis was just unfolding, and the result was a chilling effect through the entire economy. Of course, investment in biotech startups was no exception.

"In the summer of 2008 we were on a strong trajectory," Blatt recalls. "Then, by the fall, the whole world was falling apart."

LEVERAGING RELATIONSHIPS TO BEAT THE ODDS

The partners assessed their situation and decided to forge ahead. They had drawn the interest of several investors prior to the market crash and stayed focused on building those relationships — several of which had been established and maintained for many years prior. For instance, they had connections to the Roche Venture Fund, which they had interactions with during their years at InterMune and Amgen.

"I think relationships are so very important," Blatt says. "The venture capitalists see a lot of good science, but it comes down to whether or not they think that good science can be implemented. They need to feel confident that you can actually get it done."

In addition to long-standing relationships with key contacts at Roche, there also was a wild card in the mix. Blatt had previously attended the now-defunct annual C21 BioVentures Conference, an event he describes as "speed dating for startups." One promising connection he made at the event was with representatives from Novartis Ventures. Blatt's 15-minute pitch was enough for Novartis to see Alios' potential. So they decided to take the relationship to the next level, setting up subsequent meetings to gain a deeper understanding of Alios' portfolio. "They ended up being our lead investor in starting off," Blatt says. "That was pretty encouraging, considering we met them cold at that conference."

Ultimately, the partners were able to leverage the burgeoning connection with Novartis and the long-term relationships with Roche and other established investors to beat the odds in an environment in which venture funding had all but ground to a halt.

"We were able to get the company funded in spite of the fact that we were probably the only Series A done in the fourth quarter of 2008. If there were others, they were very few," Blatt says. "I think it came down to long-standing trust. Also, we had innovative ideas, a lot of experience, and a track record of success. Working for other companies, Leo and I had been co-inventors on many patents, some of which are approved drugs today, so I think they could get a real sense that we knew what we were doing."

'A PLAN FOR A FULL PORTFOLIO'

With what would amount to $32 million in Series A funding secured, Alios took a big step forward. As the cofounders moved to scale up their business, they found that the dismal economic environment did have an upside. There was plenty of affordable lab space and equipment, as well as an ample supply of talent.

With added staff and resources, they focused on advancing the most-promising programs in their portfolio.

Yet, almost immediately, they faced a challenge. One of their lead programs, a broad-spectrum antiviral that activated a component of the host immune pathway, ran into problems. The initial leads, which had been licensed by the Cleveland Clinic, were unable to be advanced. While later leads showed promising antiviral effects, they came with significant toxicity, resulting in the need to stop the development. While disappointing, for Blatt the setback underscored the importance of having a robust portfolio of potential programs in the pipeline.

"From the start, we had a plan for a full portfolio, because, let's face it, if you have one program and it succeeds, great. If it fails, you're done," Blatt says. "We knew we didn't want that, which is why we were so focused on building a portfolio of products based on nucleotide chemistry."

Indeed, the company focused on developing its entire portfolio, and by 2010 experienced success in developing a promising treatment for HCV. To accelerate that effort and access additional funding, they partnered with Vertex Pharmaceuticals in a deal that paid Alios $60 million up front for worldwide rights to two of its preclinical hepatitis C candidates, ALS-2200 and ALS-2158. The Vertex partnership delivered a key injection of undiluted financing in both up-front research funding as well as milestone funding.

GAME-CHANGING RSV TRIAL RESULTS

By early 2014, Blatt and his team were again considering the best path forward to grow the company, so they started the process of seeking Series B funding. Meanwhile, they were making significant progress on several promising drugs, including one that targeted the HCV and another that focused on RSV. The HCV therapy showed real promise, but would

require large clinical trials. They viewed their promising work in RSV as best in class. Looking to prioritize and make the most effective long-term move for the company, they decided to establish a partnership for the HCV therapy and hold on to the RSV program.

"It was a move pulled right from George Rathmann's playbook from the early days of Amgen," Blatt says, referring to the late chief executive of Amgen, who is widely considered one of the fathers of the biotechnology industry. "Amgen partnered its first assets and held on to later assets. At the time, it made sense for us to take a similar approach."

They focused energy and resources on RSV, moving the drug through development all they way into a Phase 1 challenge model. At that stage, researchers were able to infect volunteers with the RSV virus to test the effectiveness of the drug. The results were impressive and were recently published in the *New England Journal of Medicine*. Within a day and a half of receiving the drug, volunteers infected with RSV didn't show any symptoms and had completely lost the virus. In the placebo group, the virus persisted several days, as did the accompanying symptoms.

"This was pivotal data for us," Blatt says. "And based on that data, we started to get unsolicited calls from several Big Pharma groups asking if we wanted to partner our assets. We didn't want to do it. We had money. We had the support of our board. And so we said, no, no, no."

> *"Was it our intention to start a company and sell it five years later? Absolutely not."*
>
> **LAWRENCE BLATT**
> Global therapeutic area head infectious diseases and vaccines, Janssen Research and Development

GETTING TO YES

Alios kept saying no as they continued on the track to secure Series B funding. Yet, as interest amped up and broadened, simply saying "no thanks" was becoming increasingly difficult. Alios clearly had something Big Pharma really wanted — badly. Several times they were asked if — since they didn't want to partner — they would consider selling the company. After consulting with their board, Blatt and Beigelman agreed that the responsible move was to consider all options.

What followed was a heady and, at times, nerve-racking stretch in which Alios moved down several parallel tracks, assessing which one led to the most-promising future. With the recession over, the biotech IPO window was back open, and the potential to go public was real. Meanwhile they also were talking to multiple Big Pharma companies about potentially selling the company.

Ultimately, Alios started leaning toward selling and ended up with seven bids. The majority of the offers were in the same ballpark from a financial perspective. As the partners evaluated the proposals, they looked for a differentiator and found it with J&J. The J&J offer proposed that Alios join with its Janssen group. Yet, unlike typical acquisitions, Alios would, in effect, remain largely autonomous in terms of leadership, staffing, and its approach to R&D. Add to that the $1.75 billion purchase price and the ample global resources of J&J, and it was an offer extremely hard to refuse.

"It was very important that the product get to market, and that we didn't sell to a company that would mess them up, which can happen, by the way," Blatt says. "I think it was an unprecedented and brilliant plan that J&J gave us the chance to remain leaders of our program and in fact take over the leadership role for the infectious disease group."

'A BIOTECH FEEL INSIDE BIG PHARMA'

Now, almost 18 months after the deal was inked, Blatt says the transition has been remarkably smooth. The Alios team has remained intact and has developed strong partnerships with the Janssen team, as well as received steady support from Janssen leadership.

"What I've been asked to do is create a biotech feel inside a Big Pharma company," Blatt says. "Both teams have responded tremendously well."

Admittedly, Blatt says there is a difference operating in a Big Pharma environment compared to a small start-up. Yet, he said adapting to working with more-established corporate policies and procedures has been manageable. "As with anything, there is a tradeoff," he says. "Was it easier to get things done at Alios? Absolutely. Do we now have more resources and technologies and the capability to do things on a scale that we never could have done on our own? Absolutely."

Blatt says the "bigger playground" provided by Janssen will ultimately allow Alios to more effectively accomplish what they set out to do more than a decade ago — develop a wide range of antiviral drugs that make a difference in the lives of patients around the globe.

"We had a lot of ideas that we simply couldn't work on when we were small and on our own," Blatt says. "In the J&J environment we're able to build out a portfolio that I think is industry leading. When I look back and think what happened between 2008 and 2014, it's really remarkable. We have a great team that stayed focused and helped make this happen. We're in a good place."

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How Agile Therapeutics Got Through A Critical Phase 3 Trial

ED MISETA Chief Editor, Clinical Leader @EdClinical

The challenges of conducting a Phase 3 trial and then using that data to get an approval from the FDA are something every head of clinical research knows very well. The clinical team at Agile Therapeutics knows it all too well. The company has been down that road once before, only to come away empty-handed. Before its second attempt, the company hired Elizabeth Garner as chief medical officer and SVP of clinical development to take control of the process.

"The active ingredients used in the patch are already used in multiple contraceptives and have been for more than 25 years," says Garner. "Those ingredients are levonorgestrel (LNG), which is used as a standard of comparison of venous thromboembolism risk among progestins, and ethinyl estradiol (EE), a synthetic estrogen used in many currently marketed contraceptives. [Because these have been previously used], some of the information required for approval can come from other studies not conducted by or for Agile. We believe our proprietary Skinfusion technology delivers the hormone (EE, a synthetic estrogen) in a more appealing form."

Measuring the effectiveness of a contraceptive in a clinical trial is not an easy process. These studies are typically single-arm, open-label trials. Since the purpose of the patch is preventing pregnancy, the trials are never placebo-controlled. "We measure exposure over a 28-day cycle of use," says Garner. "Our studies are generally 13 cycles (one year) in duration, and the FDA requires approximately 10,000 cycles of exposure and a minimum of 200 female participants on the drug for one year."

To measure the effectiveness of its contraceptive, all contraceptive studies use a calculation known as the Pearl Index (PI). "This index can be affected by many factors," notes Garner. "There are differences in study design, sensitivity of early pregnancy tests, population, user experience, and inconsistent or incorrect use of the contraceptive method. For those reasons and more, patient engagement is something we obviously spend a lot of time thinking about."

NO APPROVAL ON FIRST TRY

The Twirla patch, also known as AG200-15, has already been administered to more than 2,100 women in completed Phase 2 and 3 studies. It has been through two Phase 3 studies, one of which was submitted to the FDA for approval and subsequently rejected. Results from those studies have shown the pharmacokinetic profile is consistent with a low-dose contraceptive, it was well-tolerated with a low rate of estrogen-associated adverse events, the Skinfusion technology performed well under normal daily activities (bathing, exercise), and the effectiveness in prior Phase 3 studies has been comparable to approved low-dose oral contraceptive comparators. The problem is, after an extensive Phase 3 study with what the company believed to be promising results, Agile still did not have a product approval from the FDA. "The FDA issued a Complete Response Letter in February 2013 citing insufficient evidence of efficacy and issues with our study conduct. Specifically, it noted the dropout rate and loss to follow-up, subject compliance with the proper use of the study drug (both the patch as well as the pill), and overall data quality. Patients were getting pregnant using a pill that we knew to be highly effective. They requested we complete a third Phase 3 study with better study conduct and improved oversight, support of subject compliance, and avoidance of dropout and loss to follow-up (i.e., patients unaccounted for at the end of the trial)." Long story short: If Agile was to complete a third Phase 3 study, Garner knew she would have to focus on selecting and working with an experienced CRO to ensure the close oversight of the trial the FDA was asking for.

THE HUNT FOR FUNDING A NEW TRIAL

The new Phase 3 trial was initiated in September 2014. This was also a single-arm, open-label study that was set to treat approximately 2,000 subjects for one year (13 cycles), at 102 clinical

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> *"To convince the investment partners that we had the right product for them to invest in, we had to demonstrate that we were working with the right CRO partner."*
>
> **ELIZABETH GARNER**
> Chief medical officer and SVP of clinical development, Agile Therapeutics

sites in the U.S. The PI would again be used as the primary endpoint. A main focus would be on correcting the deficiencies noted by the FDA, and the study was scheduled to be completed in the fourth quarter of 2016.

The first thing Agile needed to do was find the funding that would allow it to take on such an immense trial. Company CEO Al Altomari did so by taking the company public. Garner, who was involved in that process, describes going through an IPO as incredibly stressful and now compares it to the challenge of an NDA (new drug application) filing ... times three. Despite the challenges faced, the company was able to raise the money it needed.

"To convince the investment partners that we had the right product for them to invest in, we had to demonstrate that we were working with the right CRO partner," says Garner. "The investors felt some of the oversight issues we experienced in the past were due to the conduct of the CRO. In a few instances, some investors believed that some of the sites being used simply did not have enough experience in contraception. Therefore, we knew the CRO we selected would have to be experienced and well-known in the industry, it would have to have access to experienced clinicians and study coordinators, and it would need to help us enroll the right selection of study subjects. This left us with a very critical decision to make."

AN IN-DEPTH CRO ANALYSIS

But how does a small company the size of Agile go about finding a known and experienced CRO, when your size makes you feel like they won't view you as worthy of their time and effort? Garner figured the best way to start was by performing some research. She learned 64 percent of post-Phase 1 studies are outsourced. The outsourcing rate was 52 percent for large (top 20) pharma companies, but rose to 88 percent for small companies. Looking at research performed by University of the Sciences in Philadelphia, she was able to better organize her thoughts regarding the top five criteria to look for in a CRO. They are, in order of importance, a CRO your team can work with, a project management team devoted to the study, recent experience in the same indication (a criteria very important to Garner), overall experience in the therapeutic area, and the background of team members.

She also considered the results of other industry surveys which noted cost was not generally a leading criterion, but quality and timelines were, along with the process for issue identification and resolution. The most important quality attributes reported by others going through the same process, she learned, were values, work ethic, and team chemistry. That convinced her of something she had already believed: that outsourcing relationships are really about people. But one concern still weighed heavily on her mind: the size of the CRO.

"Big Pharmas generally outsource to the largest CROs," she says. "Studies also have found those that do are satisfied with the results. But only about 10 percent of small sponsors spend most of their outsourcing budget on the top five CROs. In fact, 70 percent of small companies dedicate less than 10 percent of outsourcing spend to those top five companies."

Looking at research performed by The Avoca Group, Garner also found that small and midsize sponsors that used the top five CROs to meet less than 25 percent of the outsourcing needs were more satisfied than those who used the large service providers more liberally. "It seems to me that large companies are more comfortable with the large CROs, and the small companies are more comfortable with small CROs," she says. "That finding did not really surprise me."

Overall, that same Avoca study found large CROs excelled at providing a global footprint, standardized procedures, and capacity. The medium and small CROs excelled at value, lower turnover, flexibility, and personal service, all things that she valued highly. Smaller CROs also seemed to have strong experience in specific therapeutic areas and obviously are less likely to have strategic partnerships in place that might take priority over a smaller study.

CHOOSING THE RIGHT PARTNER

Garner's research seemed to point toward working with a small or midsize CRO, although she knew the Wall Street investors who helped finance the study were looking for a well-known and established service provider. Although she now had a better-structured and researched list of criteria to look for in a partner, Garner was still no closer to selecting the right CRO. So she began a search process that would end up taking about four months to complete.

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To make the selection process easier, Garner decided to make a list of the considerations she felt were of greatest importance to her company. The top five criteria she came up with were quality (especially in the data that would be gathered), technology and systems (so as to properly monitor compliance and know when to intervene), experience in contraception studies, name recognition, and finally cost. Although Agile was able to raise funds for the study, Garner notes she still had tight budgets that had to be met.

She also decided on the process she would use to find the right partner, which would consist of an RFP, a detailed review of the responses, selection of candidates for in-person meetings, a formal bid defense of the top candidates, and finally a ranking for each candidate of the key considerations noted above.

"A critical component of the selection process was hearing directly from the candidates we felt would be a good fit," she says. "Instead of just looking at information submitted, we wanted them to make their best pitch to us in person. Therefore, the in-person meetings contained a lot of information-sharing by the contenders." Specifically, Garner asked the following questions:

- Why are you the best CRO for this project?
- What is your approach to working with small companies?
- Describe your approach to site selection, monitoring visits, and oversight.
- Describe your experience in women's health in general and contraceptives in particular.
- How many CRAs (clinical research associates) will be assigned, and what is the CRA/site ratio?
- Elaborate on your approach to subject retention and compliance.
- Provide metrics on study timelines, monitoring, and query/database lock procedures.

The information Garner and her team received was valuable and insightful. In addition to the information obtained, she also was able to observe personal qualities of the presenting teams and their ability to interact and converse with her own team members. "For me, a very important part of this process was truly about understanding the medical monitor and making sure they really understood what we needed and what we were looking for," she states.

THE RANKING PROCESS

Now that most of her work was complete, the hardest part of the selection process still remained: ranking the contenders and selecting a partner. Garner produced selection criteria for the project, which she notes can also be used for future projects simply by varying the order of importance (which might vary based on the specific needs of a trial).

For this trial, Garner placed therapeutic expertise and experience at the top. With this being the third Phase 3 trial for the patch, she knew success was critical, and that a fourth trial would not be financially viable. In fact, the success or failure of her company was likely riding on it. Rounding out the top five criteria was the CRO's CTMS (clinical trial management system), past enrollment and site performance, the site selection process, and the risk identification/mitigation process. Other criteria considered were the project management model, proposed EDC (electronic data capture) system, experience with electronic patient diaries, projected enrollment rates, timelines, site monitoring model, metrics quality, study timelines, the project team, and cost. After a very thorough ranking and evaluation process, Agile selected PAREXEL as its partner.

"For each criterion that we looked at, the compatibility with our team, our processes, and our systems were critical factors for us," says Garner. "The knowledge they had coming in and the proposal they presented were impressive. And even though they are a large company, they had the expertise and name recognition we needed, but as a small company, we also felt they would treat us the way we wanted to be treated. When they made their presentation, it was clear to us that really did their homework, took the time to understand the issues we faced, and they even went so far as to understand what is currently happening in the contraceptive market, and the pros and cons of using electronic diaries. That attention to the things we cared about really stuck with us."

Agile will continue to have statistics performed by the same vendor who provided those services for the two prior Phase 3 studies. The FDA had no issues with the analysis performed, and Garner felt there would be efficiencies by sticking with the same company they already knew and worked with.

For other small companies going through this process, Garner also recommends thinking about internal team strengths and identifying gaps that might exist. For Agile, medical monitoring, statistics, and patient recruitment were important considerations.

Although cost has to be a concern for any small company, she cautions this should never be a reason to cut corners or consider lower quality work. Instead, she recommends companies consider the potential to save money by sharing tasks with the CRO and therefore ensure the CRO selected is willing to do the same. To properly understand the CRO's processes, she recommends performing a thorough review of their SOPs.

Finally, Garner acknowledges that issues will arise in any relationship and advises companies to thoroughly explore an issue resolution/escalation plan up front. "Ensure you have a responsive point person at a sufficiently high level," adds Garner. "They will be your sounding board within the CRO. This is the person who will perform troubleshooting and problem solving, and the person responsible for adding or replacing team members, when necessary. And take the time to explore the company culture. In any relationship, people and relationships will always be the ultimate keys to success." L

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Outside Perspectives On Change

Tackling Transformations In Highly Regulated Industries

PAT CORMIER

Organizations everywhere aspire to create a pipeline of persuasive leaders who will help drive their business to the next level. Cultivating this kind of talent presents challenges — even more so when you need leaders who can steer the organization through uncharted waters and help it adapt to change. Within the life sciences sector, regulation brings a host of additional roadblocks; leaders have to be better equipped than ever to overcome the challenges.

Most organizations struggle to overcome the organizational inertia around change, adapting internal process to external realities and building buy in. Within highly regulated industries, change is often accompanied by the looming threat of legal ramifications, if handled incorrectly. In too many cases, this danger alone introduces the dreaded "compliance" question, which often shuts down any meaningful change effort before it even begins.

When it comes to change, leaders in life sciences must overcome regulatory, cultural, language, and process challenges to adapt to a world that's evolving faster every day. But it's not an insurmountable task. There are some simple concepts leaders can use to empower themselves and their teams to tackle change, even within the confines of the environment:

APPROACH CHANGE AS AN OUTSIDER

Leaders need to step outside their industry and role, leaving the typical playbook behind in order to frame the need for change and the opportunities change will present within a highly regulated environment. Taking an outside perspective requires leaders to question the messages they are delivering around change and ask how they are being perceived by the intended audience. Instead of asking, "How can we do this better?", try asking, "Why do we do it this way to begin with, and is there a better way to achieve the desired result?"

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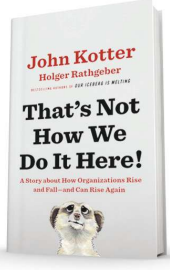

KEEP TERMS SIMPLE AND CLEAR

One of the most pervasive barriers to tackling change in any industry — but particularly in regulated sectors — is the language used to discuss alternate ways of working. Terms such as "regulation" and "noncompliant" provide natural barriers to change and eventually cut off questioning existing processes altogether. Organizations need to come to an understanding around corporate language, such as whether "compliance" refers to compliance with laws or with internal policies, in order to determine how to accurately and clearly frame the opportunity in pursuing a change agenda.

PURPOSEFULLY BUILD TEAMS OF DIVERSE PERSPECTIVES

While change initiatives invariably need input from the organization's top experts, teams composed solely of experts can be limited in their thinking, confined mainly to improving upon "business as usual." Teams that incorporate minds from all levels and backgrounds, across departments, and even geographies, however, can enable life science change leaders to inject new perspectives into the conversation, challenging basic assumptions and yielding very creative solutions.

Whether tackling transformation in medical device manufacturing processes or forging more collaborative relationships within pharmaceutical sales channels, implementing change within regulated industries requires a focused and deliberative effort. Leaders who approach change from an outside perspective, using clear and simple terminology and with support from diverse teams, are most likely to see their transformation efforts succeed. L

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