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NOVEMBER 2016

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p. 18

David Meeker, executive VP and head, Sanofi Genzyme

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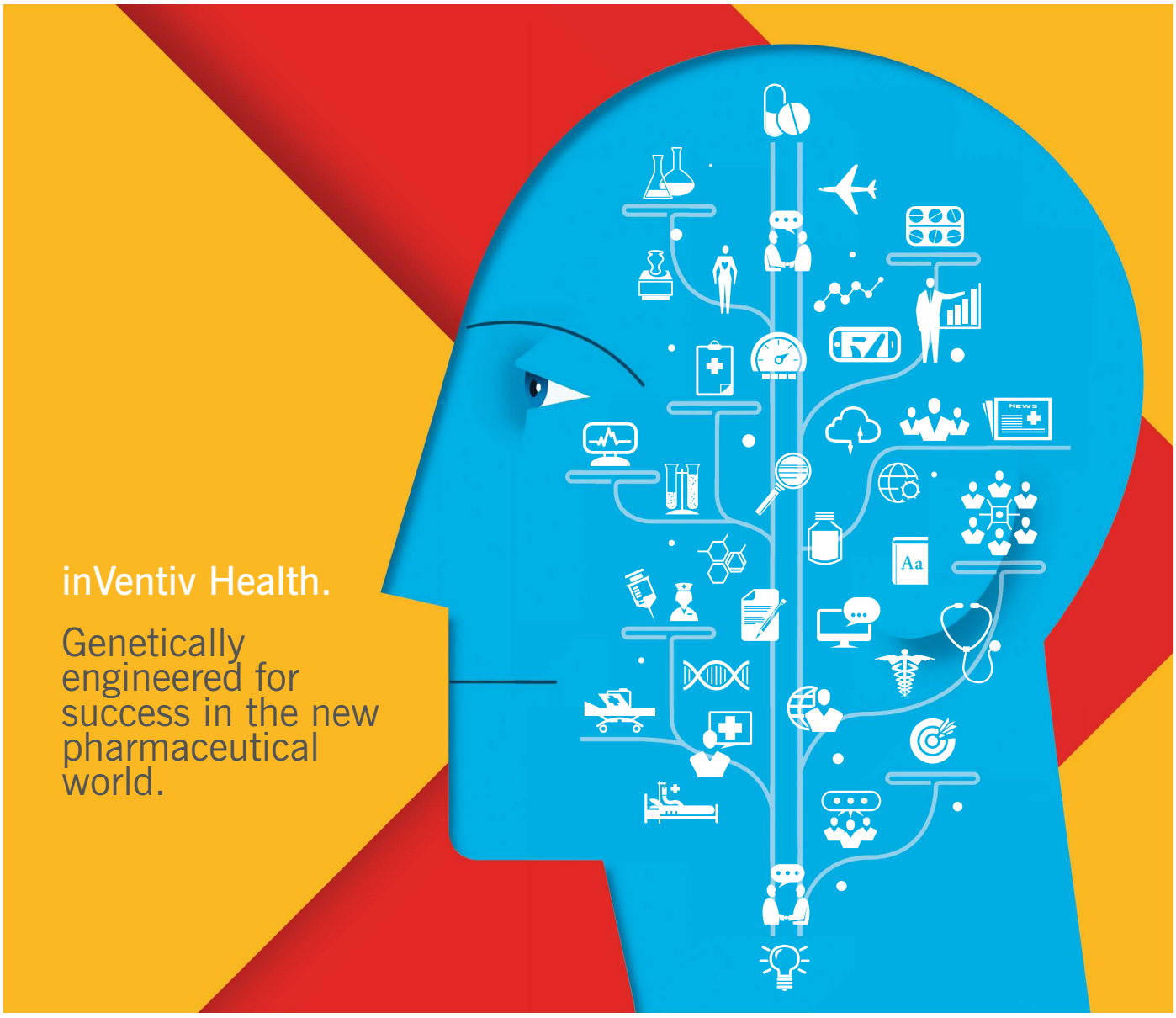

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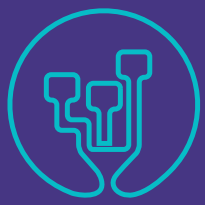

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Despite Public Sentiment, Biopharma Has *Many* Bright Spots

ROB WRIGHT Chief Editor

Tired of the biopharma pessimism? Before writing this month's Editor's Note, I reflected on what had been written in this column over the past 10 months. While I've delved into a wide variety of topics (e.g., activist investors, breakthroughs, Brexit), 40 percent of the columns touched on drug pricing (a rather polarizing subject). When thinking about all the hostility heaped on our industry — especially now during a U.S. presidential campaign — I couldn't bear entering November on note of negativity. So, I started thinking about some of the "bright spots" that have occurred in this industry recently.

First, consider the fact that, as of this writing, we have seen 58 FDA drug approvals this year, with 17 being for novel compounds. Of course, this drug-approvals bright spot isn't free of controversy, as was evident by the recent approval of Sarepta's Exondys 51 (eteplirsen), indicated for Duchenne muscular dystrophy. Janet Woodcock, M.D., director for the FDA's CDER, pushed for the drug's approval despite heated internal opposition. Dr. Luciana Borio, acting agency chief scientist, argued that its approval would lower agency standards, while Ellis Unger, M.D., director of the office of drug evaluation, called the compound a "scientifically elegant placebo." Time will tell who's right. But I admire Woodcock for her willingness to take a risk, which in my opinion is another bright spot. After all, wouldn't it have been significantly easier for her and FDA Commissioner Robert Califf to just "go along to get along?"

I came across another industry bright spot while attending *The Economist*'s 2016 War On Cancer event. One of the speakers, Kelvin Lee, M.D., of the Roswell Park Cancer Institute, shared his organization's experience in working with Cuba. When learning that the country's Center of Molecular Immunology (CMI) had developed a lung cancer vaccine (CIMAvax), he and colleagues didn't let a 54-year-old trade embargo stand in the way of bringing this innovation to patients in the states. Roswell anticipates beginning U.S. clinical trials soon, perhaps before the end of next year.

It was on the last day of the 2016 International Society for Pharmaceutical Engineering (ISPE) annual meeting that I identified my next bright spot. Presenter Dr. Frank Gupton, Ph.D., a professor at Virginia Commonwealth University (VCU), spent 30 years in industry before embarking on his second career. Since "retiring" he has given a TEDx talk, published numerous articles, and received grants totaling nearly $10 million from the Bill & Melinda Gates Foundation. One of his teaching projects seeks cheaper and more efficient ways to manufacture medicines. The first drug tackled, nevirapine, is an HIV/AIDS compound for which Gupton (while in industry) developed the commercial process. By making a few simple changes, the Medicines for All Initiative team reduced:

- the manufacturing process by nearly two-thirds
- material costs by more than half
- raw material waste by 93 percent.

They did all of this while increasing the yield from 59 to 92 percent. But most telling is the increased number of patients who can now be treated more cost-effectively. It is estimated that just a 10 percent improvement would achieve a savings of $75 million and allow the Gates initiative to treat 150,000 more patients. Following this success, Gupton's team received another $5 million to investigate improving two additional HIV/AIDS drugs (i.e., tenofovir, darunavir).

Know of a biopharma bright spot? If so, rather than assume we are already aware, please send us an email (rob.wright@lifescienceconnect.com) and let us know. For couldn't we all benefit from focusing a little more on the positive?

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Q What are the biggest challenges to biopharma companies in trying to be patient-centric, and what advice would you give for how to achieve their patient-centric goals?

A WHILE SOME COMPANIES MAY WORRY that engaging patients in the R&D process will complicate or delay the work, patient engagement makes research better. Companies won't know what patients want unless they ask. I think it is important for companies to approach patient-centricity by understanding the science of patient input in general (for example, by learning about sources of patient data and ways to measure progress), and then by integrating this science based on the company's own vantage point and therapeutic areas. Many companies are taking deep dives with the patient advocacy community to educate staff internally, which helps the researchers do their jobs and the company to chart its future course. This exchange of ideas and information is vital to the future of what the science of patient input will be and should be.

MARGARET ANDERSON
is the executive director of *FasterCures*, a Washington, D.C.-based center of the Milken Institute, driven to save lives by speeding up and improving the medical research system.

Q What are some challenges surrounding the operationalization of the data-sharing mandate posed by the International Committee of Medical Journal Editors (ICMJE)?

A BEYOND OWNERSHIP, THERE ARE OTHER QUESTIONS TO CONSIDER. For example, current consent forms address who will see the data and what will be done with it. To open up data use, consents would need to be modified. However, what if patients do not agree? Does that exclude them from the study, or would accommodations need to be made to remove their data? The language on data ownership and use is already challenging to agree upon. So what happens regarding site contracts and compensation agreements already in place? Would these agreements need to be retroactively amended? What if the shared data led to a new discovery? How does that finding go back to the data originators? Further, most clinical trial data is tightly tied to specific objectives. Without trial context information, it may be difficult to adequately interpret.

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

Q Knowing what you know now, what would you do differently when growing your company?

A
- I'd surrender faster and replace myself sooner.
- I'd control less and influence more.
- I'd think learning is a journey not a destination.
- I'd develop talent earlier and faster.

I eventually did all these things, but I clearly held onto the CEO role for too long. Controlling leaders operate in a world of addition and subtraction, while the calculus of a leader understands that surrender is built on exponential multiplication. Here's the thing – the purpose of leadership is not to shine the spotlight on yourself, but to unlock the potential of others so they can shine the spotlight on countless more. Control is about power – not leadership. Surrender allows leaders to get out of their own way and focus on adding value to those whom they serve.

MIKE MYATT
is a noted leadership expert, author of *Leadership Matters – The CEO Survival Manual*, and widely regarded as America's Top CEO Coach.

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Leaked Emails, Physician Reg Signal Risks For Rx Industry

JOHN McMANUS The McManus Group

As the most bizarre and unpredictable election season draws to a close, scrutiny is turning to wikileaked emails among senior officials in the Clinton campaign who are licking their chops to take on the pharmaceutical industry and healthcare policymaking by the executive branch.

WikiLeaks dumped thousands of emails between John Podesta, chairman of the Hillary Clinton campaign, and other Clinton advisors that revealed a general disdain for the pharmaceutical industry and looked for openings to exploit the industry for political gain.

When biotech stocks swooned last fall on Hillary Clinton's tweet that Turing's aggressive pricing was "outrageous," Clinton campaign strategist Ann O'Leary gleefully exclaimed "We have started the war with Pharma!"

Leaked emails also showed O'Leary probing opportunities to attack President Obama's nominee Robert Califf for FDA Commissioner as having "real ties to the drug industry." (Before joining the FDA, Dr. Califf was a professor of medicine and vice chancellor for clinical and translational research at Duke University.)

Another Clinton adviser, Brian Fallon, supported the idea, responding to O'Leary, "As we consider fights that fit into the larger themes we are trying to promote, this seems like a good fight to have."

While those attacks were ultimately never launched, it certainly shows the mentality of the Clinton camp that they would undermine their own party's president for political gain. And just as important, they view attacking the pharmaceutical industry as *very* politically appealing.

This is the political environment the industry is facing should Hillary Clinton win the White House.

MACRA REG STARTS SLOW BUT COULD PENALIZE DOCS FOR RX PRESCRIBING

In mid-October, CMS released a 2,398-page tome implementing the Medicare Access and CHIP Reauthorization Act (MACRA) that fundamentally changes how physicians will be reimbursed under Medicare. This law is supposed to *simplify* how physicians are paid.

Although it will take weeks for the white-shoe law firms to pore through the thousands of pages of regulations, a key takeaway is that the agency bowed to physician community and congressional pressure to minimize penalties on poor performing physicians in the first year of implementation. Indeed, nearly one-third of physicians will be exempted entirely because CMS raised the low-volume threshold to $30,000 or 100 Medicare patients, and another 8 percent are exempted from penalties for other reasons.

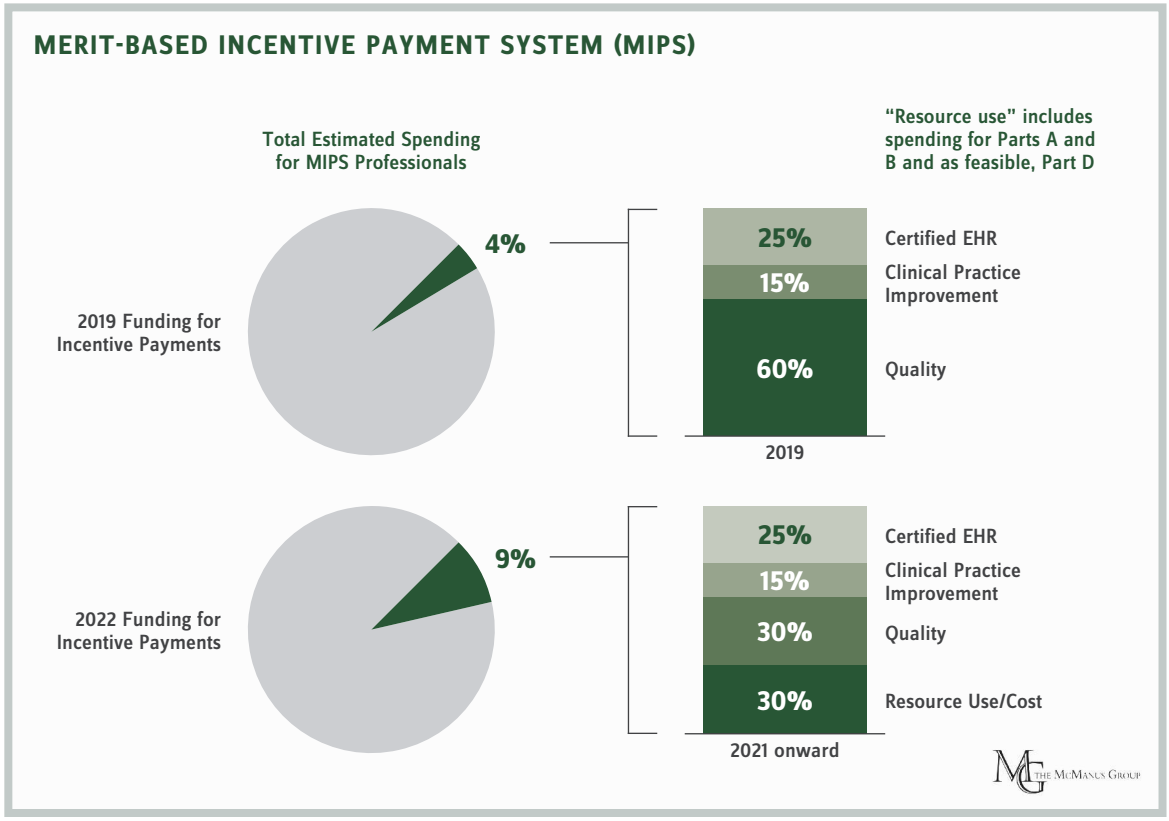
The law provides two tracks for physicians: They can remain in a fee-for-service system and participate in the "Merit-Based Incentive Payment System" (MIPS) or accept bundled or capitated payments under new Alternative Payment Models (APMs).

CMS expects most physicians — 94 percent — to remain in MIPS. Since there is a lag between the performance and payment years, in 2019, the MIPS initially puts 4 percent of physicians' payments at risk based on how they comparatively perform in delivering quality, expend healthcare resources, and use certified electronic health records (EHRs). By 2022, that portion grows to 9 percent, which policymakers believe can produce substantial behavioral change.

The political pressure to launch the new program as painlessly as possible led the agency to eliminate penalties on any practice that reported just one quality measure in each of two categories next year or report the required measures for EHRs.

The final rule provides greater flexibility for physicians — dropping the minimum reporting requirement from the proposed rule of 80 percent of Medicare patients to 50 percent of Medicare patients. Similarly, the all-or-nothing approach on EHR incentive programs is replaced with a scheme that permits a physician to choose five of 11 measures.

Acting CMS Administrator Andy Slavitt said,



"Ultimately, we believe that we're not looking to transform the Medicare program in 2017; we're looking to make a long-term program successful."

However, it is a zero-sum game. Penalties from poor-performing physician practices finance bonuses of high-performing practices. The flip side of fewer penalties is that many physician practices are wondering why they made the investments to purchase EHR technology and train their doctors to report on quality and resource measures. Bonuses will be *de minimis*.

Dr. Fred Rosenberg, president of Illinois Gastroenterology Group, remarked, "The goal of MACRA linking reimbursement to outcomes, quality, and cost is laudable, and by limiting downside risk, CMS appears to have made an effort to make participation possible for most physicians. Unfortunately, it appears that rewards for program success have been correspondingly decreased. Physicians may determine that the initial and ongoing costs (both in time and effort) for participating in MIPS, and possibly even APMs, may be greater than any financial upside."

To the life sciences sector's relief, CMS will not be judging physicians on resource and cost goals in the first year of the program. Physicians' resource use was supposed to constitute 10 of their score in 2017. The resource-use metric will now commence in 2018 and eventually increase to 30 percent of a physician's score by 2021.

Tying physician reimbursement to the costs they generate in the healthcare system could be problematic for emerging health technologies and newer drug therapies. The rule attributes to primary care doctors all the cost of the care for the patient, including prescriptions ordered by specialists to whom they've referred patients for advanced treatments.

This means there is a built-in disincentive to refer to specialists who prescribe new treatments or expensive drugs to treat complicated conditions. Many drugs and other treatments that may be seen as the standard of care do not yet have a quality metric associated with their use, as consensus guidelines typically lag clinical practice and peer-reviewed literature. As such, this rule could have a chilling effect on patient access to potentially life-saving or extending treatments for conditions such as advanced prostate cancer. Without a quality measure for such drugs, physicians face only downside risk for prescribing such drugs.

Nonetheless, the one-year reprieve provides breathing room for stakeholders to marshal data and analysis showing why this policy should be altered before it goes into effect in 2018.

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.

Can Financial Markets Solve The Ever-Increasing Costs Of Healthcare?

DENNIS PURCELL

Back in the 1840s, when the U.S. was primarily an agrarian society, the concept of a futures market for commodities was introduced. At the end of harvest season, when farmers brought their agricultural or meat products to Kansas City and Chicago, the supply of goods coming to the market at the same time put a downward pressure on prices and made it challenging for producers to obtain reasonable prices and achieve a satisfactory lifestyle. There needed to be a mechanism whereby the producers could attain some certainty over future prices for their products. The producers wanted some stability, while plenty of investors and speculators sought opportunity. A two-sided futures market was created.

Fast forward to the 1970s. The oil shock created by OPEC threatened the U.S. with an impossible future of ever-rising prices and chronic shortages. Consumers waited for hours to put gasoline in their cars. The price of a barrel of oil went from $20 in July 1973 to $50 in July 1974. The government was at a loss as to how to handle the demand/supply imbalance. The answer to the problem, once again, came in the form of a futures market that was created in energy, allowing for industry participants to sell their products for future delivery and for buyers of fuel to lock in supply. Even though the price of a barrel jumped from $15 in 1998 to nearly $150 in 2012, the price of gasoline at the pump only went from $1.06 to $3.64.

Why? The natural participants and the investors/speculators were able to come together and create both stability and opportunity in that market. Once future demand was evidenced by this trading, the industry was able to ramp up exploration and production knowing that the product that would be created was already sold. Instead of needing high-risk venture capital to finance expansion, the industry was able to borrow against future demand. Airlines began to manage their cost of fuel, and oil producers could manage their future profitability by locking in a fixed price. Today the price of a barrel of oil ranges between $40 and $50 per barrel. The United States consumes approximately 7 billion barrels of oil per year, implying a market size of approximately $300 billion annually. The futures market in oil has matured significantly.

Most other industries have followed suit. Today there is a futures market for virtually every sector of the economy. There are equity, bond, currency, precious metals, and industrial metals futures. In many industries, the products are organized on a vertical basis, whereby there is a futures market available for those who are interested in a particular type of product. There is no metals future; rather, you buy futures in gold, silver, aluminum, copper, etc. There is no agricultural future; rather, you buy futures in corn, soybeans, wheat, or cotton.

HEALTHCARE NEEDS TO EVOLVE INTO VERTICAL SEGMENTATION

Healthcare is one of the few industries organized in a *horizontal* manner. Let's look at two recent events concerning immuno-oncology and Alzheimer's disease. Bristol-Myers Squibb (BMS) shed nearly $28 billion in market value recently after the surprise failure of its immuno-oncology drug Opdivo, yet the company has many other products on the market and in its pipeline. Considering this was just a trial result, the marketplace reaction wasn't related to the profitability of BMS, but rather the disappointment of the failure of a potential new cancer treatment.

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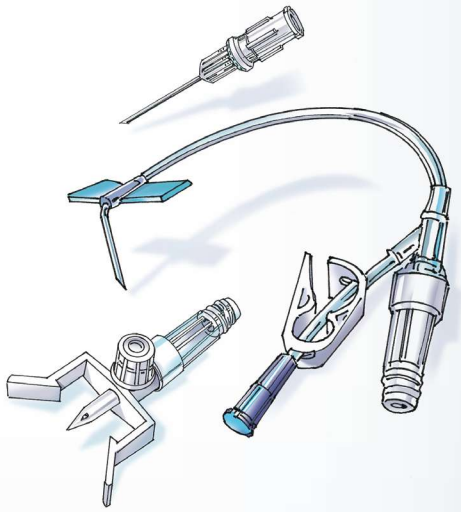

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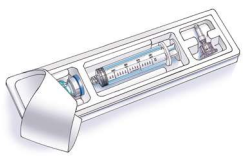


BMS is not a pure play in immuno-oncology, much like Biogen is not a pure play in Alzheimer's disease. After announcing positive Phase 2 results for its compound aducanumab, Biogen's market value increased by $12 billion, or more than 10 percent. Its stock price came right back down a few days later because the results were only interim results, years away from commercialization. Investors really did not want to invest in Biogen; they wanted to invest in Alzheimer's treatments, but currently there is no financial instrument representing Alzheimer's treatment.

Again, this is because the industry is organized *horizontally*. All Big Pharmas have products across the entire spectrum of healthcare. The financial tools are also organized horizontally. There are funds that invest in Big Pharma, biotech, diagnostics, generics, and medical devices. All of these cover all sectors. But the patients (i.e., customers) are consuming goods *vertically*. A cancer patient is given the cancer diagnostic, pharmaceutical, device, and generic.

So why hasn't the healthcare industry evolved into vertical segmentation like other industries? Until now, it's because there has been no systematic way to hedge/transfer either institutional or operating risk in the healthcare system because information gathering and delivery are generally limited and poorly organized. So, without a way to hedge, anticipated cost volatility must be built into operating margins (as a cushion against cost fluctuations). This has generally contributed to inefficiencies, perverse incentives, high barriers to entry, and reduced competition, all of which have led to higher costs. Healthcare today requires a capital market that recognizes these trends and provides its industry participants and investors the opportunity to hedge against future price fluctuations. In an industry that is 10 times larger than the oil industry, we must adapt like other industries.

A SOLUTION THAT STARTS WITH THE DIABETES MARKET

I believe it is time for healthcare to become organized on a vertical level, and the first thing to do is systematize risk in the diabetes market by using futures contracts. The aggregate cost of treating diabetes and its comorbidities is estimated to be in excess of $400 billion on an annual basis just in the United States. I propose to use per-patient cost data (much like a "spot price"), delivered on a consistent and timely basis, verified by an independent and reputable third party, to create market-based methods and financial vehicles to hedge and transfer risk. In other words, it's a futures market based on the cost of treating diabetes.

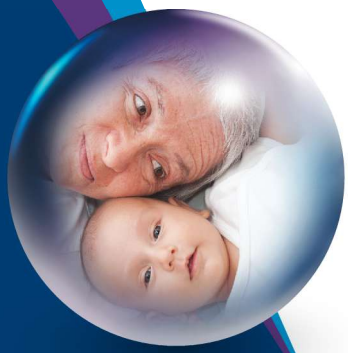
Who would benefit from such a market? First, payers of diabetes care, such as insurance companies, self-insured corporations, and governments and individuals who consume diabetes care, could utilize a futures market to cushion against future pricing shocks and thereby employ a more uniform and consistent standard of care. Second, suppliers of diabetes care, such as treatment centers, dialysis providers, hospitals, and other medical professionals, could protect operating margins, obsolescence, and patent expirations through hedging mechanisms. Third, patients who are looking for greater efficiency in the system could own financial vehicles that reflect the economic performance of their disease. And, fourth, investors, banks, and asset managers could obtain exposure to a new asset class that has limited correlation with existing products.

Think of our recent experience in treating hepatitis C. The cost of direct treatment and associated comorbidities was rising during the last decade as more people contracted the disease. The approval of Harvoni and Sovaldi became game changers. The cost of treatment has gone up in the short term as new drugs are adopted, but in the long term, the cost will decrease, as we now have potentially a long-term cure for this debilitating disease.

New hedging techniques in the healthcare industry will be positive for us all. A more efficient allocation of costs and better and more predictable price discovery will offer the ability to expand services efficiently. In addition, Medicare and Medicaid will have a private-market counterpoint to help them manage their patient needs.

After proving that diabetes is a disease that can be effectively hedged, we can create other products that address serious disease states (e.g., Alzheimer's disease, asthma). We thereby begin to bend the cost curve of the relentless increases in today's healthcare system. It is time to shift healthcare from being solely a cost to the system to becoming an asset. L

DENNIS PURCELL, a founder and senior advisor of Aisling Capital LLC, has completed over 200 transactions and supervised over $15 billion life sciences industry financing and advisory assignments.



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Catabasis

In late Phase 2 with a new DMD contender – attacking two targets at once.

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Catabasis is focused on rare diseases, in Phase 2 development with edasalonexent (CAT-1004) for Duchenne muscular dystrophy (DMD). In earlier development is CAT-4001, for treatment of neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) and Friedreich's ataxia, along with other "bifunctional product candidates" created with its proprietary SMART (Safely Metabolized And Rationally Targeted) Linker discovery platform. Its CAT-2000 series of candidates inhibit Sterol Regulatory Element-Binding Protein (SREBP), a master regulator of lipid and cholesterol metabolism implicated in severe hepatic conditions from fatty liver disease to cancer.

WHAT'S AT STAKE

There is an obvious timeliness issue with Catabasis that deserves observation but should not eclipse the whole of the company — its Phase 2 candidate for treating DMD. If for no other reason, the product warrants attention because the FDA recently approved the first-ever DMD drug, Sarepta's eteplirsen. The approval came despite wide agreement on the scarcity of clinical evidence, especially for the drug's efficacy, triggering great controversy about whether the decision signaled a drop in the agency's standards. And here comes Catabasis with another DMD candidate, taking a new approach to the disease entirely.

Among the dozens of DMD therapeutics in development by various companies, Catabasis' edasalonexent is one of the few that would treat all cases, rather than those specific to a particular gene mutation, aiming to halt or even reverse the disease. The drug targets the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway. Lack of dystrophin in the muscles of boys with DMD makes muscle fibers more susceptible to mechanical stress, which activates the NF-κB pathway. Activated NF-κB drives muscle degeneration and suppresses the ability of muscle to regenerate. "We've designed edasalonexent to inhibit NF-κB because we believe it has the potential to slow muscle degeneration and to stimulate muscle regeneration, both of which may allow patients to retain muscle function longer," says Dr. Jill Milne, cofounder and CEO of the company.

Milne founded Catabasis to create a way to make drugs that simultaneously target more than one central pathway for a given disease. The company built its SMART Linker platform to engineer "bifunctional candidates" by conjugating two bioactive compounds in the same agent. According to Milne, the conjugated drugs have the potential for enhanced efficacy and improved safety compared to separate, nonconjugated forms of the active compounds. That is because the oral-dose conjugates only cleave apart and become active against the disease pathways once they reach the inside of a cell. Edasalonexent is a conjugate of salicylate and docosahexaenoic acid (DHA), which inhibit NF-κB at two different locations. Interestingly, the company just entered a research collaboration with Sarepta to study the combination of an exon-skipper from Sarepta with an NF-κB blocker in a mouse model.

Milne welcomes the FDA's first approval of a DMD drug. "We view the accelerated approval of eteplirsen as a positive one, and it is evident that the FDA recognizes the profound unmet need," she says. "The FDA has reached their own conclusion based on their own analysis, and we believe there are lessons to be learned from the actions of the FDA in any regulatory environment. However, this does not change our overall approach, as we remain deliberate on a data-driven strategy for a drug candidate that may benefit all boys with DMD. We plan to continue to execute on a placebo-controlled trial that uses magnetic resonance imaging, or MRI T2, as an objective and quantifiable biomarker of muscle health." Milne stresses the importance of the patient community, especially the DMD group, as a "driving force" in the development of its clinical pipeline. L

JILL MILNE
Cofounder and CEO

Vital Statistics

36
Employees

Headquarters
Cambridge, MA

Finances

Series A
$48.2M

Series B
$45.8M, IPO $69M

Other
$11.5M

Public investors
Fidelity, Camber Capital, Deerfield, Wellington Management, Rhenman & Partners, Putnam Management, and Fred Alger & Co.

Research Partnership Funding

Grant funding from Muscular Dystrophy Association, Parent Project Muscular Dystrophy, and Friedreich's Ataxia Research Alliance

Latest Updates

October 2016:
Presented positive data from Part A of Phase 2 "Move DMD" trial of edasalonexent (CAT-1004) for treatment of DMD

October 2016:
Reached target enrollment for Part B of Phase 2 "Move DMD" trial of edasalonexent for treatment of DMD. Expects top-line safety and efficacy data in Q1 2017

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DAVID MEEKER, M.D.
Executive VP and head, Sanofi Genzyme

SANOFI GENZYME

– EXPANDING BEYOND RARE DISEASE INTO SPECIALTY CARE –

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

Moving from autonomous heritage to corporate integration as Sanofi's new specialty-care business unit.

Two similarities between Genzyme and its parent company Sanofi strike home — both emerged as companies relatively recently, in the 1980s, and both ultimately took the industry by storm. My first visit to Sanofi, in 1989, happened at its tiny headquarters in a second-floor office flat on a nondescript street of Paris, where its then-CEO Jean-François Dehecq told me the little enterprise would someday conquer the world. As far as I know, Genzyme never made such a claim, but its accomplishments spoke for themselves.

Sanofi grew by aggressive acquisitions, by leaps and bounds, eventually absorbing many of the largest and some of the smallest pharma companies in France, Germany, the United States, and elsewhere. In contrast, Genzyme grew organically, becoming the third largest biotech company by the time Sanofi, then the third largest pharma, acquired it in 2011. Following the acquisition, Genzyme continued much as it was before, as an independent subsidiary focused mainly on rare diseases, most treatable with enzyme replacement, and beginning in 2011, multiple sclerosis. This year, however, Sanofi finally brought the Boston-based biopharma further into its corporate fold as a business unit, not to contain its portfolio, but to expand it.

MERGER OF MODELS

Some say Sanofi has removed many valuable and independent companies from the scene, but one could also say it has saved the essence of those companies from oblivion. It has certainly kept some valuable legacies alive, such as vaccines, insulin therapy, and cardiovascular drugs. It even inherited some of the heritage of Roussel Uclaf, developer of the medical abortion drug mifepristone, though the controversial product had been divested by the time Sanofi acquired Aventis (Hoechst Marion Roussel plus Rhône-Poulenc Rorer) in 2004.

Sanofi seems to have followed its natural bent for delving into the less-traveled realms of biopharma in acquiring Genzyme. With Sanofi Genzyme, however, the company has now taken the opportunity to adopt a new business model in tune with the industry's general trend away from primary care and toward specialty care.

In the new corporate structure, Sanofi Genzyme has become the company's specialty care business unit, with responsibility for four therapeutic areas: rare diseases, MS, immunology, and oncology. It is one of five business units in the company, joining Sanofi Pasteur (vaccines), Diabetes and Cardiovascular, General Medicines and Emerging Markets (including consumer health and generic medicines), and Merial (animal health). David Meeker, who was CEO of Genzyme, a Sanofi company before the change, has taken the new titles of executive VP and head of Sanofi Genzyme — not only reflecting a more European style of management-speak, but also reinforcing his direct reporting relationship to Sanofi's CEO, Olivier Brandicourt.

From an outsider's perspective, there is an evolutionary challenge implicit in the new structure of the company, reflecting changes in the industry as a whole: Which model will prevail, specialty care or primary care? Which one will grow the fastest? Which one will prove most profitable and valuable over time? Are the business units and the models they represent

actually competing with each other in a corporate version of natural selection? The question bemuses Meeker, precisely because of its outside perspective.

"Inside the company, everyone wants to perform well, but there is no competition for survival between models," he says. "All of the units are based on viable models, but their relative roles are changing, for many reasons. Medicine is becoming more targeted, and most of the innovation is coming in the development of new targeted medicines, which tend to be biologics disproportionately so their application is more complex and most often begins with a specialist."

But it doesn't always end there; in fact, as Meeker points out, specialists can often be the gatekeepers for much broader or longer-term use of a targeted drug under primary-care supervision. Premium pricing of specialty drugs is a driving issue in the scenario Meeker describes.

"Even if you have a common disease, but the therapy for it is highly innovative, you may need to go to a specialist in the early years to access the medication — often because the payers guide you there, counting on the specialist to ensure you have taken all the steps they require to justify its use and cost. Then, over time, the medicine may move to broad-based use perhaps in the primary care setting, though it has not been launched into a primary care setting."

CUP RUNNING OVER

Growth in biopharma, it follows, may now depend largely on specialty care. The gatekeeper hypothesis explains one reason for the situation, but another reason is obviously the high revenue and profits that have returned to the industry in large part thanks to specialty care. Because of the relatively small patient populations, investment challenges, and risk-hedging in the area, specialty drug prices have lofted above those of traditional primary care products.

Several crucial distinctions exist, however, among the product types typically tagged with that term — from original drugs targeting disease mechanisms in new ways, to reformulated or repackaged older medications deemed essential for particular patient groups. For purposes of this article and its discussion of Sanofi Genzyme, specialty care drugs are innovative new agents of the type already described. And for the business unit, the specific opportunities for cutting-edge innovation lie chiefly in its therapeutic areas of focus.

Most of the unit's prior experience has been in orphan drugs, with the major exception being MS. Yet even MS has a relatively small population of about two million globally. In our recent pricing roundtable (July 2016), Meeker credited Genzyme with inventing the orphan-drug business model in 1991, when it introduced Ceredase (alglucerase), an enzyme replacement therapy for Gaucher Disease later replaced by the recombinant version Cerezyme (imiglucerase). Gaucher then had a population of only about 2,000 patients in the United States. Genzyme made a good profit that helped build a much larger company, but it caught a great deal of flak for charging about $300,000 on average per year for the drug.

Payers ponied up, though, because the drug had miraculous results, the disease was truly rare, and the company supplied the drug free to qualified patients. At our roundtable, Meeker drew an important distinction, noting that most orphan-drug developers nowadays seek indications with populations close to the 200,000-patient maximum allowed under the Orphan Drug Act, but price the drugs at the high range formerly applied to drugs that treat much rarer diseases, such as Gaucher. Many, if not most new-drug developers, especially in cancer, now routinely try to claim orphan-drug status for their candidates.

In expanding into other specialty care areas, Sanofi Genzyme intends to apply valuable lessons learned from the rare disease space, but not insist every product conform to the high-population, high-payoff orphan-drug model, according to Meeker. "We need to deal with both the lucrative and larger opportunities, but we will also have some that are much smaller and much more targeted, because that's where science takes us," he says.

"Prior to the restructuring, as a Sanofi company, we had the rare disease focus, which is at one end of the specialty care spectrum, based on the size of the target population. Now that we're scaling up in multiple sclerosis, we cannot do everything the same as before, but the principles we follow as we approach the business do not change."

Not only are patients with MS just as afflicted as those with a rare life-threatening disease, he says, but also the respective physicians treating both groups face similar challenges, such as bureaucratic pressure, time constraints, and more knowledgeable patients. The commonalities outline the unique conditions of each disease. "Specialty care is a big umbrella, and underneath the umbrella there are specific disease-by-disease differences for which we must customize our approach," Meeker says.

He suggests Sanofi Genzyme will continue to plow undisturbed ground in the rare-disease space. "There are 7,000 rare diseases, and that number continues to grow,

but only a few hundred have treatment, so there's a huge unmet need there. For many rare diseases, the populations are so small, people will argue correctly that no commercial opportunity exists. But I believe the science, and I hope the regulatory framework, will continue to evolve in ways that increase the efficiency of developing therapies for rare diseases, so even when we could not completely rationalize the investment in a particular drug, we could go ahead and pursue development."

INTO THE IMMUNE

One of the two new areas under Sanofi Genzyme's responsibility is immunology, which currently focuses on immune-driven diseases, but will ultimately steer the business toward greater understanding of the immune system's power to heal as well as destroy. The new responsibility also comes with a couple of advanced candidates: sarilumab, an anti-IL-6 antibody now in regulatory review at the FDA for rheumatoid arthritis; and dupilumab, an anti-IL-4/IL-13, also now in regulatory review at the FDA for its first indication in adult patients with atopic dermatitis. Dupilumab, recently granted priority review by the FDA, is also in development for asthma and chronic sinusitis with nasal polyposis. Both of the agents entered Sanofi Genzyme's pipeline through the collaboration between Sanofi and Regeneron.

The Phase 3 program for sarilumab included a comparison trial showing it achieved superior improvement from baseline over the leading RA treatment, Humira (adalimumab). Humira targets the tumor necrosis factor (TNF), a critical component in the disease pathway of RA and other autoimmune disorders, but Meeker suggests the IL-6 target may be even more important. "Some of the thought leaders have said, if anti-IL-6 had been introduced before anti-TNF, it might have been the mainstay of therapy instead of anti-TNF," he says.

If approved, sarilumab would be the second antibody on the market to target the IL-6 receptor, after Actemra (tocilizumab), rather than the IL-6 molecule, as does Sylvant (siltuximab). "When you're second to market, you have the opportunity to build on prior knowledge, as well as what you learn incrementally in developing your own drug," says Meeker. "One thing is especially clear at this point: The anti-IL-6 pathway is the central pathway in the pathogenesis of rheumatoid arthritis."

HEADING THE SANOFI GENZYME BUSINESS:

DAVID MEEKER, M.D.

Telling his own story and a formative moment in his company's history, David Meeker, M.D., heads the newly restructured specialty care business unit, formerly the company Genzyme and subsidiary of Sanofi:

MEEKER: I'm a physician by training, and full-time critical care was my specialty. I practiced for a period of about seven years at the Cleveland Clinic, in the faculty position I held prior to coming to industry. I love medicine, and practicing medicine in that setting was one of the most rewarding periods of my life, but the intensive care part of the job was quite demanding, and when I got to age 40, I realized I probably wouldn't be doing that until I was 60 and was open to other challenges. In 1994, a call came out of the blue from Genzyme, then a very early-stage company. The gene for cystic fibrosis was cloned in 1989, and Genzyme was one of a number of companies trying to find a gene therapy cure for CF. The belief was that it would be the first demonstration of the effectiveness of gene therapy. It was an incredibly exciting time, so I made the jump there, knowing what an incredible opportunity it was without really knowing exactly what my job would involve.

At that moment in history, a number of mostly small biotech-type startup companies and some of the best investigative researchers and molecular biologists in the world had been attracted to the field of CF gene therapy because that's where the funding was. The convener was the patient community, and the Cystic Fibrosis Foundation in the United States played a major role in bringing all of these groups together. It was a wonderful example, and regulatory authorities, including the FDA, were highly interactive. We lacked some of the formality then that governs our current interactions with the FDA, and there was a much steadier dialogue back and forth, almost patient by patient as we treated them, about every step we took. Across the entire community, many of us were competing, but in fact we were cooperating, so this was the best demonstration of "coopetition" I have ever seen.

Genzyme embarked on a number of gene therapy clinical trials for CF, but, although the studies showed evidence of pulmonary gene transfer, the efficiency was low. Over the past several years, the company has focused its efforts on developing small molecule solutions to address the underlying defect in patients with the Delta F508 mutation, the most common mutant allele in CF patients.

Dupilumab essentially hits two targets through a single pathway involving TH2 (T helper 2 or CD4+ T) cells, which is implicated in seemingly disparate allergic conditions. Moderate-to-severe atopic dermatitis is a serious, chronic form of eczema. Even though its symptoms appear on the skin, they are fueled by a continuous cycle of underlying inflammation triggered in part by a malfunction in the immune system. Asthma, of course, is a widespread and rapidly spreading disease. TH2s play a key role for a particular group of asthma patients with high levels of eosinophils, a type of allergy-related white blood cell, and possibly in a much larger subgroup with lower eosinophil counts but strong allergic activity.

"The asthma population that may be benefitted by manipulation of the TH2 pathway is larger than we originally thought," Meeker says. "Patients with the allergic-type component may be responders to this approach."

He says the actual programs had one main driver — "the biology." Expanding knowledge from the ongoing research into autoimmune and inflammatory mechanisms guided selection of the targets and creation of the candidate antibodies. "The science is so much better today," he says. "We often look at this industry and wring our hands about all the challenges we face, but we may not always recognize just how fast the science is moving and the potential we have to solve real problems in medicine because of the better science."

ONCOLOGY ONWARD

Understanding the immune system looks more and more like a convergent concept, covering more than autoimmunity and inflammation. Sanofi Genzyme enters immunology having some foundation in the field with MS. It may face a longer reach with oncology, even though Sanofi has remained active in the area ever since the initial days of Taxotere (docetaxel) and its acquisition with Aventis — via Rhône-Poulenc Rorer. But immunology could also serve as a kind of bridge to a new area of oncology, immunotherapy. Though Sanofi Genzyme may go down other avenues in the cancer area as well, most of my conversation with Meeker concerns its forays into immuno-oncology (IO). (See also, "Cancer Immunotherapy — Simpler Or More Complex?," September 2016.)

"Immuno-oncology is a revolution," he says. "It is still early, but the dramatic stories and data on some of the new immunotherapies are, I hope, just the tip of the iceberg. IO may give us the ability to harness the immune system to kill cancer down to the last cell and leave patients unharmed, unlike toxic chemotherapies, which kill only dividing cells. Now, how do we help tumors, which are not so visible to the immune system, become more visible? Which drugs should we use together to augment the response? IO will remain a major source of innovation and hope for cancer patients moving forward — though it raises some problems in the healthcare system when we start putting two or three expensive products together. That is a challenge we will have to meet."

Brandicourt has declared the company does not aspire to be the number one company in oncology or IO, but to add value and differentiate itself in the field. Its collaboration with Regeneron includes an anti-PD-1 candidate in early development, and an anti-CD38 program that could be second to market, behind Darzalex (daratumumab) from J&J.

Meeker calls the early IO candidates "building blocks" in a program Sanofi Genzyme obviously intends to expand — a pursuit where the real competition in the field currently churns. No doubt, it will be one of the chief contenders for acquisition of top-performing immuno-stimulators and vaccines aimed at turning "cold" tumors, bearing low levels of tumor-infiltrating leukocytes (TILs) into "hot" tumors with high TIL levels. (See Executive Editor's Blog: "IO: Science Still Drives The Business.")

THE MS MISSION

Sanofi Genzyme is well-embedded in the multiple sclerosis community. It markets two of the newest leading products for the disease — Aubagio (teriflunomide) and Lemtrada (alemtuzumab) — both approved in the past few years for relapsing forms of MS, and its pipeline holds an early stage candidate for the progressive form. (See "Developing New Therapeutics For Progressive MS," June 2016.) The business puts extraordinary effort into patient associations, employee participation in MS fundraisers, and other support activities. Besides brand reinforcement, what does all the interaction with the patient community do for the company?

"The key issue for the MS community is understanding and predicting the natural history of the disease in individual patients," says Meeker. "If physicians could be certain someone would develop progressive MS, they would want to use a high-efficacy therapy rather than a gentler therapy, before irreversible damage could occur. Also, as therapies improve, the expectations of the community can and should increase. Rather than slowing disease progression, patients will want to know, can you arrest it? We still don't have a cure for MS and we still don't fully understand the pathogenesis of MS."

Meeker notes the "holy grail" for the MS community is remyelination, along with neuro-protection, which could offer reversal of disease and recovery of function. But neither Sanofi Genzyme nor any other company seems to be getting closer to that goal.

Meanwhile, he says, a "second-generation Lemtrada" is in development that will improve on its targeting of the immune cells likely to cause MS. "There are many drugs that modify the immune system's response to MS disease. Lemtrada is somewhat unique; it also knocks back the immune system, but its benefit seems to be related to what happens after the repopulation of immune cells. The disease itself, in some cases, may be reset in a way that causes it to be much less severe. We continue to learn more about Lemtrada. Even though it's already approved, we haven't stopped researching it." Apparently, this is a case of learn more about the therapy, learn more about the disease.

VAULTING VALUE

The same example illustrates a separate point: Innovation, in the sense of creating ever-better medicines, can and does come in countless forms, arriving from any of an infinite set of directions, but its ultimate arbiter is biology. Meeker reflects on what Sanofi Genzyme will do to preserve and enhance its ability not only to innovate, but also to obtain the fruits of innovation as another key arbiter, the market, changes around it.

"We are not a sales and marketing industry. The only way we can create sustainable value is to continue to innovate, and by definition, the value we create will always be rewarded," he says. "We must continue to be a constructive voice at the table in shaping this healthcare ecosystem that we live in and depend on. It is both our personal responsibility and our company responsibility to be a part of the solution. For the company, innovation is not developing something new; innovation is built around understanding the problem we are trying to solve and then convincing others when we find a meaningful solution."

In practice, the newly incarnated Sanofi Genzyme has a lot of new problems, or challenges, for which it must create solutions. For starters, the venerable campus in Cambridge, MA, will grow with new workers dedicated to the unit's new therapeutic areas, immunology and oncology. Retention and recruitment will be a high priority, according to Meeker.

"The best way to attract good people is to have a true-value offering for the patients," he says. "Will your product make a difference? Is it exciting and something people want to help develop? There are many places people can earn a paycheck. Most people in this industry still want to be earning it in a place that has meaning to them, where they get the satisfaction of making a difference in the lives of patients and physicians. We keep building a culture that keeps our highest meaning and purpose front and center. That makes us attractive and has always allowed us to hire good people."

Of course, Sanofi Genzyme will continue to rely heavily on its external relationships, ranging from academia to joint ventures. And its ground-breaking work with patient associations will keep bearing fruit in future interactions, though generally, companies and patient groups will have to weather some emerging criticism of their "cozy" relationships from populist advocates. Some of the best research advances may well come from the less-heralded role of patient groups in bringing different companies together in pre-competitive interactions — a type of collaboration Meeker calls "coopetition." (See "Heading the Sanofi Genzyme Business," page 22.)

Many companies have melded into the fast-evolving world of Sanofi and faded into the corporate background. But, like Pasteur and a few others, the Genzyme name and spirit seem likely to survive in Sanofi Genzyme. As long as the specialty care model prevails or continues to play a leading role in biopharma, this business, its unique culture and capabilities, and its identity will likely remain a vital asset to its parent company. L

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HOW J&J APPROACHED CLINICAL TRIAL DATA SHARING

ROB WRIGHT Chief Editor @RFWrightLSL

In January of this year, the International Committee of Medical Journal Editors (ICMJE) published a proposal for the sharing of clinical trial data. This groundbreaking proposition, if accepted, could upend the industry's historic tendency toward data hoarding (i.e., sharing just enough clinical data in order to gain regulatory approval). This is because one of the ICMJE conditions not only requires researchers to proactively agree to share deidentified clinical data (as a condition of manuscript consideration by any of the ICMJE member journals), but to do so within six months of article publication.

JOANNE WALDSTREICHER, M.D.
Chief medical officer, J&J

While many biopharmaceutical insiders would likely agree that such data sharing could have a significant benefit on public health, the pros of such transparency have traditionally been outweighed by the realities of business. For if a biopharmaceutical company is to be sustainable, it requires revenues being generated from innovative and well-protected intellectual property. But as we have seen with a variety of industry initiatives (e.g., TransCelerate), companies are realizing, albeit slowly, that there is much more to be gained from being more open than closed. And though challenges of patient privacy and intellectual property protection for some remain immovable clinical data-sharing obstacles, for others, such as J&J, these are mere hindrances capable of being hurdled. This is why J&J proactively adopted a data-sharing approach long before the ICMJE proposal. "J&J started working on clinical data sharing as far back as 2012," says the company's chief medical officer, Joanne Waldstreicher, M.D. So how does such an immense organization develop a feasible data-sharing plan while so many others remain in the early debate phase? Here is the behind-the-scenes look at how one person's leadership changed the culture about data sharing within her large company — *and* across the industry.

CREATING THE NECESSARY DATA-SHARING INFRASTRUCTURE

A Harvard-trained physician and endocrinologist, Waldstreicher has been in the industry for over 20 years. She says it was four years ago when she saw an opportunity for J&J to "really enhance its work of serving patients and consumers." "The CEO has these small groups where senior leaders get to spend several days with the CEO," she explains. "One of the assignments for participants is to write up an idea you want to propose to the CEO." Being a scientist and a physician, Waldstreicher had an idea that had little to do with the commercial business. "I believed J&J could have a significant impact on public health and better serve patients and consumers by setting up a global science and ethics-based group within the company that was completely independent of R&D, quality, regulatory, commercial, etc." Though independent, Waldstreicher envisioned the group being responsible for important company efforts, such as the safety of J&J products or bioethical policies across the entire corporation. About a year later, Alex Gorsky, who had taken over as CEO, asked Waldstreicher to develop the chief medical officer role, a new position for J&J. "Having this role laid the groundwork for the culture, mission, and alignment necessary for J&J to pursue a data-sharing initiative," she asserts.

Once the chief medical officer infrastructure was in place, one of the first stumbling blocks Waldstreicher encountered in pursuit of a data-sharing initiative was internal. "Most people tend to view data sharing as just that, being all about the data, but that's not a very patient-centered perspective," Waldstreicher states. "You need to first step back and think about the impact patient data could have when other researchers around the world can access it. Only then do you realize that it's not just about data, but about advancing knowledge, science, and public health." In other words, if you want to advance science through data, you first need to have the proper perspective.

When the data-sharing project began at J&J, it consisted of two to three people discussing ideas with Yale School of Medicine (which we will elaborate on in a moment). "Once we realized that we had a real partner in Yale, we began to build a much larger team," Waldstreicher says. "I don't know the exact number of people we have, but in building such an initiative we included senior executives from legal, clinical R&D, and government affairs — even our CEO was involved."

THE HOW AND WHY BEHIND J&J'S PARTNERSHIP WITH YALE

Waldstreicher says J&J had previous experience sharing data (e.g., posting studies to clinicaltrials.gov and sharing via publications). "We have a policy to publish all of our clinical trial patient data. But we realized that if we started sharing summary reports, as well as individual participant-level data, we could have a much bigger impact on public health." Waldstreicher also knew that, despite J&J's size, to have the greatest industry influence would require the help of other highly credible organizations. "We decided to work closely with Harlan Krumholz, M.D., a professor at the Yale School of Medicine," she says.

Krumholz, labeled by some as the most powerful doctor you have probably never heard of, has spent decades shining the light on hospital outcomes research, long before it was fashionable. "We were both at an Institute of Medicine conference where he was a speaker on a panel," Waldstreicher recalls. "After I heard him speak, I realized we were both working toward the same goal." Waldstreicher shares that she and Krumholz actually attended medical school together, but until the conference had probably not seen each other for about 30 years. While many view Krumholz as being one of biopharma's biggest critics (and perhaps someone best to be avoided), Waldstreicher saw the potential of partnering with Krumholz as being the perfect opportunity to work with

someone sharing her data-sharing vision. Besides, Yale already had a data-sharing platform in place, the Yale Open Data Access project, or YODA for short (see sidebar).

After the conference, Krumholz and Waldstreicher met to discuss each of their data-sharing visions. From those conversations came their shared guiding principles. Yale and J&J agreed on the following core principles for advancing open science:

- promoting the sharing of clinical research data to advance science and improve public health and healthcare
- promoting the responsible conduct of research
- ensuring good stewardship of clinical research data
- protecting the rights of research participants.

"As we began our discussions, we realized that what we thought were big challenges on our independent sides were actually not that difficult to overcome," she states. For example, one challenge for J&J was how to ensure that only scientifically sound data-request proposals would be approved. "We didn't feel it would be right for just anyone to be able to look at individual participant data," Waldstreicher explains. "We felt requesters should have some sort of predefined hypothesis that they were hoping to answer by looking at our clinical data." Krumholz viewed this as a reasonable concern with a relatively simple solution. He proposed that he and his group would provide the scientific review expertise to ensure all data request proposals were scientifically sound. One of Yale's concerns was an assumption that J&J would want to have the final say on all data-sharing decisions. "Krumholz felt that for a data-sharing approval mechanism to be effective, it needed to be objective and completely independent from J&J," Waldstreicher states. "This was a big issue for him." But J&J was fine with Yale approving the data-sharing requests as long as the review process ensured approval for only scientifically

YODA: A POWERFUL DATA-SHARING ENABLER

J&J wasn't the first company to partner with Yale University on a data-sharing initiative; the YODA group had previously worked with device company Medtronic to share clinical trial data. In fact, the Yale Open Data Access (YODA) project was actually initiated in 2011, as a "trusted intermediary" approach in which an independent partner provides support, accountability, fairness, and transparency. According to Joanne Waldstreicher, J&J's chief medical officer, the difference between the Medtronic and J&J agreement is that Medtronic's was only for sharing data for one product, and it had an end date. "Our initiative with YODA is much bigger and broader, and includes all of our approved pharmaceutical products as well as our medical device products approved after 2014," she states. "We have committed (for approved products where J&J owns the data) to share data via the YODA mechanism."

The YODA system for sharing data was designed to ensure cooperation with the data owner while promoting secure, responsible access. To promote independence regarding data-sharing decisions, applicants submit proposals directly to the YODA project, which is responsible for all communication with applicants. Once an application has been submitted, YODA project scientists conduct a blinded review of proposals to ensure that a scientific purpose has been clearly described and that the request will be used to create or enhance scientific knowledge. In addition, a scientific advisory committee is available for resolving any challenging issues. However, the appropriate J&J subsidiary is responsible for conducting the necessary due diligence to ensure that J&J is the legal holder of the data, that the product has been approved, and that the data is electronically accessible. That being said, J&J cannot veto any request proposals. Though Waldstreicher mentioned that the data is not released to investigators, there is a provision that allows data to be released. However, there has to be a compelling justification as to why, and the decision to do so is made jointly between the YODA Project, J&J, and the advisory committee. Between the launch of the YODA Project platform and September 2016, J&J has prepared 132 trials and the YODA Project has approved 49 research proposals. "Yale looks at the proposals very carefully to be sure that every one is a good scientific proposal and that the data we have will answer the proposal's scientific question," she reiterates. While Waldstreicher admits that the J&J/YODA model is not perfect, she anticipates the two organizations will continue to learn, evolve, and grow. "There are a lot of different data-sharing approaches being considered (e.g., ACCESS CV, Project Data Sphere)," she states. "One thing we should be doing as an industry, regardless of the approach taken, is convening a gathering of these data-sharing groups on an annual basis so we can share lessons learned and experiences in an effort to continue to advance the science surrounding data sharing."

CHANGING THE WAY COMPASSIONATE USE IS REVIEWED

In May 2015, J&J made headlines when it announced a pilot program to change its approach to compassionate use, opting to have an independent review panel consider requests for the investigational medicine undergoing clinical testing. Referred to as the Compassionate Use Advisory Committee (CompAC), the group is overseen by Art Caplan, director of the division of medical ethics at NYU, and includes internationally recognized medical experts, bioethicists, and even patient representatives. The goal was not only to eliminate situations such as that encountered by the former CEO of Chimerix, Ken Moch, whose company's initial refusal to provide access to an experimental medication ignited an aggressive social media campaign, including death threats, but to level the playing field between the haves and the have-nots. "There will be none of this, 'Call the governor, call your rich brother-in-law' kind of thing," Caplan stated upon the announcement of the CompAC pilot.

Compassionate use, also known as expanded access, is a subject that has stymied many pharmaceutical companies. This is because the decision of whether or not to make an investigational drug available to patients that may or may not save their life can also cause a variety of adverse effects. Further, what if patients do get the medication, and yet they do not get the results for which they had hoped? There are valid concerns surrounding how a few well-publicized negative outcomes could prevent a company from getting a potential life-saving investigational medication to market. For more on how J&J "Hopes To Change The Paradigm On Compassionate Use Review," please refer to the article of the same name written by Ed Miseta in the January 2016 issue of *Life Science Leader* magazine.

sound data requests.

In 2014, J&J and Yale announced the joint agreement to work together on the YODA data-sharing project. "The first agreement involved data sharing of all J&J's approved pharmaceutical products," she states. "A year later, we announced the addition of data from approved medical devices as well."

It is interesting that prior to the ICMJE proposal the Institute of Medicine published a report in 2015 recommending data sharing and explained how to maximize the benefits and minimize risk. "One of the recommendations of that report was that journals should require authors to commit to data sharing," Waldstreicher says. As such, not only is the 2016 ICMJE proposal very similar to what the Institute of Medicine produced, but not much different from what J&J has been doing with Yale since 2014.

HOW MUCH DOES HAVING A DATA-SHARING PLATFORM COST?

Although she couldn't assign a specific dollar figure to the cost of this project, Waldstreicher says "it has been costly because we were the first to work with an external independent academic group." Moving forward, J&J hopes to spread data sharing across the industry and get more companies involved on a broader scale so that the costs come down and become routine.

One of the costs associated with this project pertained to revising processes and forms. "We are changing the template of our consent forms to inform patients of our plans to share clinical trial data in a deidentified manner," she shares. "While our goal would be to only include patients in our clinical trials who agree to share their deidentified data, there may be times when exceptions need to be made, such as clinical trials involving patients with rare conditions or children." Dr. Waldstreicher says that if J&J deems the risk of reidentification as being too high, the company reserves the right to not share certain data. "We do not think this will be a common occurrence," she states. "In fact, we have yet to be faced with such a situation. But as we don't know what the future will bring; we can't make a blanket statement that says we will only include patients in our trials who agree to data sharing." Removing patient identifiers before sharing the data is another cost associated with the project. "We now obtain a signed confidentiality agreement from researchers and scientists who want to access J&J data. The agreement requires commitment to maintain data confidentiality, and to not attempt to reidentify study participants," she explains. Another cost involves maintaining a secure data-sharing platform. Through YODA, approved external researchers are given access to the data via a platform where the data is housed. This also serves as a means of protecting patients. "External researchers can't download the data, but have to conduct all of their analyses within the website."

Waldstreicher admits that the impact of the YODA project leads to new insights that had not been considered when research studies were originally conducted. "The research proposals coming in have ideas and analyses we had never thought about [e.g., gender difference with certain products, comparing J&J data to products and studies conducted by other researchers]," she explains. Perhaps one of the biggest achievements was the actualization of the initiative itself. "Many people didn't think that what we were trying to do would ever be possible," she concludes.

5 Questions with ALLERGAN'S Chief R&D Officer

ROB WRIGHT Chief Editor @RFWrightLSL

Over the past few years, Allergan has garnered a wide variety of front-page news headlines, including a hostile takeover attempt by Valeant Pharmaceuticals and an activist investor, a subsequent $70 billion acquisition by Actavis, and a foiled $160 billion inversion merger with Pfizer. More recently, the company sold its generics business to Teva for just over $40 billion and is today rumored to be in the running for the possible acquisition of Biogen.

Although it may seem like Allergan's chess pieces are in constant motion, one has to remember that there is a lot of thinking that takes place prior to any strategic move ever being made. What follows is a discussion with one of Allergan's key leaders — chief R&D officer, David Nicholson, Ph.D. — regarding the decisions the company is making related to its R&D pipeline.

1 Why has Allergan decided to focus on seven therapeutic categories (i.e., urology, GI, anti-infective, aesthetics and dermatology, women's health, CNS, and other)?

Our goal is to have leading positions in all of the therapeutic areas where we are active and to reinforce these positions through our open-science model. When I say reinforce, I mean to further establish an R&D pipeline in the therapeutic areas in which we are working, as well as look for opportunities and adjacencies. For instance, in CNS, Allergan is active in schizophrenia, bipolar disorder, depression, and Alzheimer's disease. At the moment, we have no projects or products in Parkinson's or multiple sclerosis (MS). In GI, for example, we have projects and products in IBD (inflammatory bowel disease) and IBS (irritable bowel syndrome). However, we are not currently active in GERD (gastroesophageal reflux disease) or NASH (nonalcoholic steatohepatitis). These are examples of adjacencies surrounding our present projects and products that we would like to expand into to maintain and grow our leading positions.

2 Can you elaborate on what you mean by open-science platform?

Open science is our model for how we want to approach R&D within the modern-day biopharmaceutical industry. While our research teams are competitive and working on a global scale, the reality is we primarily fill our pipelines by connecting with folks in the outside world. This is because there is much more research being done beyond the four walls of Allergan. Ninety percent of all present-day blockbusters are marketed by companies that didn't do the original discovery. As such, it is our belief that the most productive way to fill Allergan's development pipeline is through partnership, licensing, and collaboration. Therefore, a key focus for us is developing and maintaining the core competencies necessary to successfully take partnered, in-licensed, and collaborative compounds all the way through to registration or commercialization.

3 Can you share some examples of using open science to build Allergan's pipeline?

Sure. Let me start with VRAYLAR (cariprazine), which was recently registered and launched for the treatment of schizophrenia and bipolar mania in the United States. The original cariprazine agreement was signed more than a dozen years ago (between what was once Forest Laboratories and Gedeon Richter) and is an example of an in-licensed early-stage R&D effort. Sometimes partnerships take many years of collaboration before a product hits the market. In other words, when developing biopharmaceutical collaborations, you have to be willing to be in them for the long term.

Another example is KYBELLA (deoxycholic acid)

indicated for improvement in the appearance of moderate to severe convexity or submental fullness (i.e., double chin) in adults. This product (recently approved by the FDA) was obtained through Allergan's $2.1 billion acquisition of Kythera Biopharmaceuticals. Here is an example of us acquiring a late-stage asset (right at the time of registration) that aligned with our medical aesthetic franchise. Though we have taken this product through to launch and commercialization, we continue its development outside the U.S. and are investigating other indications as well.

In 2015, we did a $560 million deal to acquire Naurex, a company developing a fast-acting antidepressant, rapastinel (GLYX-13). Naurex had generated some Phase 2 data showing antidepressant activity taking place within hours of treatment initiation in patients who hadn't previously responded to standard antidepressants. In January of this year, it was announced that Allergan had secured the FDA's breakthrough therapy designation for this agent. The point is — Allergan does collaborations and partnerships at all stages of development throughout our therapeutic areas.

4 In comparing the pipeline of Allergan (a $16.3 billion company with 65+ R&D programs) to a much bigger company (e.g., Pfizer, which generated $60 billion in revenue last year with 92 R&D programs), doesn't it seem as if Allergan is perhaps being a bit too aggressive, R&D-wise?

I avoid getting involved in interviews that compare and contrast Allergan with any other company, but we think Allergan's pipeline fits with the R&D budget and available resources. When we merged Actavis and Allergan, we took a look at the combined pipelines and prioritized projects. After a rigorous review, we decided to stop certain projects that we didn't feel were going to be registrable, innovative, or meet an unmet medical/clinical need. With regard to our R&D budget, we have a fixed percentage of turnover. Brent Saunders [Allergan's president and CEO] has made it clear that R&D should have the money that such a pipeline deserves (i.e., pipelines with an abundance of Phase 3 programs require more available resources as Phase 3s tend to be expensive). If, in the future, we have fewer Phase 3 programs — if that is ever the case, hopefully it won't be — then one can expect the R&D budget to go down.

5 Could you walk us through in a bit more detail the decision-making process behind stopping certain projects during the Allergan-Actavis merger?

I worked very closely with Scott Whitcup, who, prior to the merger, was EVP and chief scientific officer at Allergan. Prior to day one of the new company, you can't jump the gun, and you can only discuss things with each other that you would be willing to discuss with any competitor. So clearly we made sure we were respecting the regulations and relevant laws. However, what we did do (independently) was to prioritize our pipelines. To do this, we first agreed upon a common, one-page template that described our pipelined projects, therapeutic areas, mechanisms of action, patent positions, projected peak sales, stage of development, etc. Then we (independently) filled out the template and prioritized our company's pipelines prior to day one. On day one of the new company, we lifted the veil and showed each other our analyses. This made it much easier to get things up and running, because we had insight into the company's pipeline prioritized by people who were intimately familiar. Within a week of the new company, we had a joint meeting involving R&D and commercial to discuss each other's independent prioritizations. There was almost total agreement as to which projects should be stopped. Sure, maybe a few of these projects/products could have made it. But the reality is that, as a company, we can't pursue every opportunity. So the decision was made to invest in the ones we thought had the highest potential for success. For a project to be continued, it had to fit fairly and squarely within the new company's seven therapeutic areas. After that it was pretty simple stuff (e.g., does the project team know the clinical needs, is there commercial potential, what is the ability of technical and regulatory success?). If you can take a rather cold-blooded look at your projects with an objective eye, you can clearly determine which ones should be stopped. Scientists can always think of a reason why to do an experiment. And sure, it could work. But if you are able to look at it and determine that the odds are pretty slim, or put a firm decision in place that if an additional "killer" experiment/study is done and is proven to not be active, then it will be stopped. Scientists tend to respect such data-driven decisions.

What is something you learned from working at Bayer Crop Science you find beneficial in your current role at Allergan?

When you've worked for a couple of decades in R&D in the pharmaceutical industry [says Allergan chief R&D officer, David Nicholson, Ph.D.], there is the potential danger as a leader to feel you know it all or more precisely, feel you know a discipline perhaps better than some of the people reporting to you. When I stepped out of the pharmaceutical industry to work for Bayer Crop Science, I knew a lot about running R&D organizations and leading scientists, but I knew very little about agriculture. So if I was going to be an effective leader, two of the things I had to do was trust and empower the scientists who were working for me.

DAVID NICHOLSON, PH.D.
Chief R&D officer, Allergan

Women In Bio: Looking Through The Glass Ceiling

SUZANNE ELVIDGE Contributing Writer @suzannewriter

Back in 2010, *Life Science Leader* published "Women In Biopharma: Analyzing The Glass Ceiling," which looked at the experiences of women in biopharma. It's time to see whether things have changed.

The pharmaceutical and medicine manufacturing industry overall is a roughly 50-50 split and, as shown in Figure 1, sales, service, and professional posts are nearly evenly split between the genders, with slightly higher numbers of women in the sales and professional roles. However, as people become more senior, the gender split changes, with around 60 percent of first- and midlevel management and 70 percent of senior and executive level management roles going to men.

"The drop-off begins at the executive management level, as well as on the boards," says Ursula Ney, previously the CEO of Genkyotex and currently on the board of directors at Discuva. "You need executive experience to be able to get onto boards, and board experience can help you to gain executive roles. It's a vicious circle."

This disparity isn't just a challenge for pharma and biotech. In 2015, the representation of women was just 17 percent on the Nasdaq 100 boards. In the U.K., on the FTSE 100 boards (Financial Times Stock Exchange 100 Index, an index of the 100 largest companies listed on the London Stock Exchange), the figure is better but is still only around a quarter, according to the *Financial Times*. However, the number of female CEOs and CFOs is higher in the U.S., reaching 17 percent, compared with 11 percent outside the U.S., according to the 2015 *MSCI Women on Boards: Global Trends in Gender Diversity on Corporate Boards* report. MSCI is an independent provider of research-driven insights and tools for institutional investors. The report used data from its MSCI World Index, which represents large- and mid-cap equity performance across 23 developed world markets.

"When I started in biopharma, attending research and business meetings, I was surprised by the overrepresentation of men. I had expected health to be a more feminized area," says Karen Aiach, founder and CEO of Lysogene.

> *"When I started in biopharma, attending research and business meetings, I was surprised by the overrepresentation of men. I had expected health to be a more feminized area."*
>
> **KAREN AIACH**
> Founder and CEO, Lysogene

On the positive side, there is a trend of rising numbers of women at these levels, from 38.7 percent in 2007 to 41.2 percent in 2014 at the lower levels of management, and from 28.0 percent to 29.7 percent at the higher levels.

"I have been involved in the life sciences for over 20 years, and I have seen changes in both Big Pharma and startups, with an increase in the number of women at high levels," says Isabelle de Cremoux, CEO of Seventure Partners.

"I have been involved in the life sciences for over 20 years, and I have seen changes in both Big Pharma and startups, with an increase in the number of women at high levels."

ISABELLE DE CREMOUX
CEO, Seventure Partners

THE IMPORTANCE OF WOMEN IN THE INDUSTRY

The pharma and biotech industry has been managing for many years without women in senior roles. So is this actually a problem, and does it need to change? The data says yes. According to the *MSCI Women on Boards: Global Trends in Gender Diversity on Corporate Boards* report from MSCI in late 2015, companies with three or more women on their boards, or with a female CEO and at least one female board member, had a 10.1 percent return on equity, compared with 7.4 percent for companies without strong female leadership. This translates to a 30.8 percent difference. The same report suggests that the companies with more senior women are less likely to be involved in fraud, shareholder conflicts, and bribery.

"Having women on a board brings in a diversity of points of view," says Anna Protopapas, president and CEO of Mersana Therapeutics. "I believe that diversity means better judgment, which means a better bottom line."

Behshad Sheldon, president and CEO of Braeburn Pharmaceuticals, agrees: "Diversity is core to innovation and brings in diversity of thought. Otherwise, it's the same players making the same plays."

For an industry that starts with a 50-50 split at entry, not having women at senior executive and nonexecutive levels also excludes a talent pool of highly educated people with different perspectives, experience, and management and debate styles. It also has an impact on the career aspirations of women at lower levels. Seeing only men progress can be demoralizing and demotivating, which in turn will contribute to the attrition in numbers of women.

CHANGING TO A MORE GENDER-DIVERSE BOARD

For companies that want to bring women through to higher levels, attitudinal changes need to be made. This is exemplified by a party at the annual JPMorgan Healthcare Conference in 2016 that made headlines for all the wrong reasons. LifeSci Advisors chose to deal with the imbalance of the sexes at the conference in a rather sensational way. In what Michael Rice, founding partner of LifeSci Advisors, now accepts was a mistake, the investor relations company wheeled out models in short, tight black dresses to distribute champagne and mingle with the largely male guests at an evening bash at the Exploratorium in San Francisco

This resulted in an open letter to the biopharmaceutical industry and its investors from Kate Bingham, managing partner at SV Life Sciences Advisers; Karen Bernstein, cofounder and chair at BioCentury Publications; and a host of women (and men) across the pharma and biotech industry. Rice and the team at LifeSci Advisors, to their credit, subsequently took this criticism on board and made some major changes within the company, as well as putting in place some potentially more far-reaching projects.

"We have created an advisory board on gender diversity, including Kate Bingham and a number of other women, and worked to understand the issue of representation of women in the industry," says Rice. "We have doubled the number of women internally at LifeSci Advisors and created a number of projects that support diversity."

Ney, of the Discuva board of directors, also joined the advisory board of LifeSci Advisors following the JPMorgan furor, pointing out that it did at least bring the role of women into the headlines. LifeSci Advisors is the founding sponsor of Women in Bio's "Boardroom Ready" program that is also supported by MassBIO and Biogen. This program is designed to provide women with board training and support them in accessing board and executive roles in the industry. But is this just another PR stunt? According to Rice, this has awoken a genuine passion for gender equality, along with a pragmatic recognition that women at high levels are good for business.

"It's all about the data — a diversified board leads to higher return on equity, sales, and capital," says Rice. "Not only is it the right thing to do, it's just good business."

Without resorting to headline-making, other

companies are working to bring women into senior roles. As Protopapas says, the industry starts with around a 50-50 split, which puts it ahead of many industries. But why are men only recruiting men at C-suite and board level when there are women out there with the right skills?

"This is the dynamic that exists. While management teams are struggling to move drugs through pipelines and onto the market to get a return on investment, they aren't focused on making changes in the C-suite," says Rice.

Recruiting women for senior roles can require a concerted effort from women currently working at higher levels, while not compromising on requirements for skills and expertise.

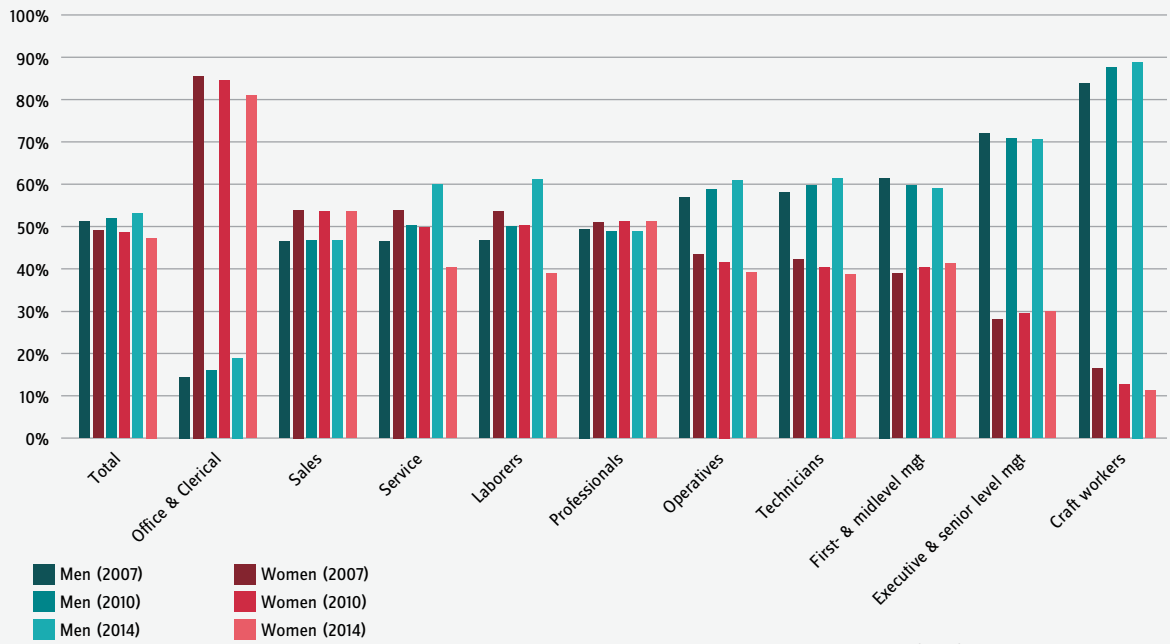
"At Braeburn later this year, we will have four of the nine posts in the management team filled by women, and I will be adding women to the board. However, I don't recruit women only for their gender, but for their talents, skills, and expertise," says Sheldon.

Aiach supports this, saying, "At Lysogene, we have a majority of women at the C-level. We looked for the right people and provided our headhunters with very objective parameters. We also have a majority of women on our board — in our last round of

"Having women on a board brings in a diversity of points of view. I believe that diversity means better judgment, which means a better bottom line."

ANNA PROTOPAPAS
President and CEO, Mersana Therapeutics

FIGURE 1: PERCENTAGES OF MEN AND WOMEN IN PHARMACEUTICAL AND MEDICINE MANUFACTURING, 2007-2014



Source: U.S. Equal Employment Opportunity Commission

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funding, we worked with VC companies with female leadership, and as a result we welcomed three women VC board members."

Another approach, which Sheldon used in her time at Otsuka, is to promote women from within the ranks, often involving double or triple promotions. These individuals would require specific support in their new roles and are examples of where mentoring can be very powerful.

Quotas for women on boards aren't universally liked, but they seem to have been working in Europe. Norway introduced 40-percent quotas for women on boards in 2003, followed by Iceland, Spain, and France. Germany brought in a 30-percent quota in 2015. These moves have resulted in an increase in women at large publicly traded companies to 44 percent in Iceland, 39 percent in Norway, 36 percent in France, 26 percent in Germany, and 19 percent in Spain.

"I would rather have a goal than a quota — for example, a certain proportion of women in the C-suite," says Protopapas.

HOW WOMEN BALANCE WORK AND LIFE

Women often shoulder the bulk of household responsibilities and so can find that they have to make compromises in order to balance both work and life.

"I have had to make sacrifices, and I believe that it has taken me longer to get here than it would have if I hadn't been a single parent," says Sandra Gunselman, vice president of laboratory operations at Assurex Health. "I have also had to learn to balance the conflicts between ambition and parenthood, and I think these factors have helped me in my success."

Aiach agreed that logistics can be a hurdle, but that working together as a family makes it possible for her, even with a severely disabled child. For others it means looking at priorities and identifying what is and isn't important. Sheldon worked out what she could do without — for her it was laundry and keeping up with pop culture. Employers are also looking to see what they can change and at the benefits that these changes have for both male and female employees.

"It's important to remember that these days, more men are juggling families, too," says Ney. "If you can compromise with people as an employer, you will get the best out of everybody. By moving away from old-fashioned patterns, you will make it easier for both women and men."

WHAT PHARMA CAN LEARN FROM CHARITY

The pharma industry can learn from the charity sector, where around two-thirds of the workforce is female, and female executives make up around half of the higher levels, according to Helen Rippon, CEO of Worldwide Cancer Research.

"I think the charity sector recognizes that you need a work-life balance and is more comfortable with flexible working, and this does help women. When I had my son, I found it easier to sort out working four days a week than my husband, who works in the pharma industry," says Rippon. "It isn't unusual for directors to work flexible hours or part-time or juggle meetings and travel around childcare. Earlier in my charity sector career, a new director was appointed when she was visibly pregnant. Her impending maternity leave was no barrier to her career progression, and she was valued for her skills and abilities regardless. I wonder in how many other sectors would that have happened?"

"At Braeburn later this year, we will have four of the nine posts in the management team filled by women, and I will be adding women to the board. However, I don't recruit women only for their gender, but for their talents, skills, and expertise."

BEHSHAD SHELDON
President and CEO, Braeburn Pharmaceuticals

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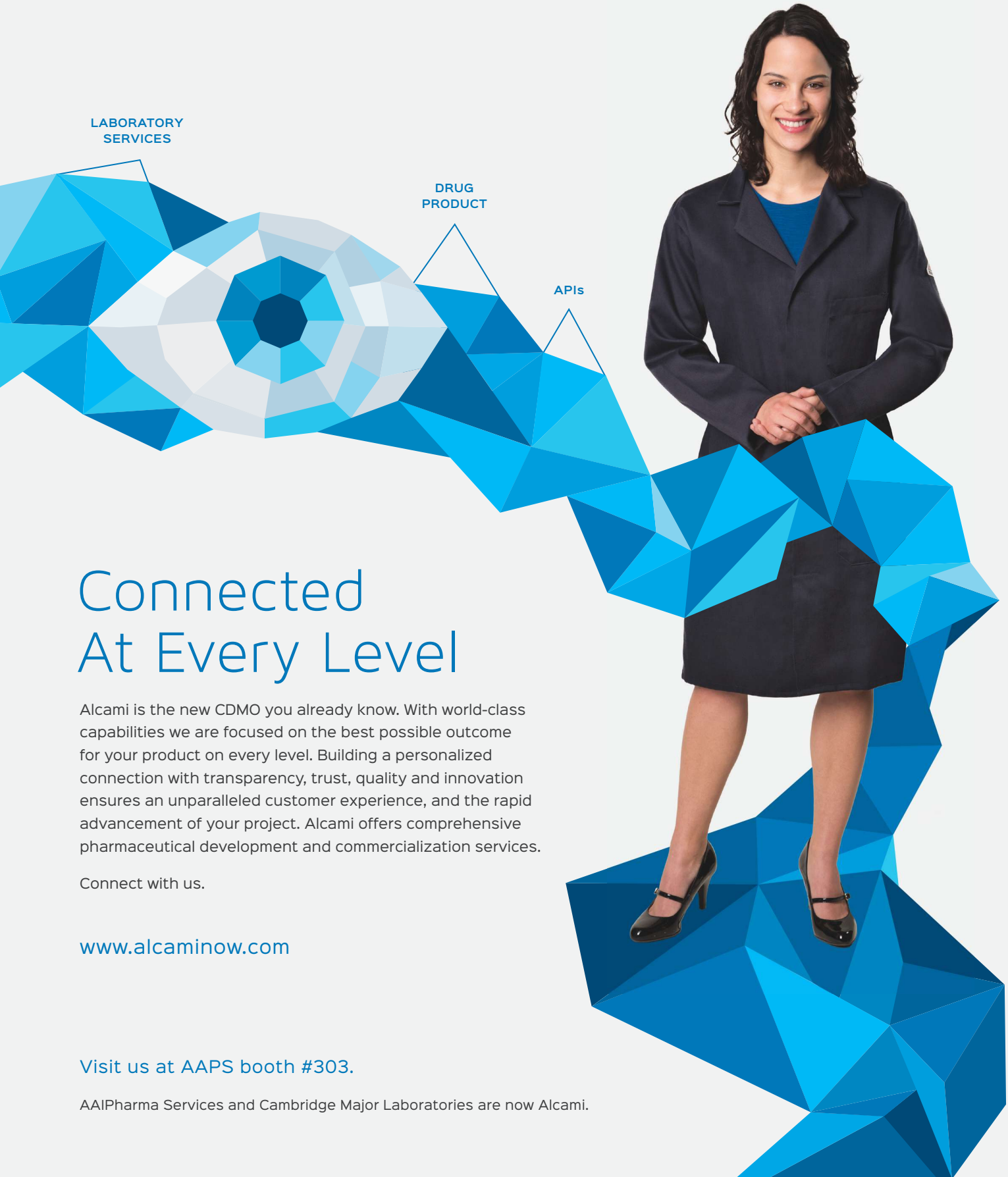

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Why An Investment Banker Returned To Drug Development

CATHY YARBROUGH Contributing Writer @sciencematter

Sandesh Seth was not considering leaving his position as head of healthcare investment banking at Laidlaw & Co. U.K. Ltd, when the board of small-cap biotech Actinium Pharmaceuticals asked him last year to serve as the company's executive chairman.

Nor was Seth thinking about returning to the biopharmaceutical industry. Early in his career, after obtaining a master's degree in pharmaceutical sciences, Seth worked for 10 years in product and business development, strategic planning, and R&D project management at SmithKline, Warner-Lambert, and Pfizer.

As a member of New York-based Actinium's board since 2011 and its board chairman since 2013, Seth understood why he was being asked to take a more hands-on role at the company. "Actinium needed additional resources, and I believed that I could add a lot of value from a biopharmaceutical executive perspective at a very important time in the development of Iomab-B," he said.

Iomab-B, Actinium's lead asset, is a first-of-its-kind radiotherapeutic agent. Actinium licensed the drug in 2012 from the Fred Hutchinson Cancer Research Center in Seattle. Physicians at the Hutch developed Iomab-B to enable a greater number of older patients with relapsed or refractory acute myeloid leukemia (AML) to take advantage of bone marrow transplantation (BMT), currently the only curative therapy for this deadliest form of leukemia.

Soon after licensing Iomab-B, Actinium began planning a Phase 3 clinical trial and compiling an IND (investigational new drug application) for submission to the FDA. Actinium's board recruited Kaushik Dave, MBA, Ph.D., who is experienced in radiopharmaceutical monoclonal antibody product development, to serve as president and CEO and manage Iomab-B's development through FDA approval.

Dave and his team soon encountered a major obstacle in the technology transfer of Iomab-B and scaling the manufacturing process to commercial and cGMP quality levels. Iomab-B is a monoclonal antibody linked to a radioisotope, which is regarded as not easy to manufacture. FDA-approved radiopharmaceutical products have been manufactured on a commercial scale by only three biopharmaceutical companies: Bayer, GSK, and Spectrum Pharmaceuticals. None of these products was designed to treat AML.

To become the fourth company to manufacture a commercial grade radiopharmaceutical drug, Actinium first had to adapt the Hutchinson Center's manufacturing process for Iomab-B. Because the cancer center needed a relatively small supply of Iomab-B for its clinical studies, the drug was manufactured at a small scale in a 50-liter bioreactor. However, for commercial-scale manufacturing of Iomab-B, a 500-liter bioreactor had to be used.

Determining the best recipe for manufacturing Iomab-B in a 500-liter bioreactor was a difficult trial-and-error process, said Seth. Each test batch took three months to manufacture and two months to evaluate. "Something would go wrong in the batch phase or the testing phase, requiring Dave and his team to start over," said Seth.

Because adjusting the Hutchinson Center's recipe for commercial-scale manufacturing of Iomab-B was time-consuming, Actinium had to delay the submission of its IND to the FDA. As a result, the company's pivotal Phase 3 clinical trial was not launched in the first half of 2015 as planned. "The market reacted negatively to this news, and our share price dropped significantly in value," said Seth.

UNEXPECTED BENEFIT

Developing a validated manufacturing process to produce commercial-grade Iomab-B "was a very big undertaking," said Seth. Actinium's board asked Dave to set aside his other responsibilities as president and CEO to focus only on perfecting Iomab-B's manufacturing

process. As a result, "We had a real need for someone with complementary skills to handle finance, strategic planning, business development, and investor relations for the company," said Seth, who left his investment banking job in 2015 to work full-time at Actinium as executive chairman. He had worked in investment banking and equity research for 20 years.

"It was certainly a challenging time for the company," recalled Seth. "But we were confident the manufacturing problems were solvable with expertise, time, and money." The manufacturing problems had an unexpected benefit — the company was able to identify areas where it could generate intellectual property related to manufacturing processes.

Meanwhile, Actinium continued to build its staff for the anticipated FDA approval of the IND for Iomab-B. In August 2015, Felix Garzon, M.D., Ph.D., who has a background in hematology and oncology drug development, joined Actinium as senior VP and head of clinical development. The following month, Actinium hired two more industry veterans. J.C. Simeon, the new executive director of quality assurance, supervises and manages Actinium's CMO relationships. Karen Louw, a clinical research nurse, trains clinical trial site staff and serves as a clinical expert for patient monitoring and safety.

Once Dave and his team solved the manufacturing problems, Actinium was able to submit the IND to the FDA in October 2015. It was approved by the agency two months later. In March 2016, Actinium received the FDA's orphan drug designation for Iomab-B. In June 2016, the company announced the launch of its pivotal Phase 3 clinical trial of Iomab-B in 150 relapsed or refractory AML patients over the age of 55. The primary endpoint of the Study of Iomab-B in Elderly Relapsed or Refractory AML (SIERRA) trial is durable complete remission lasting at least six months. The secondary endpoint is overall survival at one year.

When he was an investment banker, Seth spent most of his time in raising money for multiple companies, including Actinium. He raised capital for the company's Series E financing round in 2011 and its IPO in 2012. As executive chairman of Actinium, he said, "I spend most of my time working with the management team on things such as strategy, business development, and strengthening our operational competencies — all of which are more appealing to me than investment banking."

Seth is an atypical biotech leader. Obviously, having knowledge and experience in the financial and capital markets helped him when he was raising capital, but that expertise was also important in his daily interactions with investors. "Being able to clearly communicate our value proposition to the investment community is vital to our success as a public company, and it is a skill I was able to develop from my time in equity research and investment banking. Also, the network I have curated from my time in finance has helped identify consultants and employees who have helped Actinium."

Today, it's not unusual for Seth to be asked how a small-cap biotech company without a track record in drug commercialization succeeded in licensing Iomab-B before a global biopharmaceutical company had a chance to acquire the drug.

"I think a lot of it can be attributed to luck and being in the right place at the right time," said Seth, who learned about Iomab-B from a member of Actinium's clinical advisory board. Actinium's pipeline then included one drug, Actimab-A, now under evaluation in a Phase 2 clinical trial for the treatment of newly diagnosed AML patients who are over the age of 60. Like Iomab-B, Actimab-A is a radioimmunotherapy. It is based on technology that Actinium licensed from Memorial Sloan Kettering Cancer Center in New York City.

"The fact that we had this expertise in radioimmunotherapy with Actimab-A and experience working with radioisotopes certainly helped us when we approached the Hutchinson Center about Iomab-B," said Seth.

LICENSING IOMAB-B A NO-BRAINER

"Licensing Iomab-B was a no-brainer," Seth said. The Hutchinson Center's Phase 1 and 2 clinical studies of the drug in older patients with relapsed or refractory AML generated "compelling data" showing that Iomab-B is less toxic and more effective than high-dose chemotherapy in preparing patients for BMT.

"There are numerous biopharmaceutical companies developing therapies for older AML patients, both those who are newly diagnosed and those who are relapsed or refractory," he said. "We believe Iomab-B is the only therapy in development that is intended to be an induction and conditioning agent in one, meaning it ablates the patient's bone marrow as well as addresses the patient's active leukemia to prepare the patient for BMT."

Before receiving a BMT, AML patients must undergo chemotherapy and whole-body radiation, referred to as myeloablative conditioning therapy, to wipe out leukemia cells in their bone marrow. Because the side-effects of intense chemotherapy can be severe, many older patients with refractory or relapsed AML cannot undergo or complete the therapy. As a result, only 1 percent of older patients with relapsed or refractory AML are treated with BMT, said Seth. Without BMT, most of these patients live only a few months.

Almost all of the patients in the clinical studies at the Hutchinson Center were able to tolerate Iomab-B as an induction and conditioning therapy and thus undergo BMT. One year after their BMT, 30 percent of these patients were alive. The survival rate at one year was 10 percent when chemotherapy was used as the conditioning regimen, according to a retrospective analysis of MD Anderson Cancer Center data on older AML patients with relapsed or refractory disease. In the Hutchinson Center clinical studies, 30 percent of the Iomab-B patients survived to one year, and 20 percent survived to two years post-BMT. "Two-year survival is a landmark that is widely regarded as a proxy for being considered cured," Seth said. According to MD Anderson patient data, the two-year survival rate is zero percent for patients treated with chemotherapy to prepare for BMT.

> *"We believe this is a market we can adequately address and commercialize ourselves."*
>
> **SANDESH SETH**
> Executive Chairman, Actinium Pharmaceuticals

The FDA has not approved a new drug for older refractory or relapsed AML patients in about 40 years. If Iomab-B is approved by the FDA, it could become the standard of care for this patient population. It also might benefit patients with other forms of leukemia. Several physician-sponsored clinical studies at the Hutchinson Center suggest that Iomab-B may be safe and effective as a conditioning regimen prior to BMT in various forms of leukemia.

Actinium is not actively seeking a commercialization partner for Iomab-B. In the U.S., AML patients undergo BMTs at only 150 medical centers, 30 of which are responsible for 50 percent of the procedures. Actinium's Phase 3 clinical trial is being conducted at many of these centers. "We believe this is a market we can adequately address and commercialize ourselves," Seth said.

Actinium will seek a commercialization partner for Actimab-A, because the potential market for this drug is much larger than the market for Iomab-B. Actimab-A is designed as a first-line therapy for older newly diagnosed AML patients. This relatively large population of patients is treated at community and outpatient clinics, which total several hundred in the U.S. alone.

"This was a transformative year for Actinium because we changed from being an early-clinical-stage to a later-clinical-stage company with two drugs in trials," Seth concluded.

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What's Luring Pharma Back Into Antibiotic R&D?

MICHAEL GOODMAN Contributing Writer

Last May, a Pennsylvania woman was found to be infected with a strain of E. Coli that is resistant to a last-resort antibiotic called colistin. What was concerning was that the bacteria became resistant not through mutation but through the acquisition of a plasmid-borne colistin-resistance gene called mcr-1.

The bottom line is that plasmid-based genes can easily spread to other bacteria, perhaps to so-called "Super Bugs" like carbapenem-resistant enterobacteriaceae (CRE) that are already resistant to other antibiotics of last resort. That prospect caught the attention of the CDC and other public health officials.

Antibiotic resistance is on the rise, in part spurred by the pharma industry's 30-year neglect of antibiotic research. Most antibiotic R&D has been focused on incremental changes to existing classes of drugs; while useful, that will do little in the long term to head off antibiotic resistance. The CDC estimates that more than two million people worldwide come down with serious resistant bacterial infections each year, and at least 23,000 will die as a result.

Big Pharma has by and large steered clear of antibiotics R&D — and until recently, M&As — not wanting to get involved in heavily genericized markets where physicians are cautioned against overprescribing. But government inducements and the relaxing of clinical requirements are easing the industry's return to antibiotics.

THE PRESCRIPTION FOR MEETING THE CHALLENGE OF MULTIDRUG RESISTANCE

Government and industry are working on several solutions to solve the growing problem of resistance, including regulatory support, policy initiatives, and a renewed focus on pharmaceutical R&D.

Under the GAIN Act (Generating Antibiotic Incentives Now), which became law in July 2012, the FDA extended patent protection for qualified infectious disease products (QIDPs) by five years. It also sped clinical development by granting fast-track-priority review status to QIDPs and also by relaxing the study size requirements for QIDP trials. The EMA (European Medicines Agency), while not as far along, has put out regulatory guidance in final form that mirrors those at the FDA.

The accelerating public health crisis has pushed CMS to propose rules calling for hospitals to implement antibiotic stewardship programs to cut back on unnecessary antibiotic use. The USDA promotes similar practices among farm workers, encouraging cleaner environments for farm animals and less use of antibiotics in feed.

Hygiene is also important, particularly the use of sterile equipment and regular hand washing. But stewardship and hygiene will only prolong the efficacy of current antibiotics before resistance sets in. What's needed are novel ways of attacking bugs.

Industry and investors have responded to the GAIN act by jumping with both feet into antibiotic R&D,

developing new classes of antibiotics and markedly improved versions of existing classes.

A growing number of pioneers are focusing their efforts on the biological mechanisms of pathogen resistance rather than on approaches that directly target the bug. Some early-stage approaches being investigated include:

- A group at Tel Aviv University uses CRISPR gene editing to eliminate antibiotic-resistance plasmids in the environment before the microbes can infect a host.

- A researcher at Woods Hole Oceanographic Institute has enhanced antibiotic efficacy against multidrug-resistant bacteria by using small molecules sourced from the ocean to block the resistant bacteria's efflux pump, restoring its susceptibility to antibiotics.

But the antiresistance approaches that are most advanced and that will soon enter the clinic are in the hands of commercial companies.

TWO COMPANIES PUSHING THE NEW ANTIBIOTIC R&D PARADIGM

DR. ANKIT MAHADEVIA
CEO, Spero Therapeutics

SPERO THERAPEUTICS was founded in April 2013 by Dr. Ankit Mahadevia, its current CEO and an advisor at Atlas Ventures, in collaboration with SR One and the Partners Innovation Fund and supported by the Atlas Venture seed program.

Mahadevia stresses that Spero takes a multimodal approach to its portfolio, including novel antibiotics and programs focused on resistance mechanisms. Spero was founded on the research of Laurence Rahme, Ph.D., into virulence factors produced by a variety of gram-negative bacteria. Virulence factors typically help bacteria to invade the host and to evade host defenses. Spero's virulence blocker program was licensed out to Roche in April 2014.

But virulence blocking was quickly overtaken in priority at Spero by the potentiator program licensed in June 2015 from Northern Antibiotics Ltd. According to Mahadevia, although virulence technology has some nice benefits (e.g., you're not killing the bacteria, and you're impacting the cell in a way that doesn't lead to the emergence of bacterial resistance), there are still some scientific and clinical challenges.

The scientific challenges are surmountable, he says. But the clinical challenges are more formidable and relate to the existing development pathways for narrow-spectrum antibiotics that target a single pathogen. "Federal regulations make it difficult to create a trial design that doesn't take forever to recruit," he says. Virulence blockers typically target a single pathogen; it can take time to recruit a trial because fewer patients have that documented pathogen. Also, sponsors may have to run a protocol that calls for a large study. Mahadevia says the FDA is aware of the problem and is working hard to resolve it.

Spero acquired the potentiator program "with a lot of work behind it already." The potentiator candidate SPR741 can be combined with a variety of established antibiotics such as azithromycin and rifampicin. It works by disrupting the cell membrane of gram-negative bacteria (e.g., *E. Coli*), increasing its permeability, allowing antibiotics to enter the cell. (The composition of the cell membrane in gram-negative bacteria, in contrast to gram-positive bacteria, has been shown to be particularly resistant to antibiotics.) SPR741 has been shown to be safe in rats and nonhuman primates, and a human dose has been selected. Mahadevia expects it to enter the clinic in the fourth quarter of this year.

Spero is also progressing its DHFR inhibitor, licensed in early 2016 from Promilad Biopharma; the DHFR enzyme disrupts bacterial cell growth and division. And in May 2016, it licensed in gyrase inhibitors from Vertex Pharmaceuticals. Spero plans to pair them with SPR741. Mahadevia says the combination is 32x to 64x more potent than a carbapenem in treating multidrug-resistant infections.

FRITIOF PONTÉN
CEO, QureTech Bio AB

QURETECH BIO AB is a Swedish biotech founded in 2010 to commercialize research from groups based at Umeå University and Washington University. CEO Fritiof Pontén joined in 2014 from AstraZeneca. QureTech was formed with IP and licenses to virulence

blockers against mycobacteria tuberculosis and chlamydia. QureTech was funded by the Umeå Biotech Incubator with grants provided by the Erling-Persson Foundation.

Pontén notes that the availability of rapid and accurate diagnostics for determining the severity and progression of chlamydia infections makes it useful in the selection of a clinical regimen. He furthermore believes that this makes chlamydia suitable for a narrow-spectrum therapy, and that the FDA will agree. "This is why we chose chlamydia as a first indication," he says.

The chlamydia agent blocks the life cycle of the intracellular parasite. Soon after the dysfunctional bacterium is released to infect new cells, it's cleared by the immune system. The drug has an excellent PK (pharmacokinetic) profile and is easily absorbed. "Such compounds are rarely secreted unchanged. In the end, they'll be metabolized and won't reach the microbiome farther down in the gut," says Pontén. In short, these compounds are selective, sparing normal bacterial flora; they target a pathogenic process rather than bacterial survival, reducing the risk of developing drug resistance.

Tuberculosis is a more serious disease. QureTech saw that by up-regulating the enzyme KatG it could not only boost the efficacy of isoniazid, a mainstay drug against TB, but also reverse resistance to it. Also, long duration treatment with antibiotics, typically six to nine months, gives the bacteria time to evolve resistance. But QureTech sees signs that it can shorten treatment to approximately one month, representing a potential breakthrough in TB therapy and saving approximately $5 billion in global drug costs.

Finally, there is no indication that the FDA would place regulatory restrictions on a drug to treat as threatening a disease as TB. In addition to life-threatening side effects, the direct and indirect costs (treatment, lost productivity, etc.) for a TB case ranges from $282,000 for a patient resistant to at least two drugs of last resort to $646,000 for a patient extensively resistant to key first-line and second-line TB drugs.

Pontén says he needs about $10 million for each program — to bring them through remaining preclinical work and early clinical trials.

OF EXITS AND PRICE FLEXIBILITY

The antibiotic M&A market has been relatively quiet over the past decade, sustained largely by Merck's acquisition of Cubist for $8.4 billion in 2014, by Cubist's acquisition of several smaller antibiotic specialists, and by the M&A activity of Allergan and its constituent companies, Forest Laboratories and Actavis.

But Mahadevia says that in the post-GAIN Act world, "you'll see companies both large and small viewing this as an opportunity rather than a challenge."

Spero's lead potentiator program presents several options for monetizing the asset. Insofar as it holds the key to restoring the efficacy of many old-line antibiotics whose utility has been limited by bacterial resistance, it could build a commercial organization and sell the combinations itself. Or it could license the potentiator component on a nonexclusive basis to numerous parties. Mahadevia expressed a willingness to explore both options.

QureTech, at an earlier stage, hopes to get the funding, either through VC investment or through a partner, to advance its chlamydia program to proof-of-concept in man and its TB program to Phase 1. Pontén says he has noticed an uptick in EU venture interest in antibiotic plays. Rather than commercialize his pipeline, he plans to partner his two assets relatively early in development.

"Industry and investors have responded to the GAIN act by jumping with both feet into antibiotic R&D."

Whereas Spero can rely on a syndicate of investors and on funding from BARDA (Biomedical Advanced Research and Development Authority), a division of the U.S. Department of Health and Human Services, and from the Department of Defense, QureTech is at the mercy of a comparatively anemic venture climate in Europe.

Both companies believe that they will not be bound by the low prices of old-line antibiotics. Rather, the novel and superior attributes of their assets, particularly in the context of a worsening public health crisis, will raise the value of their pipeline in the eyes of payers and Big Pharma. L

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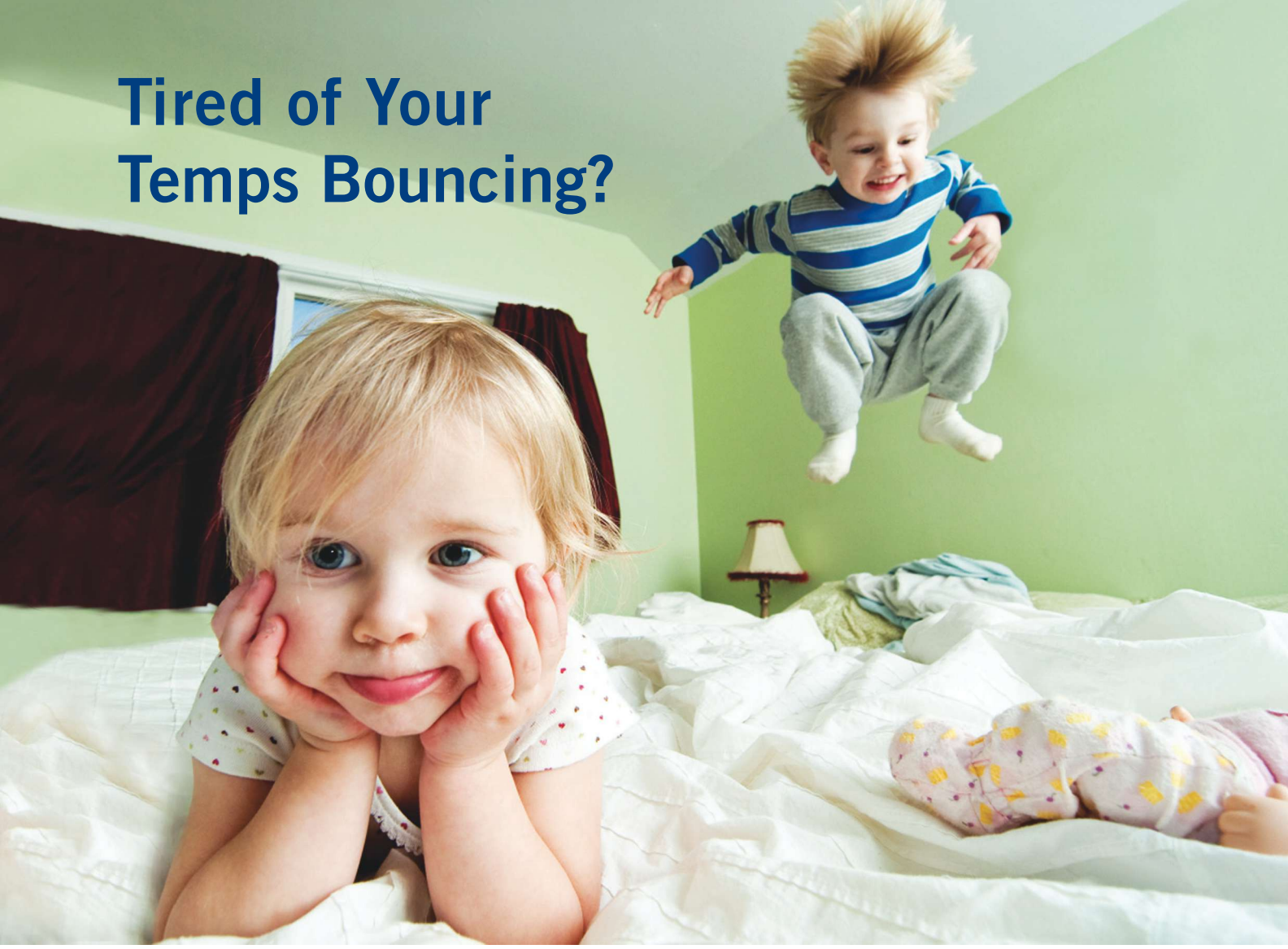

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Clinical Trials In China: A Model For Advancing Cancer Therapies

ED MISETA Chief Editor, Clinical Leader @EdClinical

Increasingly, pharmaceutical and biotechnology companies are enrolling patients in countries outside the U.S. Richard Brand, CFO for BeyondSpring Pharmaceuticals, believes this trend will continue going forward, especially for larger Phase 3 clinical trials.

China, with its considerable population and large number of patients diagnosed with cancer, has been of particular interest for clinical trials where genetic differences between the Chinese and Western populations are not a factor. CROs, consulting companies, and drug development firms that have assisted Chinese drug development companies with clinical trials and the regulatory review process have attracted interest from Western drug development companies, especially those that are seeking to effectively and efficiently navigate the procedures in place in China.

For U.S. pharmaceutical companies aiming to work in China, the country poses new and unique compliance challenges. The Chinese government has been proactive in quickly approving new pharmaceuticals, while also focusing on safety to protect its patient population. But while China provides a burgeoning market for pharma companies, there are many factors relating to its review process, specifically to the oncology market, that companies must understand.

"Recently it has become more difficult to recruit patients for clinical trials, which is of great concern for major sponsor companies," says Brand. "Studies show that only 3 percent of U.S. cancer patients participate in clinical trials. As treatments have become more targeted, the desired population for clinical trials has become even more narrowly defined. Patient enrollment and retention is now a major contributing factor to the cancellation of many clinical trials. "

According to Brand, this issue presents an opportunity for companies that have a unique relationship with the China Food and Drug Administration (CFDA) and connections with hospitals in China that can generate quality data that meets U.S. GCP standards. Cancer care in China continues to be highly centralized. The National Academy of Science Tumor Hospital in Beijing, the largest cancer hospital in China, had 800,000 patient appointments in 2015. It also treats over 2,000 new lung cancer patients each year.

"Unlike the U.S., where most residents have access to radiation and chemotherapy in close proximity to their homes, individuals who are diagnosed with cancer in China must travel to the advanced cancer centers that are located in Beijing, Shanghai, or Guangzhou," notes Brand. "That limited number of advanced cancer centers often results in concentrated and rapid enrollment for clinical trial participants."

WHY CHINA IS IDEAL FOR PHASE 3 STUDIES

Although the centralized care model in China can help overcome enrollment challenges in Phase 3 oncology trials, the CFDA will present challenges to

CONSIDER MANUFACTURING OPTIONS AS WELL

While China might be a good place to conduct clinical trials, Brand notes it might also be a good place to conduct contract manufacturing. A law that was passed in 2015 now allows manufacturing to be outsourced to a contract organization in China. He believes this will be advantageous to U.S.-based pharmaceutical companies.

"By making use of the manufacturing capabilities available in China, an innovative drug development company could focus on its R&D strength and avoid investments in plant and equipment," adds Brand. "Those same companies might also avoid the costs of manufacturing control and manpower management that are sure to follow. This will be particularly useful for small molecule drug developers, as many companies that develop biologics tend to build their own plants for fear of losing the clone to its biologic drug to the CMO."

"Studies show that only 3 percent of U.S. cancer patients participate in clinical trials. ... Patient enrollment and retention is now a major contributing factor to the cancellation of many clinical trials."

RICHARD BRAND
CFO, BeyondSpring Pharmaceuticals

the uninitiated sponsor. Established relationships with key principal investigators at the large cancer centers can greatly help a company doing business in China. In addition, qualifying a drug candidate program for Category 1 and fast-track review by the CFDA can expedite the entire process.

Brand cites a couple of examples to show the benefits of having access to patients in China. In 2013, the Phase 3 global clinical trial of Boehringer Ingelheim's lung cancer drug Giotrif (afatinib) enrolled 240 patients in China in just six months. The remaining 28 percent of the trial's patients were recruited outside of China. The Phase 3 clinical trial of another drug, Icotinib (a second-/third-line non-small cell lung cancer [NSCLC] drug) enrolled 400 patients in China in just nine months.

Many of the smaller, Phase 1 and 2 trials are manageable in Western countries. But, according to Brand, this concentration of individuals who are seeking treatment in China can be particularly valuable when pharma companies are enrolling patients in large Phase 3 trials that might require thousands of patients.

FDA VS CFDA: SAFETY AND EFFICACY MATTER

The greater propensity for cancer patients in China to participate in Phase 3 clinical trials may be due in part to the CFDA's more stringent requirements for allowing a Phase 3 trial to commence.

The Clinical Trial Application (CTA) in China is equivalent to the Investigational New Drug (IND) program the FDA grants to allow a clinical trial to start in the U.S. The IND is the means by which a pharmaceutical company obtains permission to ship an experimental drug across state lines before a marketing application for the drug has been approved.

"China's Phase 3 CTA differs in that the CFDA requires the drug candidate to demonstrate both efficacy and safety in prior clinical trials before granting the CTA to initiate a Phase 3 trial that will enroll Chinese patients," says Brand. "The U.S. FDA only requires that the drug demonstrate safety in its prior trials before granting the IND to proceed with a Phase 3 study. In other words, China's government further seeks to protect its people from trials with a large number of patients if a drug candidate has not demonstrated proper efficacy."

The data gathered from that trial should indicate sufficient efficacy, which could be used when launching an IND from the U.S. FDA for a global Phase 3 trial. A CTA can also be received from the CFDA at that time.

"To receive an NDA from the CFDA, a Phase 3 clinical trial must have at least 300 patients," he adds. "Therefore, the Phase 3 trial design that's submitted to the FDA should be for at least 300 patients in China."

THE CHINA REGULATORY REVIEW PROCESS

The CFDA conducts a special examination and approval of China domestic Category 1 new drugs. That process is carried out via the CFDA's 2009 Provisions on the Administration of Special Examination and Approval of Registration of New Drugs, or the Special Examination and Approval Provisions, if the drugs are:

- Extracted from a material in nature and preparations of it are newly discovered and never marketed in China before
- Chemical-based drugs and their preparations whose biologic product has not been approved in China or outside the country
- New drugs that exhibit obvious advantages in clinical treatment of priority illnesses, including AIDS, malignant tumors, or rare diseases
- New drugs for diseases that have no effective treatment methods.

This is a more straightforward regulatory pathway compared to new drugs that are already marketed outside of China by multinational companies. Current statutes have not revised this ruling.

There are a couple additional options to consider. "A drug can obtain additional accelerated review by the CFDA if it is submitted by a recipient of China's prestigious Thousand Talent Innovator Award, if the drug is included on China's national priority list, and/or if a drug candidate has received the prestigious Drug Development Innovation Grant Award from the Chinese government," adds Brand. "The CFDA may grant regulatory approval to a drug demonstrating similar efficacy in its primary endpoint and superiority in one of its secondary endpoints compared to another drug for the same disease that has already been approved for the market." L

The MENA Pharma Market: An Untapped Opportunity

KARIM SMAIRA

The total size of the MENA (Middle East and North Africa) pharmaceutical market is estimated at $36 billion, which is only 2 percent of global pharmaceutical sales, but it has one of the highest growth rates (9 to 11 percent until 2020, based on info from IMS Health) in emerging markets.

That growth rate is driven by the significant rise of chronic diseases — diabetes (affecting 25 percent of the nationals in the Gulf Cooperation Council [GCC]), cardiovascular, cancers, respiratory — and due to lifestyle changes and better education. For example, lifestyle changes are leading to an increase in chronic and "lifestyle diseases" (e.g., lack of exercise and bad diet leading to diabetes and hypertension, smoking leading to COPD and lung cancer). Better education and increased health and medical knowledge is making the general population more demanding when it comes to the quality and reach of medical services and access to drugs. Furthermore, as a result of cultural reasons such as consanguinity rates, the incidence of genetic diseases is significantly high, creating opportunities for companies focused on producing drugs for orphan and rare diseases. Governments, particularly those of Egypt, Algeria, Iran, Saudi Arabia, Jordan, and the UAE (United Arab Emirates), have recently supported the birth of local and regional drug manufacturers.

Due to the MENA region being the last frontier for many healthcare companies, regulators have implemented rapid reforms to improve the business environment and access to medicine. For example:

- Faster marketing authorizations for FDA- or EMA-approved drugs. The GCC has introduced an efficient centralized regulatory procedure.
- Harmonized pricing based on the international referencing system and a benchmark with the country of origin
- Universal healthcare coverage for GCC nationals and higher reimbursement coverage across the region with newly introduced, mandatory basic insurance schemes

Contrary to common perception, the MENA region is very heterogeneous, spanning from Morocco in the south to Iran in the north. It is clustered into three main subareas:

1. **GCC:** Saudi Arabia, Kuwait, UAE, Oman, Bahrain, Qatar, and Yemen, whose economies are mainly dependent on energy exports
2. **THE LEVANT:** Lebanon, Jordan, and Syria — with main economic drivers in services, tourism, and agriculture — and oil-dependent Iran and Iraq
3. **NORTH AFRICA:** Egypt, Algeria, Morocco, Tunisia, and Libya, combining services and energy sectors

Although mostly bound by a common language and religion, the MENA population is influenced by diverse cultures and past civilizations. This is observed in the genetic composition of the inhabitants. Some important characteristics to retain are:

- The population of almost 300 million continues to grow rapidly at >2 percent annually. *(source: World Bank)*
- It remains largely young, with 20 percent between the ages of 15 and 24. *(source: Youth Policy)*
- Life expectancy is an average 74 years. *(source: World Bank)*
- The female-to-male ratio is 49.65 percent respectively. *(source: Trading Economics)*
- The literacy rate has progressed from 59 percent in

HEALTHCARE EXPENDITURE, TOTAL % OF GDP/COUNTRY

MENA COUNTRY	1995	2014
GCC		
SAUDI ARABIA	2.9	4.7
KUWAIT	3.7	3.0
UAE	2.6	3.6
QATAR	3.7	2.2
OMAN	3.6	3.6
BAHRAIN	4.1	5.0
LEVANT		
IRAQ	N/A	5.5
JORDAN	8.5	7.5
LEBANON	12.6	6.4
SYRIA	5.5	3.3
IRAN	3.7	6.9
NORTH AFRICA		
ALGERIA	3.7	7.2
EGYPT	3.5	5.6
MOROCCO	3.6	5.9
TUNISIA	5.9	7.0
LIBYA	3.3	5.0

Source: WorldBank

1990 to 78 percent in 2010. (*source: World Bank*)

- The GDP per capita, with Qatar boasting $132,100 and $2,900 in the Palestinian Territories, and the percentage spent on healthcare, are very disparate. (*source: the CIA factbook*)

KEY SUCCESS FACTORS AND MARKET STRATEGIES

In addition to deciding which operational strategy to implement, it is critical for companies to consider some of these key success factors:

- Ensure that the product mix fits the region's needs by addressing unmet medical needs and supplying innovative drugs that compete on added value and not on price only.
- Avoid "me-too" products and competition with local manufacturers.
- Ensure the right regulatory sequence to secure the best pricing across the region.
- Diligently choose the regional partner needed for regulatory and commercial support.

- Hire, train, and retain staff who have the best expertise and cultural knowledge to navigate the local nuances. The region suffers from a scarcity of talents.
- Collaborate with local organizations that have a strong network with key decision makers and have multinational experience in launching and managing the life cycle of products.

The business model depends mainly on the level of risk and investments companies are willing to allocate to the MENA region as part of their expansion strategy. Some of these penetration strategies to consider are:

- Setting up a legal entity with full-fledged operations
- Registering a licensed scientific office to promote pharmaceutical products
- Contracting the marketing and sales to a regional player, whether fully or through comarketing and copromotion arrangements
- Out-licensing rights to the product with a royalty deal
- Engaging in M&A and joint ventures with existing local or regional players
- Partaking in local manufacturing by contract manufacturing or owning facilities (Several companies have recently decided to sign agreements for second brands anticipating the patent expiration.)
- Setting up a central distribution hub to control the flow of product and the quality aspects.

The increasing competition and the fast maturation of the MENA markets are facts. With a large potential for growth, this region commands a long-term strategy instead of an opportunistic approach. L

Karim Smaira is the founder and CEO of Genpharm, a pharma company providing market access and strategic advice into MENA markets. It focuses on specialty, rare and genetic diseases, orphan drugs, and diagnostics. He has been in the pharma industry since 1999 and is a frequent speaker on emerging markets and orphan drugs.

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Active Targeting:
A New Wave In Drug Delivery

GEORGE YEH

Although the history of drug development contains many stories of serendipitous discovery, critical advances often emerge by setting out to address specific challenges. Today, many challenges associated with older drugs are being solved with new delivery technologies. These new forms of delivery are capable of guiding a drug directly to the targeted disease tissue or a specific cell type. For many drugs, effectiveness is limited by toxicities resulting from the exposure of healthy, nondiseased tissues to the drug. The expectation for new forms of delivery is that improving old drugs with targeting technology will meaningfully and reproducibly improve therapies across a wide range of disease areas.

THE QUEST FOR THE RIGHT TECHNOLOGY

Developing a targeted therapy requires not only a deep understanding of how this therapy will be applied clinically, but also an understanding of the practical limitations of the technology itself. For example, one type of a targeted drug is an antibody-drug conjugate, where therapeutic molecules are chemically linked to antibodies with specific affinity to a cellular target. While this approach has produced approved drugs, its activity and broad utility in many contexts may be limited by the low ratio of therapeutic payload molecules to the number of antibodies.

One way to address the issue of payload ratio may be through the use of lipid-based nanoparticles, coated with antibody fragments to provide cellular targeting, each containing thousands of drug molecules. Although the hope of this effort and others is to demonstrate an efficient and broadly applicable technology, there may not be a one-size-fits-all approach for targeted delivery. Still, the promise of antibody-based targeting technologies for improving efficacy and reducing toxicity is clear.

CHOOSING THE RIGHT INDICATION

The concept of targeted therapies is particularly compelling in oncology, where dose-limiting toxicities — common consequences of cytotoxic drugs — significantly limit a drug's therapeutic potential. Other areas where more targeted therapies could benefit from this approach are those where disease biology is mediated by specific cell types, including infectious diseases, brain disease, heart disease, diabetes, or lung-specific drug delivery. In addition to disease biology and side effects of existing treatments, important considerations in determining an indication for development of targeted therapeutics are the costs of treatment and costs of manufacturing. Many drugs using existing targeting technologies are exceedingly costly to manufacture, so a careful analysis of both treatment limitations and costs is required.

ADVANTAGES OF INCREMENTAL ENGINEERING

From a high-level view, narrowly addressing the drug delivery component of a new therapy, such as adding targeting capabilities, has additional advantages. Changes in biodistribution resulting from targeted delivery can be relatively straightforward to assess in preclinical models, thus reducing the risk of unexpected effects during clinical development. In addition, incremental changes to delivery can be evaluated for their effects on known safety risks, which can be more easily avoided early in the development process. Optimizing drug delivery by improving targeting, isolating only that variable in the overall process of drug development, also helps in defining clear clinical benchmarks. This is in part because non-targeted versions of a similar therapy provide an easy point of comparison for an actively targeted therapy.

While there is much work yet to be done in refining targeted drug delivery technologies before advances are reproducibly and broadly demonstrated in the clinic, the promise of the concept justifies current widespread efforts. L

GEORGE YEH is president of TLC, a biopharmaceutical company developing therapies in the areas of oncology, ophthalmology, and pain management through the use of lipid-based drug delivery technology.

The Space Squeeze: One Challenge In Building A Biopharm Lab

AMRIT CHAUDHURI

Any biotech or life sciences company in Boston — early-stage or mature — is no stranger to Kendall Square's lab space squeeze. As the top-performing lab market in the U.S., Kendall Square is especially sought after by life sciences companies — ranging from emerging startups to Big Pharma. Securing lab space in the world's largest biotech hub is a nearly impossible mission, especially as the price tag tied to leases in the Kendall Square area have skyrocketed in recent years. The nonstop demand for space has allowed landlords to raise the rent, further enhancing the competition among space-deprived life sciences companies.

WHAT'S THE DRIVER BEHIND KENDALL SQUARE'S SPACE SQUEEZE?

The biotech space crunch is driven by the fierce competition between early-stage startups and Big Pharma for access to innovative research ecosystems like Kendall Square. It is a battle between the Johnson & Johnsons of the world that want to lease 150,000 rentable square feet (RSF) and the Oncoruses of the world that only need 2,000 RSF. Both types of companies need the space for different reasons, but ultimately they're all after the same prize: lab space in the heart of Kendall Square.

The goliath of this situation is taking all the cake off the table and leaving barely crumbs behind for the small, innovative companies that are actually driving the future pharma pipelines with future partnership opportunities.

According to JLL's Q2 report on the Kendall Square lab market, there is virtually no vacant space left as biotech companies are continually flowing in at rapid speed. In Q2, direct vacancy sat at 0.8 percent, dropping below 1 percent for the first time since 2001. With companies willing to pay large sums of money for space, landlords have upped the rent, which is now at an all-time high. In fact, the average rent climbed to $65.33 per square foot triple net in Cambridge last quarter.

Emerging life sciences companies need both business and lab space when considering a location. The R&D space should be able to accommodate the company's specific type of research and support the continuous stages of evolution throughout the R&D process. One trend we've been seeing here in Kendall Square is that landlords are starting to convert space from office to lab in an effort to meet the market demand.

A NEW OPTION

Accelerated commercialization spaces offer a crossroads for partnerships with life sciences companies, CRO service providers, instrumentation vendors, and investors. It can take four to seven months to build out a traditional lab space; however, by using accelerated commercialization spaces, biopharmaceutical companies not only save start-up time, but also money by avoiding the high price tag associated with a traditional lease, sourcing operations, support, and hiring. These arrangements can be especially helpful when a company only needs lab space for a specific amount of time (e.g., three years).

The heart of Kendall Square is home to life sciences and biotech businesses ranging from fledgling startups to mature pharmaceutical companies. As lab space in the area continues to become more absorbed every day, competition among companies remains relentless. With little relief in sight, more and more companies are turning to accelerated commercialization spaces and accelerators to help them overcome time, money, and space hurdles on their way to achieving milestones. L

AMRIT CHAUDHURI is the CEO and cofounder of Mass Innovation Labs and seeks to remove obstacles and understand pain points for Boston-area biopharma companies.

Management Is Dead.

Stop Managing And Start Coaching!

TERRI LEVINE

TERRI LEVINE is a best-selling author, keynote speaker, popular TV personality, and host of "The Terri Levine Show." Find out more at www.todayscoaching.com.

Finally we have realized you can't manage people, you can only manage things. Behaviors are manageable, and people certainly are not, so we need to stop trying to manage people. We must start to learn skills to coach people to success.

WHAT IS BUSINESS COACHING?

Business coaching is helping people to be inspired to achieve more than they may have ever dreamed possible. A great coach is not a manager who tells others what to do. A great coach invites colleagues to work with them to solve problems creatively and works with people to achieve common goals. Business coaching means you inspire, empower, and energize the people on your team. You seek answers from those you work with and solicit suggestions and ideas of others. People like to be led if those who coach and lead them are empathetic and compassionate.

COACHING YOUR TEAM

Shifting to a coach versus a manager means you are willing to set directions for others and mobilize individual commitment of team members. Great coaches empower people on their teams by letting them know they make a difference. If and when there are problems that show up, never criticize the person. Behaviors or systems are problems — never people. Your job is to coach people into success. Coach them through to solutions.

Ask team members for advice. Coaching is based on asking a lot of questions and inviting your team to give their input. Always acknowledge and honor others, and thank them for their input and contributions. Get team members to add to your thoughts and improve on your ideas and help to achieve the best outcomes.

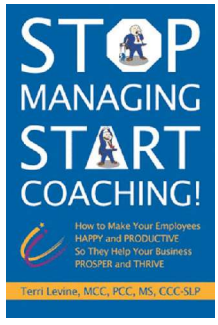
Coaching teams means the entire team has a hand in ownership and making changes and implementing all ideas. There is a sharing of ownership and no longer is there top-down management. Coaching is collaborative. When everyone feels ownership, things happen. Productivity, profitability, and morale automatically increase.

THE BEST COACHING PRACTICES

Companies that have the most successful coaches have a clear vision their teams get behind. Everyone is working toward a common goal. There are shared values, and everyone is working jointly and not trying to be the star. It is truly a cohesive effort. In fact, there is shared ownership for all the results because it is a team effort. Coaching is used to develop all team members to their fullest potential.

You will enjoy your job more when people self-manage and you stop trying to manage people. Allow people to lead themselves and stop trying to control them and command them. No need to instruct them. Just guide them with coaching and questions and you will soon empower them. They will begin to rely on their judgment and intuition and be empowered and enjoy their jobs more, too. You will notice you have more motivated, engaged, and enthusiastic employees.

Get out there and stop managing and start coaching. Make business fun, and get people excited about working as a team!



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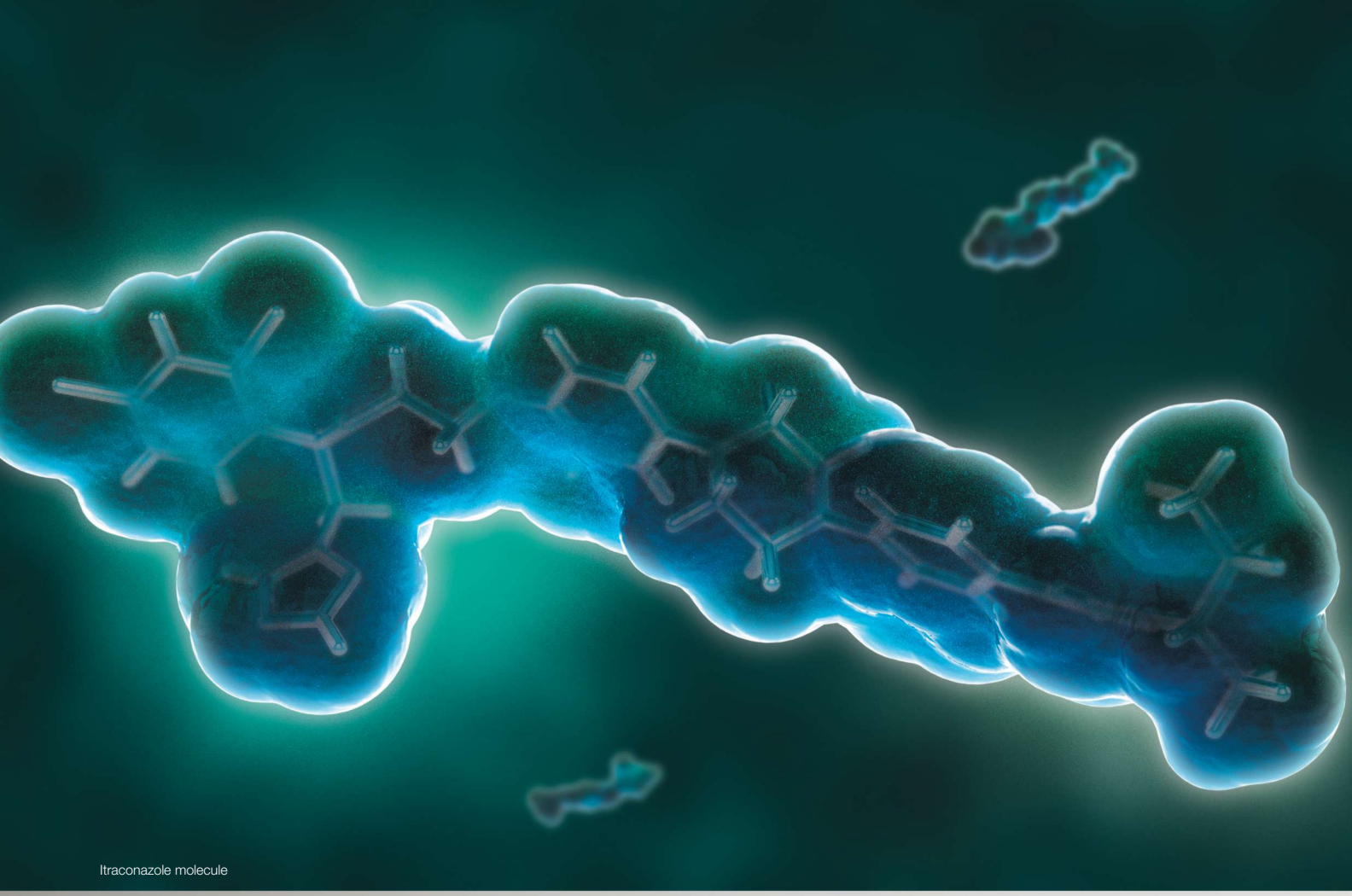

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