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How Biogen Is Preparing For The Biologics Tidal Wave

p. 20

> “When you work in operations, you’re waiting for moments like these, because this is your chance to come through — in a big way.”

John Cox
EVP Of Pharmaceutical Operations And Technology, Biogen

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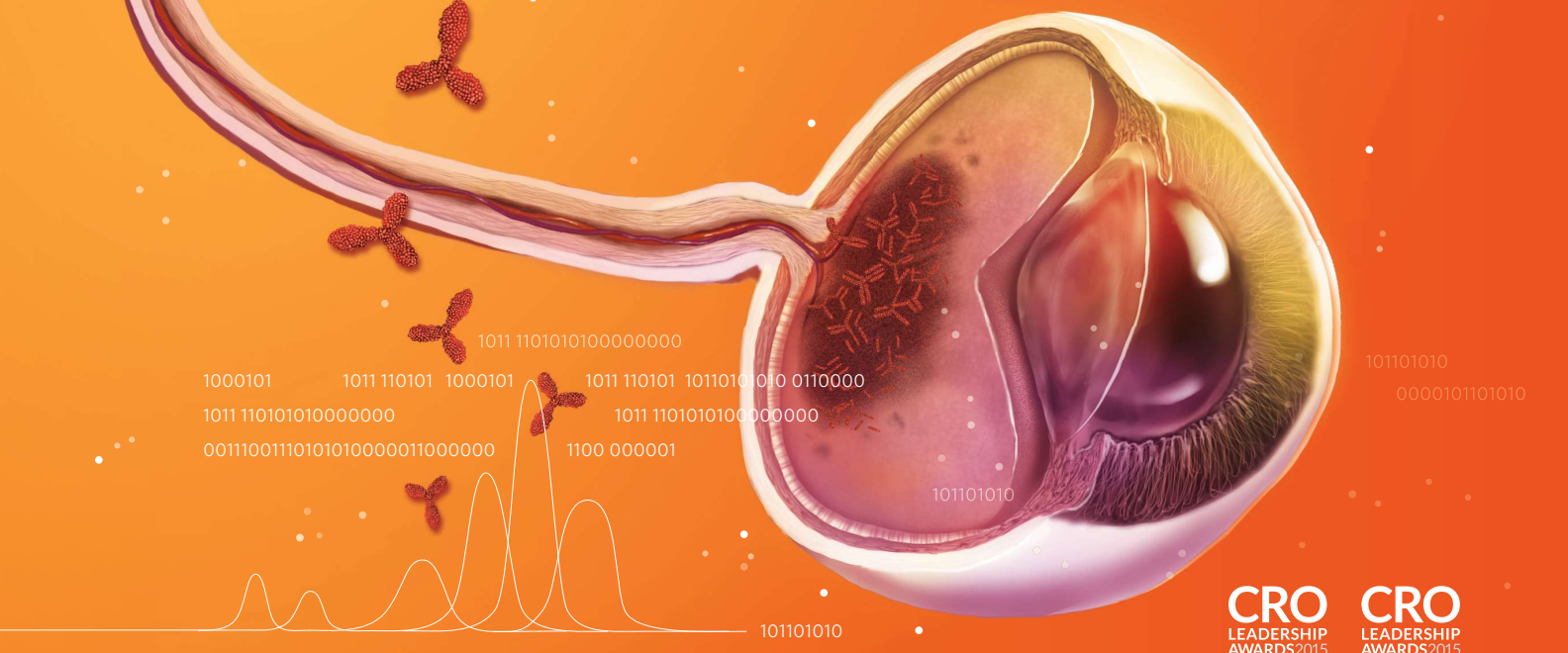

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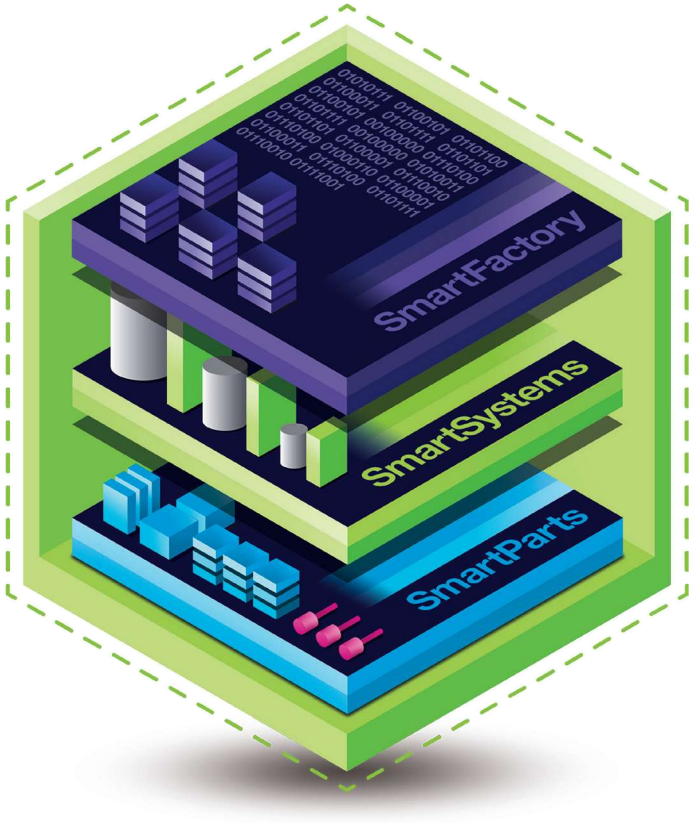

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Will Biologic Growth Overwhelm Your Ability To Manufacture?

ROB WRIGHT Chief Editor

Some biomanufacturing experts have recently begun referring to the expected growth of biologic therapeutics as an oncoming tidal wave or tsunami. Like the natural disasters these terms describe, there can be harmful repercussions — both to the industry's reputation and the patients in need — if companies are not adequately prepared for the impending biologic manufacturing capacity crunch.

Although biologics make up a mere 20 percent of branded prescription drug sales today, this number is expected to exceed 50 percent by the year 2020. One person sounding the alarm on the importance of preparing manufacturing for this significant increase is Andy Skibo. A 40+ year biomanufacturing veteran, the EVP of biologics supply at MedImmune/AstraZeneca (AZ), and 2015 chair of the International Society for Pharmaceutical Engineers (ISPE) says using terms like "massive," "unprecedented," and "historical" to describe the current situation is not an exaggeration. According to Skibo, "Companies are no longer using thousand-liter multiples to describe their oncoming biologic manufacturing needs. Instead, we are using whole sites (i.e., three to five 'Fredericks') as measuring sticks." The AZ Frederick, MD facility to which he is referring originally encompassed 90,500 square feet. But that isn't the three to five times figure Skibo suggests you consider. Rather, contemplate Frederick's more current and expanded size, 710,000 square feet (i.e., 16 acres), with plans soon to add 40,000 more. Biologics already represent nearly half of AZ's R&D pipeline (i.e., approximately 120 with more than 30 in clinical development). As a result, Skibo is well attuned to the significance of the situation.

If you are involved in planning for biomanufacturing capacity needs at your company, Skibo recommends taking into account the following considerations. Through 2020, the CMO space for bulk bio drug substance production will be very constrained. "We are not in a time period where if we guess wrong on the low side, we can just pick up the phone and find a CMO or partner with a lot of spare capacity," he states. "Further, pipeline accelerations have cut drug development cycle times from eight to 10 years down to three to four. However, it still takes about five years to design, build, commission, and license a large-scale bio drug-substance facility." Committing to these major capacity builds without a confirmed need is a major financial guessing game.

One company currently involved in a major biomanufacturing capacity initiative is Biogen. Sparked by positive Phase 1b clinical trial results for aducanumab, its experimental drug for Alzheimer's disease (AD), Biogen fast-tracked the compound straight to Phase 3 clinical trials. Imagine being faced with the prospect of being manufacture-ready to potentially serve millions of people suffering from a very debilitating disease, now under a much more accelerated time line. What would you do? This month's cover article on p. 20 features Biogen's top manufacturing exec, John Cox, EVP of pharmaceutical operations and technology. Cox shares his insights as to how exactly Biogen is preparing to meet its biologic manufacturing needs, including the decision to build a billion-dollar biologic facility in Solothurn, Switzerland. Interestingly enough, the word "panic" never seemed to enter into the conversation. L

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

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

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

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

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

EXECUTIVE EDITORS
Wayne Koberstein
wayne.koberstein@lifescienceleader.com

Louis Garguilo
louis.garguilo@lifescienceconnect.com

Ed Miseta
ed.miseta@lifescienceconnect.com

Trisha Gladd
trisha.gladd@lifescienceconnect.com

Ken Congdon
ken.congdon@lifescienceconnect.com

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

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

PRODUCT DIRECTOR
Jenell Skemp
jenell.skemp@lifescienceconnect.com

PROJECT MANAGER
Megan Rainbow
megan.rainbow@lifescienceconnect.com

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

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

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

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

ENGAGEMENT MANAGER
Kevin Morey
kevin.morey@lifescienceconnect.com

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

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

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

PRODUCTION DIRECTOR
Lynn Netkowicz / Ext. 205
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Q How can manufacturing executives prevent supply chain partners from becoming bottlenecks to quality manufacturing?

A IT BEGINS WITH STRONG, OPEN, COLLABORATIVE RELATIONSHIPS between buyers and sellers. Establishing effective relationship governance at the working team and executive levels between companies ensures goal alignment and execution in accordance with mutual expectations. Resourcing these teams with capable and skilled talent fosters effective communication and trust, accelerating their ability to deal with inevitable challenges. KPIs (key performance indicators) that measure a set of elements for the supply relationship (e.g., quality, service, costs, environmental, safety) further enable supply reliability. Supply risks need to be understood for product/material supply linked to key product lines, and appropriate measures to mitigate risk (e.g. dual sourcing, inventory strategies and supplier development resourcing) must be implemented and managed.

ANU HANS
is VP and chief procurement officer, enterprise supply chain at J&J. She also serves as a board member for DCAT.

Q What are the components of a regulatory intelligence function in pharma?

A IT BEGINS WITH DEFINING THE SCOPE (e.g., GxP, quality), stakeholders, and communication channels. Understand the direction of the organization and its products, build the process, then refine and measure. The value of a dedicated in-house regulatory intelligence function should not be discounted. At its core, this function is responsible for ensuring awareness and preparation in response to changes in the global regulatory landscape, although the latter [preparation] may differ in maturity depending on the defined scope, resources, and expectations of the organization for this function. Regulatory intelligence is not just data mining. Minimally, this function should be responsible for impact assessments, stakeholder identification, prioritization, regulatory trending, follow-up, and evaluation. In some cases it can also be involved in regulatory strategy or even act as the conduit for comments and responses with health authorities.

JASON URBAN, PH.D.
is director of global quality risk management and compliance at Celgene.

Q What advice do you have for preventing/minimizing a counterfeit situation from disrupting your manufacturing process?

A IMPLEMENTATION OF AN INCIDENT MONITORING PROGRAM allows you to study patterns by supply chain segments and identify anomalies. Randomly purchasing your product from all channels of trade (including the Internet) can help you test your supply chain's integrity. Establish intelligence-sharing relationships with government and law enforcement agencies so you can stay up to speed on the latest counterfeiter trends. Adding anti-counterfeiting technologies, including serialized packaging, can help with early detection. Ensure that all distributors/retailers purchase your products only from you or an authorized company agent and audit them regularly. Analyze returned goods for breaches in product integrity or fraud. Lastly, implement strict procedures to ensure that damaged/expired supplies, finished goods, as well as retired production equipment are destroyed and witnessed by company personnel.

RON GUIDO
is president of LifeCare Services, LLC. He has more than 36 years of experience in the healthcare industry with J&J and is also a consultant on brand protection and supply integrity issues.

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Vascular Pharmaceuticals

A company tackling diabetic nephropathy through a new pathway

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Vascular Pharmaceuticals is a private company developing a drug to treat diabetic nephropathy, based on a novel molecular pathway company researchers identified that contributes to diabetic kidney disease. With help from its partner Janssen, the company has moved its lead monoclonal antibody (mAb) compound through preclinical and Phase 1 studies and is now beginning the treatment stage of a Phase 2 program. Janssen has the option to acquire Vascular upon completion of the Phase 2 trial.

WHAT'S AT STAKE

Okay, I'm stuck on kidneys. Two months ago, this column spotlighted a company with drugs in development for kidney damage and disease, including diabetic nephropathy — the target of Vascular Pharmaceuticals' lead drug. There is a good reason for the conjunction. Early this year, I began to encounter companies developing drugs with new, unique mechanisms of actions (MOAs) in the diabetes/endocrinology space, which for many years has been relatively quiet, even sleepy. I interviewed a small sample of those developers with the idea of eventually creating a series to look at the new MOAs the way we examined cancer immunotherapy during the past year in our "virtual roundtable," using CtW ("Companies To Watch") as a vehicle for whetting readers' appetites. As stated in the August CtW, "Any so-called competition in a dormant space tends to increase awareness and market potential of that space." Certainly, Vascular Pharmaceuticals is enlivening the area with its own unique approach to preventing and treating diabetic nephropathy, the main cause of chronic kidney disease.

Vascular spun out of research at UNC-Chapel Hill School of Medicine that discovered a causal relationship between the high-glucose blood levels in diabetes and cell-signaling changes that disrupt the kidney cells involved in filtration (leading to kidney damage). It now has an mAb drug candidate, VPI-2960B, entering midstage development designed to down-regulate the activation of a key receptor in the kidney cells, $\alpha V\beta 3$, an integrin, or cellular adhesion protein. The MOA differs categorically from the anti-fibrotic and anti-inflammatory approaches to kidney disease by other companies.

"Not by antagonizing the receptor but by normalizing its activity with VPI-2960B, we hope to stop the progression of damage in the kidney and hopefully even reverse diabetic nephropathy," CEO Richard Shea says.

The move to founding a business began in 2005, but Shea says Vascular's operations actually ramped up in 2009, when the company received a $1.2 million STTR (Small Business Technology Transfer) Phase 2 grant. "Although the grant was for a relatively small amount of money, it was significant because it was the first outside recognition of our potential," he says. "The grant funded our proof-of-concept preclinical program." About the same time, Vascular received further validation in signing a development pact with Janssen, later terminated and replaced with a funding agreement giving Janssen an option to buy the company once it completes its current Phase 2 trial. Janssen facilitated the formulation and optimization of the VPI-2960B mAb for clinical trials. VC funding has sustained Vascular in the meantime.

"In our Phase 2 trial, the drug is given as a biweekly injection, but the half-life would support extending the injection interval in later trials," says Shea. "The Phase 2 trial uses an adaptive design, starting with 100 patients. We will monitor their progress over six months, then evaluate whether to enroll a second cohort of 200 more patients. Patients will be treated for one year. VPI-2690B has produced impressive results in our animal studies in both rat and pig models. We believe that the pathway will translate into humans, and our current Phase 2 trial will validate that hypothesis." Phase 1 showed good safety. Now, in larger human trials, the toughest test begins.

RICHARD SHEA
CEO

Vital Statistics

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Focus On Pricing Puts Rx Industry On Defensive

JOHN McMANUS The McManus Group

When the candidates in the Democratic presidential debate named their biggest enemies, Hillary Clinton placed drug companies next to Iran. Drug companies! Those totalitarian, human-rights-abusing foes — mitigating and eradicating horrific diseases, supporting over 3.5 million high-paying jobs in the U.S., contributing over $50 billion in annual R&D to conquer devastating diseases like Alzheimer's — are being fingered along with the Mullahs of Iran as the principal enemies of the most likely next president of the United States.

It is certainly not because drug companies have campaigned against Hillary Clinton. Since her first Senate campaign in 2000, she has collected more than $1 million from drug and health companies. So far this year she's collected more than any other presidential candidate as well.

Hillary Clinton is an adroit politician. She identified drug companies as villains because she is tapping into a growing political concern regarding the aggressive pricing strategies of many pharma companies. An August Kaiser Family Foundation poll found that 72 percent of Americans feel that drug costs are unreasonable, and 74 percent feel that drug companies put profits over people.

First came Valeant, the Canadian-based firm that earned a reputation for acquiring companies with limited-competition products, pricing those products at a premium, and then shuttering most of the R&D capacity of the acquired companies. Valeant tripled the price of Isuprel and hiked the price of Nitropress, another heart medication, by six-fold soon after acquiring them. Both products are generic.

Then Turing Pharmaceuticals, an obscure drug firm recently acquired by a young, avaricious hedge fund manager, ignited the recent firestorm when the *New York Times* skewered its effort to hike the price of Daraphim, a product marketed since 1953 to treat toxoplasmosis infections for those with weakened immune systems, from $13.50 to $750 per pill.

Bad behavior does not go unnoticed, and, for Turing and Valeant, overly aggressive price increases attracted prosecutorial attention to the companies' general business practices. Turing is now being investigated for anti-trust activities by the New York attorney general for restricting sales of the product to a select few pharmacies. Turing's CEO is also being investigated for violations of allegedly misusing company funds while at Retrophin, another company he founded.

Meanwhile, Valeant was subpoenaed in October by federal prosecutors looking for information on its patient assistance programs, drug pricing, and distribution practices. This follows congressional investigations by the Government Reform and Oversight Committee's Ranking Member Elijah Cummings (D-MD) and Senator Bernie Sanders (I-VT), who is running for president.

Sensing a political opportunity, Clinton released her plan to combat drug prices a few weeks ago. Her package includes a number of familiar proposals — negotiation of prices for Medicare drugs, drug importation, reducing exclusivity of biotech products from 12 years to seven, and extending Medicaid-style rebates to Medicare plans serving low-income seniors. But it also included ideas that are percolating in several states, including limiting profits of pharmaceutical companies to an arbitrary metric. The announcement of Clinton's plan sent

"It's high time to develop and convey more forceful arguments regarding the value of innovation in driving down overall healthcare costs."

biopharmaceutical stocks tumbling, with over $40 billion in market value wiped away in a few hours

Feeling vulnerable, PhRMA turned guns on Turing — condemning the dramatic price hikes of these products as outliers that do not represent the industry's standards. Biogen CEO George Scangos, who is also the chairman of PhRMA, characterized the price hike as a "perversion of the system" and called the move by Turing "arrogant and naïve." (Neither Turing nor Valeant are members of the trade association, nor do they perform even minimal research to develop new products.)

The *Wall Street Journal* piled on with a lengthy piece in early October documenting substantial wholesale price increases on many leading products. When the *Wall Street Journal* attacks, it's hard to know where the industry can find shelter.

That analysis of wholesale prices of course fails to paint the full picture because it excludes the significant discounts health plans negotiate with manufacturers and even greater price concessions through pricing schemes run by public payers. Moreover, most companies offer generous patient assistance programs to reduce or eliminate obligations for patients who cannot afford their medications.

The industry has made headway in explaining the transformative power that medicines can have. Most payers are now covering the Hepatitis C cures, which have been lifesavers for patients and eliminated the need for costly liver transplants. But the public's ire over pricing now appears to be most acute regarding existing products that have been on the market for years.

The pharmaceutical industry has historically relied on arguments that pricing reflects enormous and risky investments in research and development. The Tufts Center of Drug Development found that just 12 percent of drugs that enter clinical trials make it to market. But those arguments are beginning to fall flat, and some want those costs explicitly and publicly spelled out.

Now some states are considering legislation that would require disclosure of R&D expenditures related to particular products, and many would even limit prices based on those expenditures. More troubling, the White House is now allegedly working on a comprehensive package to address drug pricing that may include similar ideas. The industry is waiting with bated breath.

The National Association of Manufacturers (NAM) has responded forcefully, stating, "There are efforts underway to require manufacturers to turn over highly sensitive operational information, such as pricing on specific products, marketing costs, and product development funding streams. From the view of the manufacturer, publicly releasing this kind of information is contrary to commonly understood business practice, surrenders federal protections, leaves markets and their company open to manipulation... ." NAM is right. However, telling the story of products whose price exceeds the marginal cost of production in the short-run while the long-run economic and clinical benefits are much more difficult to quantify is complicated. Scurrilous demonstrations from the campaign bully pulpit are far easier.

Since enactment of the Affordable Care Act five years ago, the industry has experienced a relative lull in activity as the policy focus has been on implementing that gargantuan law. But increased public ire at both real and perceived pricing issues means that the industry must move rapidly to a war footing in Congress.

A new opportunity to educate policymakers on the role and economics of pharmaceuticals presents itself with the ascension of Stephen Ubl as president of the lead trade group, PhRMA. Just 46 years old, Mr. Ubl is an experienced operator in Washington but brings new energy and focus to an industry now finding itself in a defensive posture. It's high time to develop and convey more forceful arguments regarding the value of innovation in driving down overall healthcare costs and assisting society in addressing unmet medical needs that no other sector can deliver. L

JOHN MCMANUS is president and founder of The McManus Group, a consulting firm specializing in strategic policy and political counsel and advocacy for healthcare clients with issues before Congress and the administration. Prior to founding his firm, McManus served Chairman Bill Thomas as the staff director of the Ways and Means Health Subcommittee, where he led the policy development, negotiations, and drafting of the Medicare Prescription Drug, Improvement and Modernization Act of 2003. Before working for Chairman Thomas, McManus worked for Eli Lilly & Company as a senior associate and for the Maryland House of Delegates as a research analyst. He earned his Master of Public Policy from Duke University and Bachelor of Arts from Washington and Lee University.

Why A Seasoned Management Team Is The Ultimate Competitive Advantage

ALLAN L. SHAW

The biopharma capital markets, driven by many fundamental factors, have been on an unprecedented tear for the last three years, exemplified by the twofold increase in the NASDAQ Biotechnology (^NBI) even after the sell-off that dropped its recent peak by 25 percent. While it is unclear where we go from here, it would be unreasonable to expect that the industry as a group will continue its gravity-defying returns, particularly when considering the implicit risks and execution challenges coupled with the increasing need to successfully adapt to a fluid and fast-changing environment. When considering the plethora of factors that go well beyond an organization's direct control (e.g., capital markets, science, regulatory, development, commercial, competition, reimbursement), management team quality is the fundamental differentiator in determining the winners from the losers, particularly when the waters get rough.

Given the choice, I would choose the combination of a mediocre asset and a great management team over a great asset and a mediocre management team. Simply put, management teams can create or destroy value. Let's face it, things rarely go according to plan, and time is always the enemy, which makes it even more important to have an objective, principled, and agile management team of fact-based decision makers who have the capacity for ingenuity, determination, and perseverance. The importance of these qualities cannot be understated, particularly in a very competitive landscape that requires differentiated strategies for success (e.g., innovative medicines in noncompetitive categories), given the increasing prevalence and clustering of activities concentrated on common targets further compounded by long developmental time lines.

To better illustrate the impact of management on value creation, let's take a quick look at NPS Pharmaceuticals — a company that was on the precipice of extinction until a leadership change turned it around and recently sold it to Shire for $5.2 billion. In a nutshell, new leadership:

1. changed strategy to a focus on rare (orphan) diseases by repurposing pipeline assets on innovative targets for unmet patient needs
2. transformed the business model from a fully integrated pharmaceutical company into a lean and agile organization, retaining only core competencies in-house and contracting or outsourcing all other operational activities
3. created an entrepreneurial culture that was anchored by core values, embodied by the leadership team and adopted throughout the organization.

In my opinion, leadership's capacity to identify opportunities and recognize failure was the most important factor that contributed to NPS's success, as well as a critical trait embedded in the DNA of great management teams. Management's ability to recognize and capitalize on opportunities is often underappreciated and highlights another leadership trait to be considered and valued when separating the "wheat from the chaff." This is clearly much easier said than done, as evidenced by the increasing prevalence of repurposed drugs, reflecting overlooked opportunities generated from someone else's failure. Conversely, intellectual honesty and objectivity (completely detached from emotions) are fundamental management qualities that enable timely recognition of failure, or put another way, knowing when and how to pivot (or cut your losses) are equally important.

"The biopharma industry tends to hire from within and generally prefers leadership/ management from other life sciences companies, akin to the recycling of coaches and managers in professional sports."

Throwing good money after bad will only accomplish one thing: destroying shareholder value. It is not unusual for individuals to become emotionally attached to developmental projects or business combinations that no longer make sense, such as those devoid of scientific and market reality (e.g., competitive landscape, patients' needs). In some cases, people are simply trying to keep the plates spinning (which could also be characterized as job preservation). This reminds me of sage-like wisdom bestowed by a mentor: "If you make a wrong turn and continue going down the road, **it is still a wrong turn!**"

Great teams and companies require diversity of thought, skills, passions, and backgrounds. With that said, the biopharma industry tends to hire from within and generally prefers leadership/ management from other life sciences companies, akin to the recycling of coaches and managers in professional sports. It is interesting to observe the divergence in hiring practices between scientists and business people, whereby the entire world is scoured and every rock turned over in pursuit of the best scientific talent available while the resource pool for business people is artificially limited to those playing in the industry's sandbox. Objectively speaking, this makes as much sense as a commercial fisherman choosing to fish in a pond instead of the ocean. The industry's insular and inward ways have fostered this inbreeding, which inevitably perpetuates the same ideas not only within a company but also throughout the industry. Companies in this scenario often ignore outside influences with alternative perspectives, which in turn, makes it difficult to accept/embrace new business practices. Ironically, this is the last thing the industry needs (e.g., a prescription for disaster) as the healthcare (HC) ecosystem embarks on unprecedented change to fundamentally reform itself. The old ways of doing business are going the way of the dinosaur and will simply not work in the future. It is time to embrace new talent and leadership with cross-functional skills and expansive experience with the strategic vision and understanding of macro issues, new ideas, and business models necessary to successfully navigate the rapidly evolving HC landscape.

As a result of the incredible capital market run and industry growth, human resources have supplanted financial resources as the most significant gating factor for successful execution and value creation. Human capital is becoming an increasingly scarce resource, reflecting the pressing need for experienced business leadership capable of operating in a changing HC environment and creating differentiated strategies necessary for success. This situation has become more acute with the parade of IPOs and the consequential proliferation of "green" management teams. The latter are inexperienced at operating a business in the public fish bowl, lack the dexterity to optimally handle Wall Street's cast of characters, and in many cases, are ill-equipped to manage the growth that is implied by their companies' valuations. Let's remember that the biopharma sector is not for the faint of heart; the industrial jeopardies are pervasive and represent significant operational and strategic challenges that make the likelihood of success dependent on the readiness of the firm's leadership to meet business challenges. Put another way, a company's greatest strategic asset (or liability) is its management.

The ultimate competitive advantage, in my view, is a seasoned management team with a macro understanding and diverse industry background in companies of various sizes who have "been there and done that" and can provide a veteran's perspective on how to build and scale organizations in a dynamic environment. Given recent capital market turbulence, let's see where all this ends up. But if the supply of cheap capital starts to dry up, it would be the beginning of the end of the joy ride that we have been on, putting a further premium on the quality of leadership. In a stock market that is up over 200 percent, everybody looks smart. It is when things get tough that the fortitude of management teams is tested. As such, pick your jockeys wisely. L

ALLAN L. SHAW is a member of Akari Therapeutics' board of directors and serves as chairman of the audit committee as well as an independent board member of VIVUS. He recently was managing director - life science practice leader for Alvarez & Marsal's Healthcare Industry Group, and he was formerly the CFO of Serono.

The Buzz Around Oncology — Update On Biologics Approvals

NIGEL WALKER
Managing Director
at That's Nice

In 2014, the FDA's Center for Drug Evaluation and Research (CDER) approved 41 new molecular entities (NMEs) and new therapeutic biological products; it was an exciting year for the biopharmaceutical industry. These approvals set a record not seen since 1996, when 53 new NMEs were passed.

These 41 novel drugs were approved to treat a broad range of diseases. The three therapeutic areas that received the highest number of approvals were rare/orphan diseases, infectious diseases, and oncology. It is noteworthy that all eight novel cancer drugs were included in the FDA's count for rare disease drugs. The momentum for innovative drugs has continued into 2015. As of October 6, 2015, the FDA has approved 28 NMEs, six of which are new oncology drugs.

According to Nice Insight's *Annual Pharmaceutical and Biotechnology Outsourcing Survey*, oncology has consistently been a therapeutic focus for drug pipeline development since 2012. Despite a slight drop in overall focus on oncology from 38 percent in 2014 to 32 percent in 2015, specialty pharmaceutical companies and emerging, niche, or start-up companies are demonstrating a strong interest in developing cancer drugs. For example, in 2014 only 12 percent of emerging, niche, or start-up companies focused on oncology. This number increased to 27 percent in 2015. Meanwhile, 30 percent of specialty pharmaceutical companies have a focus on oncology, up 8 percent from its 2014 level. A slight increase (3 percent) was observed in Big Pharma companies, which rose to 38 percent in 2015.

In the race to develop novel oncology drugs, Big Pharma and biotechnology companies are leading the competition. As seen in 2014, seven of the eight approved new cancer drugs were developed by the global top-25 pharma companies (Table 1). To date in 2015, three of six approved new cancer drugs were developed by Big Pharma companies, and two of those three were sponsored by Novartis (Table 2). This Swiss multinational company has the most robust oncology pipeline with multifold NMEs. Recently, its oncology portfolio has been further expanded by completing the acquisition of GSK's entire oncology business.

One prominent trend in drug discovery is the shift of focus from small molecule to large molecule biologics. This shift is clearly reflected in drug approvals and especially evident in the oncology field. In 2014, 11 new biologic license applications (BLAs) were approved, representing 24 percent of novel drug approvals. Of those 11, four BLAs were for marketing cancer drugs — monoclonal antibodies, representing 36 percent of total BLAs issued or 50 percent of approved new cancer drugs. Two new biologic oncology drugs, Blincyto and Keytruda, are identified as first-in-class for their innovative nature in activating patients' immune systems to kill cancer cells. In the fight against cancer, the debut of new oncology biologics indicates a promising future for cancer immuno-therapeutics. Additionally, among the top eight best-selling drugs of 2014, seven were biologics, and three of them (Rituxan, Avastin, Herceptin) are for cancer treatment.

The increased interest in biologic product development is also demonstrated in Nice Insight's *Annual Pharmaceutical and Biotechnology Outsourcing Survey*. The percentage of respondents whose business is engaged in the development of biologic-based therapeutics continues to increase — up 9 percent from 73 percent in 2014 to 82 percent in 2015. There is also a slight increase (1 percent) in their annual R&D expenditure on biologic development from 57 percent in 2014 to 58 percent in 2015. The increase in biologics investment offers enormous opportunities for contract service providers with expertise in developing and manufacturing biological products. In addition, the industry recognizes a shortage of specialty CMOs for biomanufacturing at a global scale.

However, the profit margin for CMOs may be limited in the space of oncology. According to Nice Insight's annual survey, the overall annual outsourcing expenditure was increasing as more businesses were moved from the lowest-spending category — less than $10 million (16 percent in 2015 vs. 29 percent in 2014) — to mid-level between $10M and $50M (62 percent in 2015 vs. 47 percent in 2014). The fraction in

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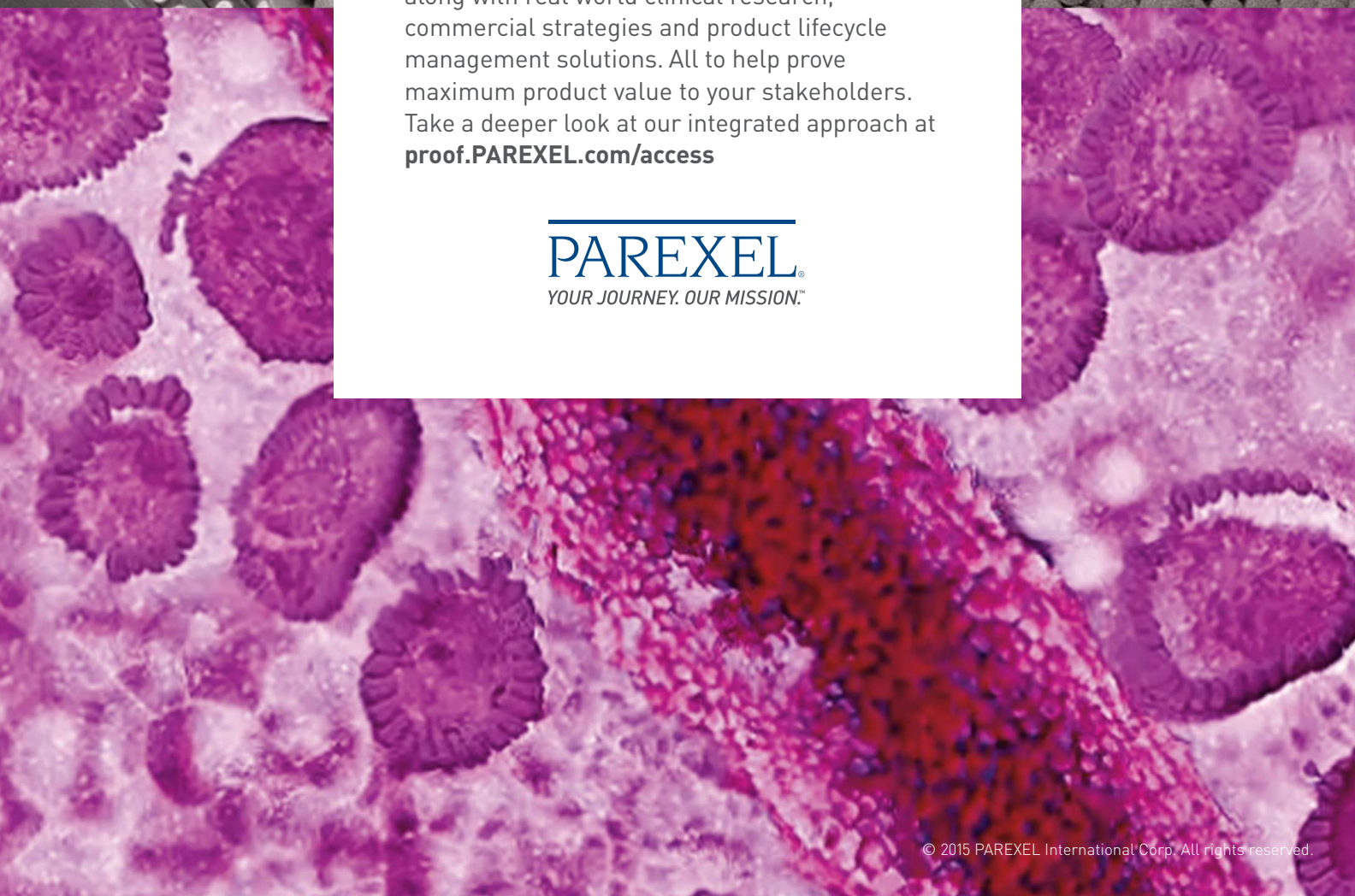

top-level spending — more than $50M — remained steady (23 percent in 2015 vs. 24 percent in 2014). In contrast, those businesses whose therapeutic area of focus is oncology were cutting their top-level (> $50M) outsourcing expenditure: 29 percent in 2015 vs. 34 percent in 2014. This trend may lead to decreased outsource spending in oncology.

In addition, Nice Insight's 2015 survey of 2,300 pharmaceutical and biotechnology executives involved with outsourcing shows that 30 percent of sponsors in North America and 25 percent in Europe outsource biomanufacturing. Of those that outsource biomanufacturing, 53 percent in North America and 56 percent in Europe will outsource mammalian cell line-based biomanufacturing, while 74 percent in North America and 83 percent in Europe will outsource microbial-based manufacturing.

If you want to learn more about Nice Insight, the reports, or about how to participate, please contact Nigel Walker by sending an email to nigel@thatsnice.com.

TABLE 1: 2014 FDA APPROVED NEW MOLECULAR ENTITY AND NEW THERAPEUTIC BIOLOGICAL PRODUCTS IN ONCOLOGY

DRUG NAME	ACTIVE INGREDIENT	SPONSOR	INDICATION	MECHANISM OF ACTION
Beleodaq	belinostat	Spectrum	Peripheral T-cell lymphoma	Histone deacetylase inhibitor
Blincyto	blinatumomab, mAb	Amgen	Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL)	Induce T cells to exert cytotoxic activity on malignant B cells through CD3 and CD19
Cyramza	ramucirumab, mAb	Eli Lilly	Advanced stomach cancer or gastroesophageal junction adenocarcinoma	Angiogenesis inhibitor (VEGFR2 antagonist)
Keytruda	pembrolizumab, mAb	Merck	Advanced or unresectable melanoma no longer responding to other drugs	Programmed death receptor-1 (PD-1) inhibitor
Lynparza	olaparib	AstraZeneca	Advanced ovarian cancer	PARP inhibitor
Opdivo	nivolumab, mAb	Bristol-Myers Squibb	Unresectable or metastatic melanoma no longer responding to other drugs	PD-1 inhibitor
Zydelig	idelalisib	Gilead	Relapsed chronic lymphocytic leukemia (CLL), follicular B-cell non-Hodgkin's lymphoma (NHL) and small lymphocytic lymphoma (SLL)	Phosphoinositide 3-kinase delta (PI3K delta) inhibitor
Zykadia	ceritinib	Novartis	ALK-positive metastatic non-small cell lung cancer (NSCLC)	Anaplastic lymphoma kinase (ALK) inhibitor

**Drugs gained approval for new indications were not included in this table.*

TABLE 2: 2015 APPROVED NEW MOLECULAR ENTITY AND NEW THERAPEUTIC BIOLOGICAL PRODUCTS IN ONCOLOGY (AS OF OCTOBER 6, 2015)

DRUG NAME	ACTIVE INGREDIENT	SPONSOR	INDICATION	MECHANISM OF ACTION	APPROVAL DATE
Farydak	panobinostat	Novartis	Multiple myeloma	Histone deacetylase inhibitor	2/23/15
Ibrance	palbociclib	Pfizer	ER-positive, HER2-negative breast cancer	Pyridopyrimidine-derived cyclin-dependent kinase (CDK) inhibitor	2/3/15
Lenvima	lenvatinib	Eisai	Progressive, differentiated thyroid cancer (DTC)	Receptor tyrosine kinase (RTK) inhibitor	2/13/15
Lonsurf	trifluridine & tipiracil	Taiho Oncology	Metastatic colorectal cancer no longer responding to other therapies	Combination of a nucleoside metabolic inhibitor (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil)	9/22/15
Odomzo	sonidegib	Novartis	Locally advanced basal cell carcinoma that has recurred following surgery or radiation, or patients who are not candidates for surgery or radiation therapy	Hedgehog pathway inhibitor	7/24/15
Unituxin	dinutuximab, mAb	United Therapeutics	Pediatric patients with high-risk neuroblastoma	Bind to the glycolipid GD2 & induce GD2-expressing cell lysis	3/10/15

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2014-2015 report includes responses from 2,303 participants. The survey is comprised of 240+ questions and randomly presents ~35 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top ~125 CMOs and ~75 CROs servicing the drug development cycle. Five levels of awareness, from "I've never heard of them" to "I've worked with them," factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences as well as barriers to strategic partnerships among buyers of outsourced services.

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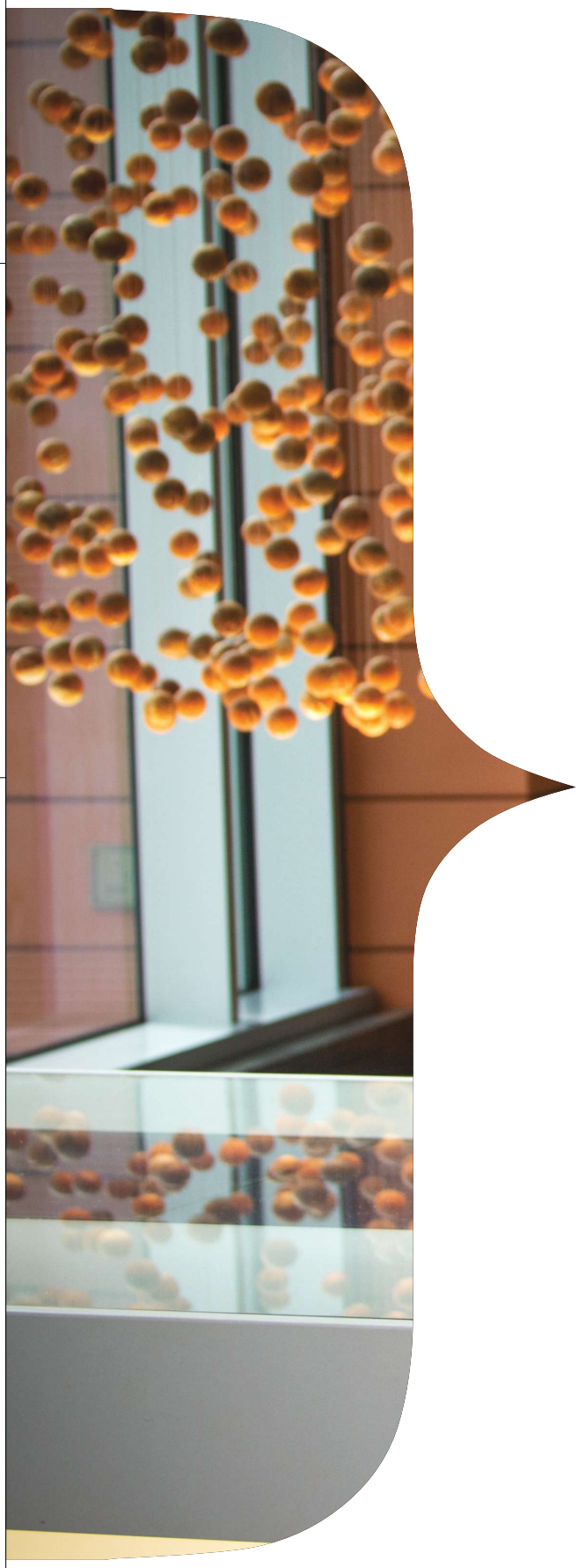


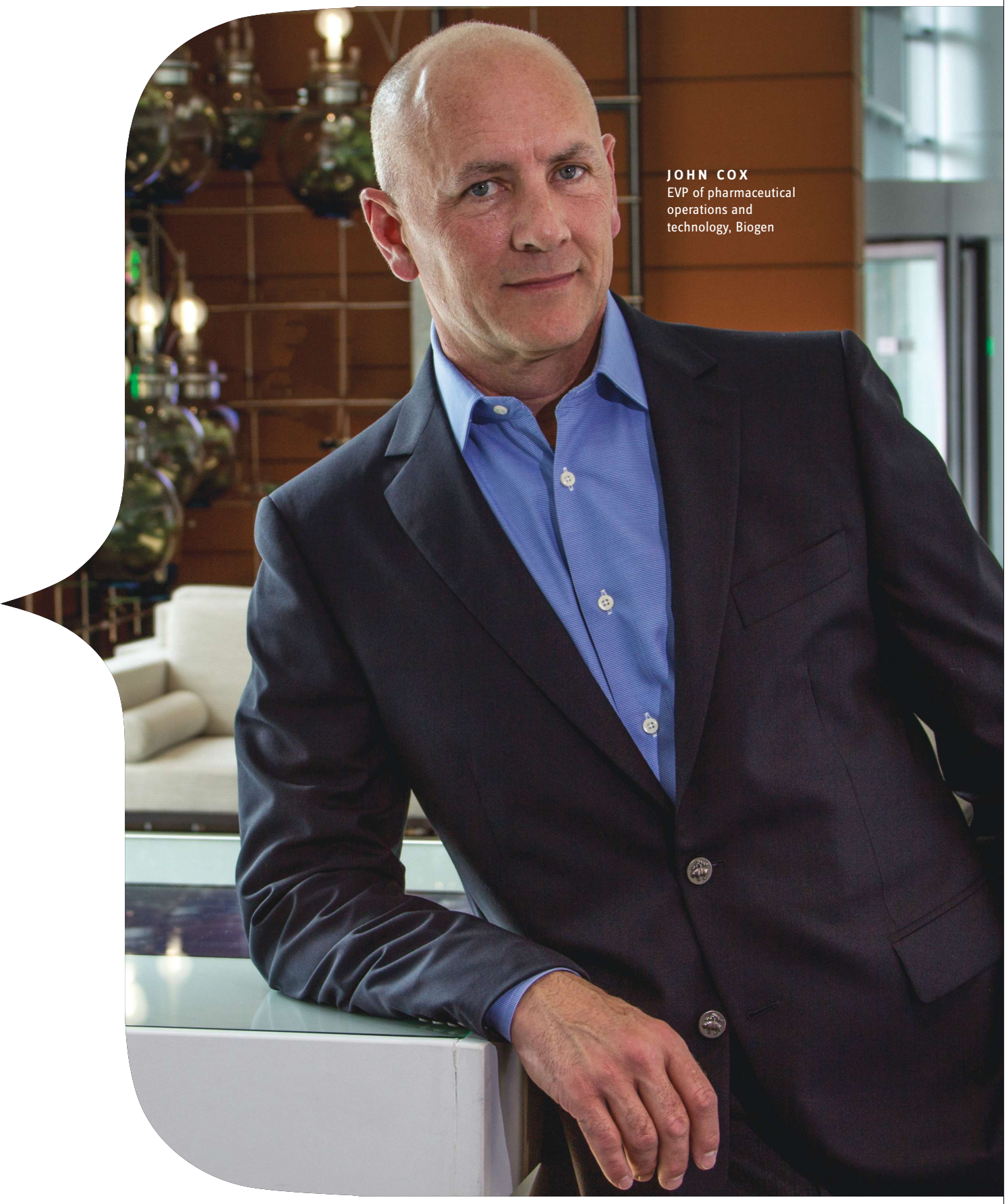
HOW BIOGEN IS PREPARING FOR THE BIOLOGICS TIDAL WAVE

ROB WRIGHT Chief Editor @RFWrightLSL

In early December 2014, Biogen got some huge news that sent its already pricey stock ($328.52) up nearly $19 — in just one day! The company had achieved positive Phase 1b clinical trial results for its experimental Alzheimer's drug, BIIB037 (aducanumab). The data looked so good, in fact, that Biogen announced it would be fast-tracking the drug straight to Phase 3 clinical trials.

As soon as John Cox, Biogen's top manufacturing executive, heard the news of the Phase 1b trial he called a meeting of his senior leaders. "I said, 'Now is the time to go after more manufacturing capacity,'" recalls the EVP of pharmaceutical operations and technology. This was a bold, proactive statement considering Biogen hadn't even finalized the plans for the two, 18-month, Phase 3 studies which would begin enrollment in the studies sometime in the second half of 2015. But Cox knew that if those Phase 3 trials were successful, the timeline for Biogen to be ready to supply the drug was getting shorter — rapidly.

"We had been preparing in technical development for a few years to be ready for a situation like this," Cox explains. "Every year we go through the pipeline from a capacity planning perspective to assess what our commercial and late-stage products look like, and then we create models for a variety of scenarios based on that data. We knew there were a couple of products in our pipeline, aducanumab being one, and that if we got positive data we absolutely had to be prepared to move fast. When you work in operations, you're waiting for moments like these, because this is your chance to come through — in a big way."



JOHN COX
EVP of pharmaceutical operations and technology, Biogen

Prepare Years In Advance

This past summer, Biogen announced the centerpiece of its strategy for being operationally ready for biologics coming out of its R&D pipeline — a new biologics manufacturing facility to be built in Solothurn, Switzerland. To make this happen, multiple disciplines such as technical development, quality assurance, formulation experts, project and process engineers, and manufacturing worked collaboratively.

Cox explains that when planning for future capacity his team considers the product, its potential, how many patients have to be served, the dosage required, and throughput capabilities of existing plants. "You have to model all the different capacity scenarios and project what output can be achieved."

Cell culture titers (i.e., the productivity of the cell lines) are also a big part of that planning process. "You can be working years in advance trying to get the maximum output from your cell lines prior to a commercial manufacturing need," he explains. "At the same time, you have to consider the engineering requirements needed throughout the process — upstream and downstream — to achieve maximum throughput and minimize bottlenecks."

From an engineering perspective, he says it's best to have a layout for what a plant might look like years in advance of critical data readouts. Some of the questions his team faced when considering the new plant included:

- Is it a cut-and-paste of an existing facility?
- Are there new technologies to put in place?
- How will we balance the upstream and downstream to achieve and maximize the necessary throughput based on the results of the development processes?
- How many patients will need to be served?

Of course, one of the biggest questions they had to answer was "Where will we build it?"

> "You have to continually invest in plants, and you can't take shortcuts on preventive maintenance or shutdowns."
>
> **JOHN COX**

Key Factors Of Biologics Facility Site Selection

Cox explains that the first step toward selecting a site location involved forming a team that consisted of people from engineering, manufacturing, and finance, each of whom is involved in the site selection process.

He adds that it was important to select a place with a very stable business environment that fit with Biogen's overall business structure. "This is one reason why we have a significant presence and history in Switzerland," Cox states. "Talent is another extremely important piece that always comes into play; we needed people who were trained in biotech, people who know how to work and run these kinds of plants." Sustainability and utilities also were important in the site-selection process. "For example, a plant like the one we are planning to build in Switzerland has to have a good water supply," comments Cox.

When asked about the trend by some companies to locate in close proximity to strategic partners/suppliers, Cox had this to say. "Whether in the U.S. or Europe, at Biogen we feel we are able to find really competent, sophisticated suppliers for our equipment needs, and we can generally handle the logistics to get what we need to the site, no matter where it is located in the world." As to the role government incentives should play in the site-selection process, he says, "Honestly, government incentives are not a big driving factor. To be

Oh, What You Can Learn By Walking The Manufacturing Floor

"From a leadership perspective, I think if you're going to run operations in this business, you have to love being on the floor," says John Cox. "In fact, if you're an operations executive, you have to miss being on the floor." Biogen's EVP of pharmaceutical operations and technology believes walking the manufacturing floor is important from a leadership perspective, but to do it well, it has to be natural and done by someone who wants and enjoys doing it. In the manufacturing setting, this means showing up at a shift exchange occasionally. "I like to show up in the evening," Cox confides. "My favorite place to walk through is a warehouse." According to Cox, if you want to get a sense for how well an operation is working, the best place to do so is the warehouse. "If it is organized and moving well, you will learn if a plant is working well – and if the culture is right."

Biogen's manufacturing executive likes to take the same approach with external plants too. "I can tell in a matter of minutes how a plant is working – not from the management team, but from the people on the floor," Cox attests. "No matter how automated or shiny it looks, if you don't get the sense from the people on the floor that they are proud of what they are doing – they want to show it off to you and talk about the facility – you need to find another supplier." Cox's advice is to look for people who are really engaged in their work, the process, and the product, and give them the opportunity to share their enthusiasm. Also, be sure to assess the staff's attention to detail (i.e., cleanliness). "You can pick that up in any corner of the plant," he says. "If they feel it's theirs, they will take real pride in it." Finally, Cox says, when you go to a plant, make sure it isn't just a conference-room meeting or billed as some big event. "Look, I've worked in a plant," he attests. "So I know there is a lot that can go wrong and happen unexpectedly. But being hoodwinked – that is, being fooled about a plant's culture – shouldn't happen, especially if you are practicing manufacturing leadership by walking around."

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> "Using outsourcing can be great. But we also want to have some insourcing capability to secure the product launches we think will be critical for us in the future."
>
> **JOHN COX**

competitive, it is more important to build in an area with a stable government, business infrastructure, and tax structure."

Over the years, Cox has been involved in a number of site selections. As such, he has accumulated some valuable lessons. "This may sound cliché, but don't underestimate the importance of building a relationship with the local community," he says. "Where we have had success at different sites around the globe is in communities with local officials who want to work with us as much as we want to work with them."

He also suggests talking to other companies in the area, particularly if they are in a similar technical field. "This can be very helpful in assessing if the environment is really conducive for hiring and employment," he states. And finally, he mentions the importance of geographic diversity as it pertains to supply. "Some companies have put everything in one location and gotten themselves into problems as a result," he explains.

Part Of The Plan: Acquiring An Outsourcing Partner

For Biogen, which ended 2014 with nearly $3 billion in profits, building a billion-dollar facility in Switzerland is a big risk. To help minimize that risk, Cox says the company took a diversified approach. "Using outsourcing can be great," he states. "But we also want to have some insourcing capability to secure the product launches we think will be critical for us in the future." This was part of the rationale behind Biogen's acquisition of Eisai's Research Triangle Park (RTP), N.C., manufacturing campus. "In the biologics industry there tends to be a tremendous amount of focus on drug substance production because these are big, huge investments," Cox shares. "Often the challenge is regulatory delays. However, there are also supply challenges in the area of drug product and aseptic fill. Historically, these have been pieces of our business we have outsourced completely."

While the Eisai acquisition announcement may have come just two weeks after the Switzerland build decision, Cox says there is tremendous benefit to being able to try a manufacturing facility before you buy a manufacturing facility. Toward the end of 2012, Biogen and Eisai announced a strategic, capacity-sharing, manufacturing alliance. "When we started working with Eisai, it was with oral solid dosing manufacturing," says Cox. "One of our key products, not a biologic, is a small molecule, Tecfidera, for Multiple Sclerosis. Eisai possessed a manufacturing capability that we did not have internally." But more than Eisai just having the capability to do that type of operation, there is tremendous benefit to being able to have Biogen employees work closely with the people from Eisai. "Though the formal integration only has recently started, because our employees really know their employees, the transition has actually been happening for two or three years," he explains.

When Biogen entered into the collaborative agreement with Eisai, company executives believed a future acquisition of the drug-product-filling facility was a possibility. "We talked about the various possibilities of working together in the space," he said.

But if the alliance was working so well, why not just continue to outsource rather than add a large fixed cost to the company's balance sheet? Cox explains that the demands on capacity and the at-risk capital investments have gone up. "Over the past few years, there has been a biologics capacity shortage that has been building, particularly when it comes to the production of monoclonal antibodies. CMOs are trying to fill that gap with investment and added capacity. Many companies decide to work with CMOs to deal with capacity shortages. But, if the timing and planning are not right, and

What Biogen's EVP Of Tech Ops Gains From Serving On Repligen's Board

You might wonder what is to be gained from a biopharma executive serving on the board of another company. Biogen's John Cox has been a member of the board of directors for bioprocessing company Repligen since November 2013. "In my position as EVP of pharmaceutical operations and technology for Biogen, I tend to deal with big questions related to capital, strategy, and business in general. Being on the board of a company focused on bioprocessing and related technologies helps me better appreciate some of the challenges in my job." For example, Biogen recently announced the decision to build a new biologics manufacturing facility in Solothurn, Switzerland. One of the biggest challenges of increased cell line output is how to handle the processing and purification. Cox envisions the Switzerland plant being able to produce about 10 metric tons of monoclonal antibodies on an annual basis. However, to be able to process and purify these large quantities will require the introduction of new technologies, including bioprocessing technologies, into the facility. Cox says these new technologies will be crucial to Biogen's success. Cox's understanding of the bioprocessing field has been augmented by his service on the board of Repligen, which in turn has been beneficial in his evaluation of the bioprocessing requirements for Biogen's new manufacturing facility.

The Rationale Behind Biogen's Modular Facility Design

When planning to invest a billion dollars in building a biologics manufacturing facility, it is important to take a very forward-thinking view. John Cox, EVP of pharmaceutical operations and technology at Biogen, says "Regarding our new Solothurn, Switzerland facility to be built, one of the keys was to minimize any bottlenecks in the upstream and downstream production processes. In addition we wanted to have a site location and design that allowed us to be able to add to the same basic footprint in a logical sequence so as to avoid creating future bottlenecks."

One of the benefits of using a modular design is being able to set up your infrastructure (e.g., utilities) for rapid future expansion. "Using a modular design puts us in a rather favorable position," he says. "If we find that more patients need our drug, instead of spending four years trying to get a facility up, running, and validated, we should be able to do that in two. Modular design is all about adding capacity as quickly as possible."

For those who aren't biomanufacturing experts (yours truly included), you might assume that quick expansion requires the incorporation of single-use systems. But Cox says this facility will have primarily stainless-steel systems with select disposable single-use technologies employed.

the CMOs have other clients, the capacity you need may already be consumed," he states.

The Power Of Preventive Plant Maintenance

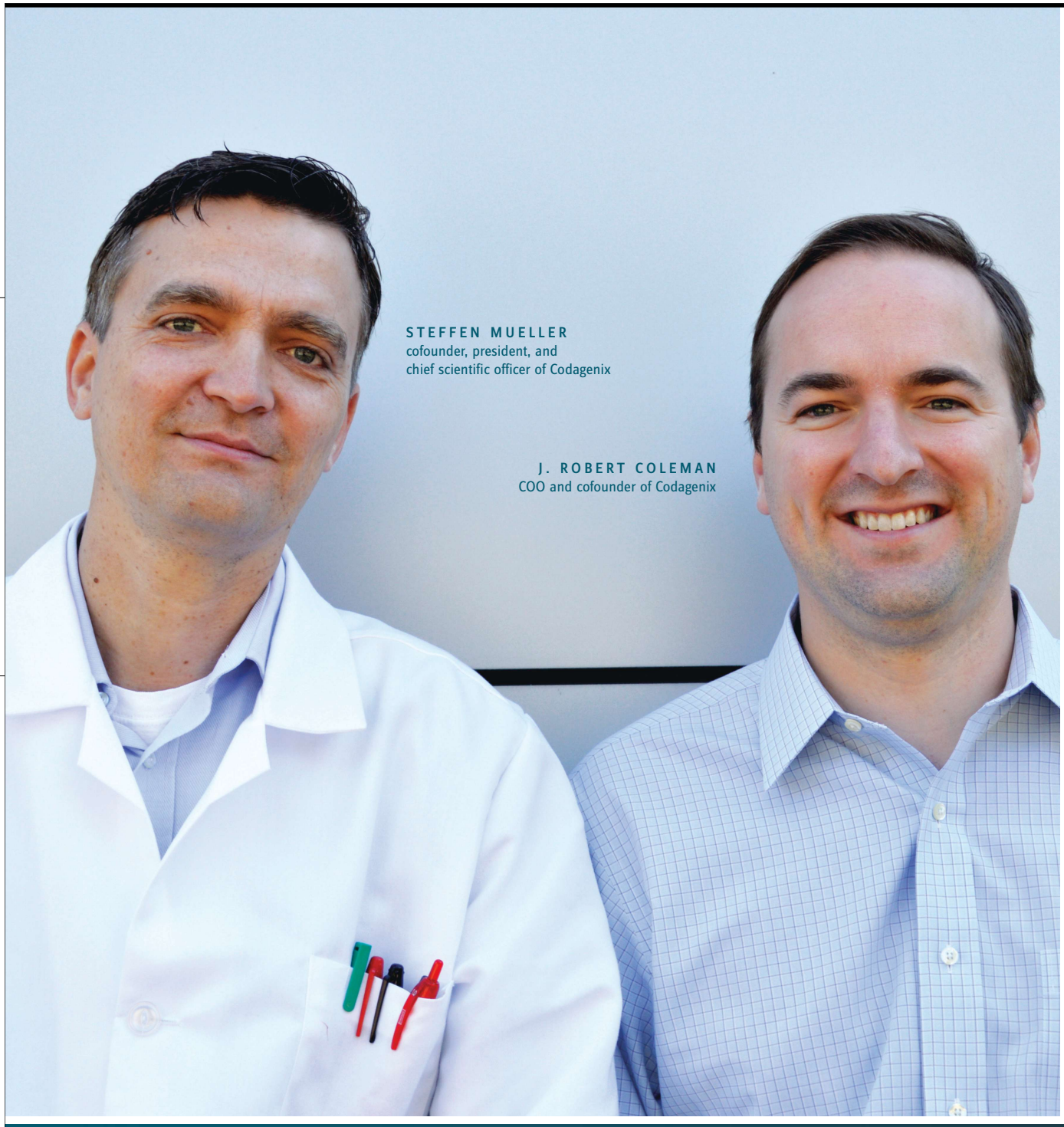
Aside from the addition of new facilities, Biogen's manufacturing/operations team was also applying its ubiquitous proactive nature to another element that would help the company prepare for an influx of biologics — preventive plant maintenance. "You have to continually invest in plants, and you can't take shortcuts on preventive maintenance or shutdowns," attests Cox.

As an example, he cites how Biogen made investments in its RTP facility five or six years ago to make it capable of even higher titers. "That was long before we had high-titer processes to put into that facility," he says. "Today, because we invested heavily in those technologies, that facility is being used for a number of higher-titer processes."

Biogen's EVP says it takes discipline and courage to make sure you are investing in your plants. Many companies only look at the short-term savings of delaying maintenance or upgrades; after all, this is a capital-intensive business. But Cox is adamant that focusing on long-term objectives — especially as they pertain to biologics manufacturing — is the only way to be in the optimal position in the event a drug like aducanumab finally gets approved.

Making sure what is engineered in Biogen facilities matches what is coming out of the company's pipeline two, three, or four years into the future requires complete alignment of the operations team. "We make sure our technical development, process engineering, manufacturing, and quality organizations work as one team," Cox says. "There are no hand-offs from one group to another; we are completely accountable as a single group."

It is projected that biologics will account for more than 50 percent of total sales of the top prescription products by 2020. When you consider that biopharmaceuticals make up about only 20 percent of the pharma market today, this 30 percent increase represents what some describe as a biologics R&D tidal wave. With the changes and the planning Cox and his team have made at Biogen, it seems the company is well prepared operationally to surf this pending wave.



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START-UP DATE: March 2012

NUMBER OF EMPLOYEES: 5

FOCUS: rational gene design for the construction of viral and bacterial vaccines

One egg per person. That is what it takes to produce a flu vaccine. The standard, predominant method has not changed in more than 70 years. What has changed dramatically, however, is the per-unit cost of goods, price, and scarcity of the product; all have risen steadily, to the point now where the old model of universal vaccination seems more antiquated than the aforementioned egg. Arguably, newer, recombinant and cell-based production technologies have only compounded the cost/supply dilemma for vaccines, without a commensurate rise in mass efficacy. What if a company had a technology that could sharply lower CoG (cost of goods) and ensure the highest possible availability and effectiveness of an influenza vaccine — even though the company were a David up against the flu-shot Goliaths?

Codagenix believes it is that company. Starting with flu, then moving on to other disease vaccinations, the tiny start-up wants to turn the entire field of action around.

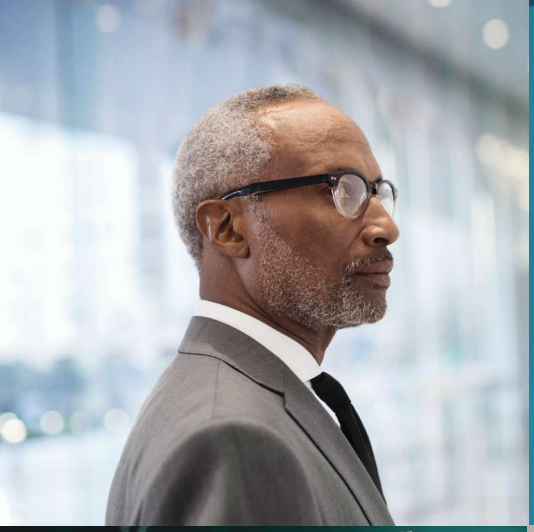
A MARKET ADRIFT

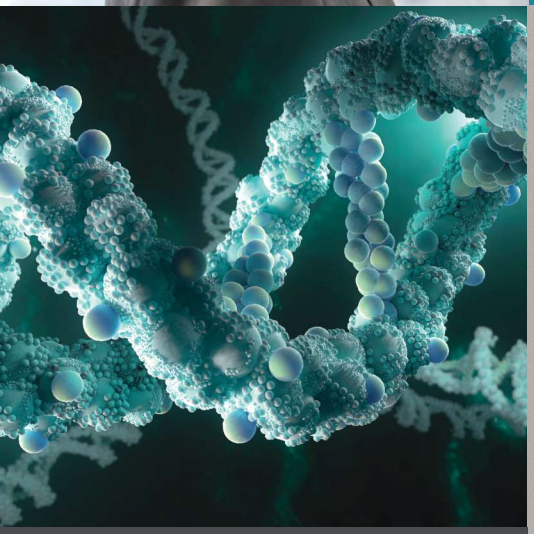
It had been a long day, and the late-evening reception was dying down. I found a couch in a side area where my tired old bones could rest. Soon others joined me on the couch and nearby chairs, and I struck up a conversation with the person next to me, who turned out to be Steffen Mueller, cofounder, president, and chief scientific officer of Codagenix. Beside him was COO and cofounder J. Robert Coleman.

Yet, even before Mueller and I exchanged cards, we had already dived into a discussion about vaccines. Unlike most of the people around us at the time, I was alive during the great polio epidemic following World War II. I lost my older brother to the disease in 1950, later tagged along with my mother each year in the March of Dimes, and lined up with just about every other kid in the country for the first vaccine. But I was struck by how close Mueller's views of the situation were to mine. We both expressed dismay at the drift of vaccination from a universal, public-health-driven enterprise, to a fragmented and fractious, albeit high-profit endeavor. Unlike me, however, Mueller and his company may have a solution — not just another way to make more vaccines, but a way to make them better, by many thousands-fold.

Months later, I followed up on our chance meeting in a longer talk with Mueller and Coleman for this article. The story of their little company carries a large meaning. Any real challenge to the status quo of vaccines could only come from an obscure entity such as Codagenix. From a business standpoint, scant motivation for change exists; vaccines have become highly profitable for large companies almost in direct inverse proportion to the drop in their universality. When everything is so cozy for the establishment, the desire to shake things up may grow stronger in the outside player.

Other vaccine start-ups have also entered the field lately, such as the mucosal vaccine company Mucosis, covered recently in Companies to Watch, which only reinforces the medical need for new approaches in the space. Codagenix





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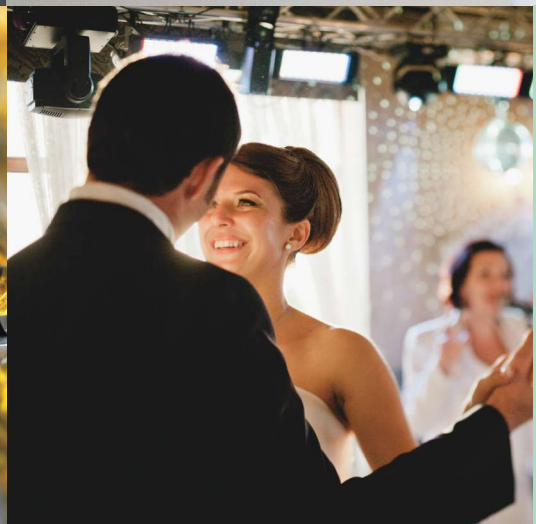

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VACCINES: CHANGING A CHANGED WORLD

A new biography of Dr. Jonas Salk, inventor of the first killed-virus polio vaccine in the 1950s, describes how the entire U.S. society mobilized to find a cure or prevention for the disease. Housewives joined the March of Dimes by the millions to educate their communities, collect donations, and even gather patient data for clinical trials. They also made sure all children lined up to receive their vaccinations. The question is, could such a united public health effort happen again, for prevention of diseases that threaten us all? Steffen Mueller, president and CSO of Codagenix, answers:

> "I believe not, because in today's Western society, people are no longer confronted as much with infectious diseases, and polio is a prime example. It was very visible in the 1950s. When someone had polio, everyone saw it, and it was scary as hell. But such fear of infectious diseases is now gone, and instead we have all the vaccine deniers trying to poison the well, and unfortunately a lot of people listen to that. With the first polio vaccine, the risk-benefit calculation back then was made at the highest level. Now it's an individual risk-benefit analysis, and that's dangerous, because it leaves it to the individual to decide, 'Do I want to vaccinate or don't I?' Many people now say, 'I don't see these diseases, so I'd rather not vaccinate myself.' Eventually, it will swing back to where too many people choose not to vaccinate, and then, boom, all the old infectious diseases will come roaring back. I'm afraid that is what it will take for the population to wake up and say, 'Why are there no vaccines? Where is the vaccine for this disease?'"

makes a good choice for The Enterprisers because its audacious mission, set against the high risk of development still at the preclinical stage, signifies not only a potential vaccination breakthrough, but also a significant entry into synthetic biology. Its technology is meant to replace the age-old trial-and-error method of vaccine creation by configuring the entire genetic makeup of the live attenuated virus to be mass produced. So rather than competing with other new approaches, it may actually be complementary or compatible with them.

VIRAL TAMING

Codagenix counts on its Synthetic Attenuated Virus Engineering (SAVE) platform to transform vaccine creation into an exact science. SAVE is proprietary software for configuring live vaccines made of viruses that match the wild types in every respect except one: their ability to cause disease. With SAVE, the company synthesizes the whole genome of a virus, but with strategic changes in certain codon pairs to "de-optimize" the mechanism supporting its virulence.

The technology emerged from research headed by Eckard Wimmer at Stony Brook University. Wimmer made history, and stirred some controversy, by synthesizing the polio virus for the first time in 2002. SAVE has passed proof-of-concept studies in animals successfully and will soon face its next big test in human trials. Like so many of the novo-vaccine companies, but perhaps with stronger logic to support it, Codagenix has chosen flu as its lead vaccine target. In keeping with SAVE's broad potential, however, the company also has pipeline programs for respiratory syncytial virus (RSV), Dengue Fever, foot and mouth disease virus (FMDV), pathogenic E. Coli, and other diseases.

"We are developing our approach to dramatically impact global health by making designer vaccines that are genetically stable, safe, and effective. That is the central core of the company," says Coleman. "Our platform is a software-based approach, a genome-design technology. It is a platform because theoretically we could apply it universally, to any virus."

The term "platform" does apply to SAVE, but in an unusual sense — the platform consists of bytes, not material bits. SAVE is also unusual in what it produces at the end: an entire genome rather than the virus-like particle or backbone virus with a few antigens attached in current vaccines. The SAVE-modified genome is synthesized in its DNA form and recovered by recombinant DNA technology in appropriate tissue culture cells. Uniquely, SAVE faithfully reproduces the wild-type virus for a vaccine, but de-optimizes

> When we started trying to raise private money for our clinical work, we met with a lot of resistance.
>
> **J. ROBERT COLEMAN**

codon pairs in the viral genome involved in causing the host cell to produce proteins for the virus. The de-optimization slows down the protein production to the point that, when the vaccine activates an immune response, it also buys time for the immune system to overwhelm the virus before it can adapt and escape.

So what is "de-optimization?" My take on the concept: Codon pairs are redundant genes that reinforce each other's activity. If you exchange a key protein-encoding codon for a similar but less active codon copied from elsewhere in the viral genome, it will still stimulate protein production but at a much lower rate. Although the host's immune system sees the reengineered virus in the vaccine as identical to the wild type in the proteins it engenders, the vaccine virus lacks the wild-type ability to coax host cells into producing those proteins fast enough for the virus to outrun the immune response and survive. The deoptimized virus dies off, leaving the host immunized against the wild type as would a traditional weakened-viral vaccine — but potentially with much greater efficiency.

"Forever in the vaccine industry, companies have always tried to make more antigen, but our approach is actually to lower the level of translation of the virus," Coleman says. "Wild-type viruses use codons and codon pairs that the human host cell reads quickly. We use exactly the same amino-acid sequence as the wild type, so our vaccines are a perfect match to the target at the protein level. But

we encode those proteins using codons the human host cell reads much more slowly."

Mueller explains what the de-optimization MoA (mechanism of action) means to the end product: "The vaccine virus presenting to the immune system is a 100-percent identical replica of the real thing, so the immune response should be the best possible match, which seems to be the reason our vaccines can be effective at an extremely low dose. The effective dose appears to be orders of magnitude lower than any other vaccine approach we've seen or read about in the literature, and it could be a real game changer."

BUILDING EXPECTATIONS

The Stony Brook research team headed by Wimmer began work on SAVE around 2004, eventually yielding several papers, including two strong studies published in 2010 — one in *Science* on the possible applications of synthetic viruses, the other in *Nature Biotechnology* on using a computer-designed synthetic virus as a flu vaccine. Then they waited for thunder on the horizon. Alas, they waited in vain.

"Because our technology is so cool, we always hoped the Big Pharma companies would just run to us and break down our doors. But nobody came knocking," Mueller recalls. Mueller, then an assistant professor, and Coleman, a graduate student, were both on Wimmer's team and were determined to carry the flag forward. Coleman left to complete his postdoc at Albert Einstein and his MBA at New York Institute of Technology, but Mueller had already incorporated the company during a Stony Brook business workshop in 2009, though he had since come up empty in repeated applications for SBIR (Small Business Innovation Research) start-up grant money from the NIH. After Coleman returned in 2011, however, the two reapplied for an STTR (Small Business Technology Transfer) grant with Dr. Wimmer, and this time were successful. They booted up the company and moved into its current laboratory at the Long Island High Technology Incubator (LIHTI), adjacent to the Stony Brook campus. Since then, the company has lived mostly on additional grants, though it finally closed on its first VC investment this year.

Both Coleman and Mueller acknowledge the quest for venture and other equity funding has turned out to be more hard-going than they once expected — in fact, their biggest hurdle so far. They have developed a more seasoned view now, coming to see vaccines in general, and their company's approach in particular, as appropriate only for a special kind of investor.

"It takes someone with a long-term view of investment and perhaps being a bit more philanthropic than profit-driven," says Mueller. "I am sure many investors prefer something with a higher profit margin than vaccines."

Coleman adds that investors in vaccines naturally have a longer time horizon, which limits the potential VC and partner pool for Codagenix. "Vaccine investors must also have some interest in global health, because vaccines will never be a product for which you can charge prices that make it extraordinarily profitable at the individual unit level," he says.

"Obviously, if you have a successful vaccine, you will sell a lot, and that could be profitable, but the time from bench to market for vaccines is probably the longest of any medicine. There are also a lot of other early vaccine developers with essentially me-too technologies, and the lack of novelty has cooled investment in the space as well. We finally found some investors who had a yen for the long-term horizon and saw our flu vaccine as not just another me-too, but as a potentially disruptive technology."

> "Because our technology is so cool, we always hoped the Big Pharma companies would just run to us and break down our doors. But nobody came knocking."
>
> **STEFFEN MUELLER**

CHASING GOLIATH

Codagenix has one thing in common with other new vaccine companies, however — its choice of influenza as the target of its lead program. Many analysts, reporters, and investors have wondered aloud why every young David in the business wants to take on Goliath. But Mueller and Coleman believe targeting flu is the most definitive way to demonstrate the economies of scale afforded by a SAVE-produced vaccine.

"When we started trying to raise private money for our clinical work, we met with a lot of resistance," says Coleman. "Investors would say, 'Why would you want to make a flu vaccine? There is already one that makes $4 billion or more a year! So unless you have one that is really fantastic, don't even bother.' But that is what we are trying to do — make a disruptive vaccine. The current standard flu vaccines have very low efficacy, especially year to year. For example, last year's H3N2 component of the current vaccine had only

about a 9 percent efficacy rate. We still tell people to get their flu shots, because even a poor vaccine can produce some herd immunity. And they are profitable. But our flu vaccine may achieve universal efficacy at a greatly reduced cost of goods."

Coleman argues that growing vaccine virus in eggs makes them inherently less immunogenic, and at best, he says, current flu vaccines offer only a 25-percent match to the strains specified by the WHO each year, by matching only two of the eight major influenza virus proteins. "Our platform is capable of providing a vaccine with a 100-percent match; thus we hypothesize it may have greater efficacy than the current flu shot — and that fits the definition of a disruptive technology."

Through the rough times of chasing private equity, the company kept its concept alive mainly with the help of the U.S. government. SBIR and the USDA repeatedly came to the company's aid with money to finance its next needed steps. But Coleman has one suggestion for improvement in the programs.

"The granting agencies should place more emphasis on the earliest of stages in vaccine development," he says. "It is the hardest step for a vaccine company. For other drugs, maybe the Valley of Death is Phase 1 to Phase 2, but for a vaccine company, it comes at an earlier stage, even before getting into the clinic. That is hard because there is a lot more government support for vaccines after you get through proof-of-concept."

Undoubtedly, new vaccines and other high-potential technologies experience some of their toughest tests at their earliest stages, as do the companies that champion them. Perhaps, too, the more radical the changes to be wrought by those technologies, the more critical is early financial support to their success. Rather than "kill early" in such cases, maybe the operative principle should be "nurture early" to prove or disprove the concept. Not only could such a practice winnow the chaff from the wheat among development candidates, it might also ensure the surviving candidates enter clinical trials with the strongest possible data to support them. Codagenix appears confident its preclinical work has laid a long, wide, and breakthrough path for its synthetic-virus vaccines. L

How One Biopharma Improved Patient & Clinical Site Relationships

ED MISETA Executive Editor @outsourcedpharma

Eileen Daniel has spent over 25 years working in the clinical trials industry. During those years, there were times when she became quite disillusioned. Daniel, now the executive director of clinical operations at Nektar Therapeutics, always felt there were ways the clinical trial planning process could be improved.

"I always felt there could be fewer intermediaries between the site and the sponsor," she says. "When the clinical trials team at Nektar came up with the idea of implementing good human practices (GHP), we knew we were doing something that would benefit the relationships between sponsors, CROs, sites, and most importantly, patients. I think we are already seeing good results from our efforts."

Daniel notes the core of GHP involves doing the right thing for people as well as the project, an idea that is not new to pharma companies but requires dedication to keep it in focus. The whole push throughout the implementation process has been to figure out how to stay as close as possible to the people who are working hard on each study.

"For all intents and purposes, we should never be more than two layers removed from our sites, or even two layers removed from our patients," she states. "It is much more difficult for a sponsor to have a great depth of oversight if they are distant from the site and patient. By applying simple, GHP principles to day-to-day activities, from prestart-up through to the end of the trial, we end up with an inspection-ready oversight plan that allows the executive director of clinical operations to have in-depth conversations with sites on a much more frequent basis. This allows them to learn more about how studies are operating and adopt a more adaptive-learning approach."

A NEW WAY TO INTERACT WITH CROs

The value of better communication with sites became clear to Daniel when she received a call from a site coordinator. The coordinator was requesting information on a medicine that one of her patients took as part of a trial. After looking into the request, Daniel found the drug had been approved and would be imminently available for use by the patient. Unfortunately, the coordinator was never notified of the results.

The clinical team at Nektar decided it was time to implement some additional processes and practices that could enhance interactions with sites. The goal was to streamline the flow of information from the sponsor, to a project manager with the CRO, to a manager at the site, and then back up the chain of command. Depending on the size of the companies and the trials being conducted, such communications are not always one-to-one and frequently occur via emails or database queries.

It was evident communication could be enhanced, and one person who was instrumental in this effort was Craig Coffman, Nektar's executive director of clinical business operations & outsourcing.

"We knew we had to start at the very beginning," says Daniel. "That meant thinking about how we engaged with CROs. We felt that one of the first things to be addressed should be the initial presentation from a CRO. The majority of those presentations cover subjects including capabilities, structure, SOPs, compliance, and bandwidth. As we already had a process in place to evaluate those factors, we felt the presentations were somewhat unnecessary."

Instead of a presentation, Daniel and Coffman asked potential CRO partners to come in and talk to them about how they would tackle the program. They felt this approach was the best way for individuals from both companies to get to know each other as potential fellow team members, as the most important consideration for the Nektar team was how both sides would interact. During the conversations, Nektar representatives presented their thinking in regard to a trial and inquired as to how the CRO could adapt its organization and teams in order to make it happen.

"It's definitely a different kind of CRO

engagement and selection process," Daniel notes. "Once they are on board and have a taste of what we are trying to do, we move on to the next stage, which is a kick-off meeting. We take a very different approach to that as well. We let them know that they are our partner, that this is a study team, and that we are all in it together. We also emphasize the fact that the relationship is more inclusive than just Nektar and the CRO. It must also include representatives from all the other service providers that are needed in the study, which could number from seven to 10 different providers on a complex study."

WHAT ARE ALL THESE PEOPLE DOING HERE?

At a typical kick-off meeting, a CRO will go through the entire contract, making sure all of their management hours and project management buckets are aligned. Nektar delays that part of the process until after a study team meeting that is a bit more difficult. During that meeting all parties walk through Nektar's protocols from the perspective of the site and then again from the patient's point of view.

A key concern for Daniel is having the right number of appropriate team members on hand to engage in conversations around the various aspects of the protocol.

As a result, a typical study team launch meeting can get pretty crowded. At one such meeting, there were more than 50 people sitting in a room for two days.

"It is hard to describe," she says. "We had whiteboard walls. We involved people from data management who would be creating the databases. Many of these folks had probably never been involved in one of these discussions before, yet here they were learning important details about the study and what their role in it would entail."

Needless to say, some CROs are a bit taken aback by the approach. When one CRO hosting the meeting heard what Nektar wanted to do, the response was, "You want to do what?"

This novel process certainly took some getting used to, especially on the part of the CROs. "When a meeting is scheduled, the first thing a CRO usually does is send out an agenda," notes Daniel. "Throughout this process, one of the things we tried to do was fight the regular, SOP-driven agenda templates that are common. Most CROs have an SOP for conducting a kick-off meeting, and we would encourage them to disregard that template and start from scratch. By setting aside predefined processes, we were able to brainstorm and come up with new ways of tackling issues."

This example also illustrates why it is so important to have a good relationship with partners. Daniel will press CROs for

what her team wants and notes that most CROs will also press back on certain issues that are important to them. During conversations with the CRO, she will often ask if a certain request will prevent them from doing their job, or if a particular procedure they have in place is necessary to perform a task that was delegated to them and for which they will be held accountable.

UNDERSTAND THE FIRST CONTACT

Since one of Nektar's primary goals was developing strong relationships with sites, everyone knew the first contact with a site would be very important. Daniel wanted to know what that first contact between the CRO and the site would look like, what was being said, whether Nektar's name would be included in the correspondence, and if the proper message was being conveyed. When site management is outsourced, this messaging can be left up to the CRO, but Nektar felt it was important to get deeply involved in the process.

When the CRO formed a team to engage the start-up process and start sending letters, emails, and faxes to sites, Nektar opted to work with them to decide who would make the first contact and what the messages would say. To illustrate the importance Nektar placed on this step, Daniel also insisted on driving the communications, not just having input to them. To do so, an internal communication platform was set up that could also be accessed by CROs and service providers.

"We now have the ability to directly communicate with sites and distribute news, study documents, and protocols via this platform," says Daniel. "Sites are also using the platform to provide us with comments on documents and feedback on protocols. Some CROs voiced concerns, but so far things are working well. We get to manage our own communications platform, and the CROs are providing us with material to send or simply uploading the documents themselves."

One of the harder things Nektar had to work through was its mission to become more electronic and modern and eliminate paper throughout the trial process.

"We should never be more than two layers removed from our sites, or even two layers removed from our patients."

EILEEN DANIEL
Executive Director of Clinical Operations, Nektar Therapeutics

According to Daniel, one of the challenges was in getting service providers to understand that Nektar did not want them to turn into a print-and-ship shop.

"The amount of paper that circulates in a clinical trial is extraordinary and can be hard to manage," she states. "We have seen CROs design a form and blast email it or do a mass print run and send it to study sites. With the number of stakeholders participating in a trial, sometimes things can happen without you knowing it. Those actions can send a different message to a site than intended by the trial coordinator. By working closely with our CROs, we are doing a good job of managing that process."

Daniel and the Nektar team already have feedback from sites, and so far it is looking good. "The feedback has been very positive," she adds, "and they have been nothing short of gushy about the entire experience. Even when offering critiques about things that did not work well, they are still overwhelmingly positive. I think that is a positive sign for us going forward. They feel comfortable enough to tell us where we need to improve because they know they are a trusted partner in the process."

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Redefining Clinical Research
In The Age Of Genomic Science

TOM MARTORELLI

In 2013, TransPoC, Inc. (Translational Proof of Concept) was formed to solve a serious problem: the diminishing number of new drug therapies resulting from oncology research. This problem has become more challenging given the overwhelming volume of genomic data available since the completion of the Human Genome Project in 2003.

Like others, TransPoC's founders believe the way to accelerate discovering new therapies is through collaboration and data sharing on a large scale. They see it as a classic collective action problem. All "discovery-enabling organizations" know there are inefficiencies and duplication of effort in oncology research. They also see the potential in pooling resources to work from a shared platform.

TransPoC's success hinged on developing incentives to overcome two key hurdles. First, the participating organizations must share research data, which many guard as trade secrets. And second, they need to commit start-up funding to a collective, instead of spending it themselves. Since its founding in 2013, TransPoC has made a lot of progress toward overcoming these barriers, but its success remains incomplete.

The challenge is more complicated than a scientific problem for researchers needing to share data; it's also larger than the business problem of independent companies being unwilling to fund a collective effort. TransPoC believes there may also be a language barrier preventing researchers from fully understanding the data from each other's studies. Lihua Yu, VP of bioinformatics at H3 Biomedicine, one of TransPoC's founding organizations, explains how access to the data itself is a major hurdle.

"TransPoC wants to build a BioIT platform to answer drug discovery questions in the way oncology researchers ask them," explains Yu. "Today, even a single study produces terabytes of data. And that data is complex, multidimensional, and math-oriented. The chemists and biologists who need it most can't gather the data they need or format it in a way that is useful for designing new studies. They have to wait for mathematicians to go into these huge files, pull data, and organize it. TransPoC's goal is to remove this time-consuming bottleneck and create an informatics system that is more user-friendly, allowing scientists to access the platform on their own, giving them the opportunity to compose and evaluate many more hypotheses."

Other organizations before TransPoC have attempted similar, if limited, collaborative research efforts, with varying degrees of success. But each of these collaborations limits itself through a narrow definition of what is "precompetitive." The fact that it found precompetitive information at different stages of the research process led to TransPoC's big idea: Why not create a research organization dedicated to precompetitive data sharing *for its own sake*, at multiple stages of research?

SHARING DATA WHILE STILL PROTECTING TRADE SECRETS

TransPoC's solution is designed to address the twin problems of scale and sharing intellectual property. The platforms TransPoC envisions require collective funding; they are so enormous that even the largest pharmaceutical firms would struggle to build them. TransPoC's sponsorship model bases fees on the degree to which sponsors use its platforms and encourages them to share some data while keeping valuable trade secrets proprietary.

TransPoC's business plan includes four basic elements:

- Cancer Cell Proof-of-Concept Network, (CPN or Cell PoC)
- Mouse Clinical Trials Proof-of-Concept Network (MPN or Mouse PoC)
- Integrated Genomics, Bioinformatics, and Scientific IT (BioIT)
- Physician/Patient Proof-of-Concept Network (Patient Portal or PPN)

TransPoC's founders knew the incentives that would encourage discovery-enabling organizations to join their efforts would not be easy to design. Researchers might be willing to share research data, but certainly not all of their trade secrets. Start-up costs needed to be funded, but they might not reach their goals through donations alone. Dr. Markus Warmuth, CEO of H3 Biomedicine and president of TransPoC, remembers these deliberations very well.

"First, we focused on the value for scientists," Warmuth says. "TransPoC's translational approach allows researchers to expose their original hypotheses to as many data points as possible to 'pressure test' them before going to clinical trials. One molecule can be tested against thousands

of cell lines, not just one. And since it is an integrated platform including xenographic data, patient-derived cell lines, and its own informatics system, TransPoC can rightfully claim a unique space having all three of these."

Warmuth recalls this as the easy part. The tougher challenge would be convincing the CFOs of potential sponsors. "We had to offer a precompetitive, capital-efficient answer to the 'build or buy' question each of these organizations face. And we wanted the answer to be 'buy TransPoC.'"

To create their best answer, TransPoC's staff and board hammered out the details of a multitiered sponsorship structure with annual fees based on company size. There would be separate fees for each of TransPoC's CPN and MPN platforms. CPN fees would range from $200,000 to $2 million per year and would buy access for testing 10 to 100 compounds. MPN fees would range from $850,000 to $2 million per year buying access for 40 to 100 PDx (patient-derived xenograft) models. Sponsors would be required to match each proprietary compound submitted to TransPoC's CPN and MPN PDx platforms with another nonproprietary compound. The data resulting from these nonproprietary compounds would be made available to the public, while the data from proprietary compounds would remain the intellectual property of the sponsor. Dr. Warmuth recalls the devil in these details.

"We were looking for a very specific balance, because we needed to articulate our mission and value proposition at the same time. We had to appeal to scientists seeking the benefits of data sharing while also convincing corporate managers we would protect their IP. TransPoC's collaborative model reduces the pressure a company faces in focusing expensive clinical trials on compounds with the highest chance of success. Furthermore, discovery-enabling organizations can develop their own compounds and PDx models in a shared research platform, concentrating efforts on projects with the best potential for success."

In 2015, TransPoC has made progress toward implementing its business plan, launching its nonprofit organizational structure, and designing pilot studies to demonstrate its value proposition to potential sponsors. TransPoC is still seeking its start-up funding, but its founders remain optimistic. Josh Sommer, executive director of the Chordoma Foundation, a founding partner, thinks TransPoC is an idea whose time has come.

"TransPoC, or an organization very much like it, will succeed one day. But it may need a 'Switzerland' — a large, neutral funding source to contribute the funding that my organization and others are hesitant to invest on our own. One day, the right scheme of incentives will encourage enough organizations to take the risk of collaboration and data sharing that will lead to greater success in the new world of genomic research." L

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Tom Martorelli is a historian, nonprofit strategist, and writer. He has worked with community organizations in Boston for more than 40 years.

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Expanded Access Trials Complex, But Improving

GAIL DUTTON Contributing Editor @GailLDutton

Expanded access (compassionate use) clinical trials aren't as straightforward as they seem, and applications to expand access for cannabinoid drug trials are even more complicated. "Although the application process outlined on the FDA website seems very clear, the reality, unfortunately, is not like that," according to Ricardo Alvarez, M.D., director of cancer research at Cancer Treatment Centers of America's Southeastern Regional Medical Center in Atlanta and clinical assistant professor at Georgia Regents University. "I typically see eight- to 10-page applications," Alvarez says, "but they take too much time. They're the equivalent of filling out the paperwork for CDER (Center for Drug Evaluation and Research) trials involving two companies. That requires a lot of staff support."

To participate in expanded access trials, Alvarez says physicians need the support of a team, including a care manager, to contact the pharmaceutical company and to fill out the necessary forms. The current application form, FDA 1571, requires 26 data points and seven attachments. Filing for FDA permission to launch an expanded access trial is much the same as filing to participate in investigational new drug (IND) trials. Physicians must obtain a letter of authorization from the pharmaceutical company allowing the IND to be used for expanded access for their specific patients, and they also must develop trial inclusion and exclusion criteria, a patient protocol, and patient exposure data. Additionally, the patient must be examined by the physician applying for the trial and sign a consent form that clearly outlines the risks and potential benefits.

Once the paperwork is filed, physicians say it takes about 15 days to gain FDA approval, although emergency approval is possible within a few days. Historically, the FDA approves 99.5% of all compassionate use requests.

A STREAMLINED FDA APPLICATION

In February 2015, the FDA issued a draft guidance proposing a new form for expanded access trials to replace Form FDA 1571. The new form, FDA 3926, is not yet finalized, but it is expected to streamline the application process for physicians enrolling patients in expanded access trials.

Form FDA 3926 asks for, among other things, clinical information, treatment information, letter of authorization from the drug's manufacturer, physician's qualifications, physician's contact information and the physician's IND number (which differs from the manufacturer's IND number), request for authorization to use draft from FDA 3926 rather than Form FDA 1571, and a certification statement and the physician's signature.

FDA documents say the new form should take about 45 minutes to complete. When finalized, it is expected to have eight data points and require only one attachment.

PHARMA – NOT THE FDA – PREVENTS EXPANDED ACCESS TRIALS

"Getting approval from a pharmaceutical company is the biggest hurdle to gaining access to expanded use trials," says Steve Jensen, SVP of the regulatory consulting practice at the Weinberg Group. The reason, he says, is fear. "Pharmaceutical companies don't want to generate data that doesn't need to be generated." There's no motivation, therefore, for them to allow expanded access trials.

"Compassionate use really is a clinical trial," notes Paul Lyons, M.D., Ph.D., medical director at Virginia Comprehensive Epilepsy Program. "In the past, compassionate use medications were open label and unregulated. Expanded access trials have become more rigorous, however, and require physicians to report patient data and adverse effects just like other clinical trials."

Pharmaceutical companies with early-phase trials may restrict expanded access because of limited information about the drug's safety, mechanism of action, or efficacy. "Other times, the issue is supply. Many companies — especially smaller companies in early-stage investigations — don't have much drug on hand. Alternatively, requests for expanded access may be for indications the company hasn't investigated," says Robert Church, partner at the international law firm of Hogan Lovells. "Any of these factors

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could make a company reluctant to participate."

Alvarez notes that sometimes companies are flexible, but it depends on the compound. "For example, when the clinical trials for Gleevec (imatinib mesylate) became fully enrolled, Novartis opened an expanded access program." Novartis doesn't routinely allow expanded access trials when its planned trials are fully enrolled, however. He says the reasons for denials aren't always clear.

Persuading a pharmaceutical company to allow an expanded access trial takes time. Gaining approval from the FDA and the pharmaceutical company took a total of about 50 days for each of the two trials Alvarez requested in 2014.

"The landscape for expanded access trials has changed over the past decade so that drug companies are taking greater steps to make investigational drugs available," Church says. "At the outset," he continues, "companies with drugs that treat serious or novel conditions often sense that people will ask for expanded access. They typically develop internal guidelines to determine when in the developmental cycle to make a drug available. If the drug or patient request doesn't meet those guidelines, the company may decline individual requests unless enough pressure is brought to bear by patient advocates."

PATIENTS LOSE PATIENCE WITH DELAYS

A patient's continued commitment to an expanded access trial also often wanes during the application process. At the onset, patients are briefed on the course of action and what that means to them in terms of potential risks and benefits. They also are asked to meticulously log their symptoms and reactions to the medication, attend follow-up appointments, and allow additional blood draws.

In Alvarez's experience, patients abandon the expanded access process because of the lengthy paperwork and time spent waiting for approval.

FOR CANNABINOIDS, THE DEA IS THE HOLDUP

The process for gaining expanded access to cannabis-based therapeutics (cannabinoids) is significantly more complex. An article ("Boy Interrupted") in *Wired* magazine last July brought attention to this issue, citing 100-page applications and very long approval time frames.

In this case, manufacturers aren't a barrier. "Cannabinoid manufacturers want to make their compounds available to prescribers, to move those compounds from the shadows to the mainstream," Jensen says.

Instead, the challenge is to get approval from the Drug Enforcement Agency (DEA), he continues. "The FDA and DEA are struggling to get their heads around the cannabinoid issue. As a Schedule 1 drug, the missions of these two agencies are diametrically opposed."

The FDA's mission is to bring effective therapeutics to patients. But, according to the DEA, Schedule 1 drugs have "no currently accepted medical use and a high potential for abuse."

Lyons knows the challenges firsthand. He recently added three patients to an expanded access trial for the cannabinoid Epidiolex, by GW Pharmaceuticals.

"It took me 13 months to get a Schedule 1 license," says Dr. Lyons, who then had to meet state requirements for inventorying and dispensing the drug. "That required bolting a 40- to 50-pound safe into the office."

The second hurdle was persuading the manufacturer to supply the patient with medication. "This is a small barrier. Most pharmaceutical companies are happy to do this," he says.

The third barrier, he says, was bureaucratic. "To add patients to my existing expanded access trial, I had to submit brand-new applications, as if nothing ever had been submitted. I'm trying to run a placebo, double-blind trial for the same drug, with the same nurses, same disease state, same doctor, and same program, yet I had to submit a new application to the DEA and the FDA," Lyons says. After three months, a DEA field agent informed him the three patients were accepted into the expanded trial.

KEY RESOURCES TO TAP INTO

From a patient's perspective, hiring a consultant to speed access to an expanded access trial is unnecessary, both Lyons and Alvarez say. Some pharmaceutical companies, however, find consultants helpful in writing trial protocols that meet the combined concerns of the DEA and FDA.

"Expanded access trials have become more rigorous."

PAUL LYONS, M.D., PH.D.
Medical Director, Virginia
Comprehensive Epilepsy Program

For example, GW Pharmaceuticals in the U.K. hired consultants to work with the FDA and DEA to help write protocols for its Epidiolex orphan drug program. Lyons says, "I doubt I would have succeeded in gaining access for my patients without their support."

Some of the simplest resources for patients and physicians seeking to gain access to expanded access trials are the Web pages of the American Cancer Society (ACS), the National Cancer Institute, and now, the FDA. As Alvarez explains, "These sites translate the process into plain language and tell patients what to anticipate." They include information about costs, how to access drugs and trials, and how to get additional information. The ACS site also tells patients what to ask their physicians about unapproved medications." The new FDA compassionate use Web page (www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse) specifically for physicians also has detailed information on topics such as how to apply for expanded access to an investigational drug under a single patient IND and what to expect after submitting that request.

Clearly, it's becoming easier for physicians to launch expanded access trials, as these sites show. Nonetheless, overcoming pharmaceutical companies' objections is still the greatest hurdle.

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A Manufacturing Executive's Role In Establishing A Quality Culture

JIM ROBINSON

Jim Robinson is a retired life science executive who has spent more than 30 years in management, manufacturing, process development, facilities engineering, and project management facilities. He serves on the editorial advisory board of *Life Science Leader*.

Creating the appropriate quality culture is arguably the most important element of being a manufacturing leader in the life sciences industry. Yet, reflecting back on my long career, I have not seen a single recipe for doing this, and I don't profess to have a well-documented approach myself. But, boy, do I have some stories.

IT'S HOW WE WANT PEOPLE TO ACT

Let's define culture as the behaviors we accept in our company. Expanding this definition, accept can be substituted with tolerate, encourage, demonstrate, and reward. A key corollary of this rule is "who we promote speaks volumes on what we truly value." The leaders set the tone and manage behaviors that deliver the desired culture.

I remember discussions on what our company's definition of quality should be. As Lewis Carroll once said, "If you don't know where you are going, any path will get you there." The definition of the target condition can vary from "perfect" to "conforms to specifications" to "fit for purpose," and each of these will lead to potentially different decisions and discussions within your organization.

I recall a meeting with my leadership where we hoped to define how we wanted people to act and what consistent guidance we might provide to every worker touching our product. I remember the rhetoric about how important our products are to the patients who rely on them, but I was frustrated with the lack of specific direction we had developed for the front line. I remember asking, "Can we tell people they can stop the line if they felt the quality was not what it needed to be?" Often the response was something like, "We should be able to, but management wouldn't like that." Needless to say, after discussing our own concerns about quality, we did stop all production for a number of months and corrected all critical issues. We set longer-term plans for reaching a higher and sustainable quality state over time. We had the full support of our company's CEO, and we made a very strong statement to every employee in our division about how serious we were about quality. It was a painful step that led to some product shortages, but it galvanized the team and created a visible example of acceptable behavior as demonstrated by the leadership team.

ARE WE REALLY ALIGNED?

When defining quality for our group, a gap became clear in our leadership team. Operations was focused on efficiency, costs, and managing labor issues — not deliberately at the expense of quality and compliance, but perhaps not in balance with it either. Quality assurance was focused on internal and external inspections, interpreting agency communications to the industry, and how to reduce risk by enhancing systems, in-line checks, and procedures — not intentionally at the expense of cost and efficiency, but also not in balance. The only way to find a balance was to work together, identify the right risk-based compromises, and define our quality and the actions and risks we would all stand behind in executing an aligned target for change. We created a group that met weekly and managed all quality and compliance issues in full transparency while understanding consequences of options and aligned with our target condition. This was another key to getting us all on the same path to the future.

We started as an organization in need of serious remediation. Once stabilized, we recognized that cost and quality can be at odds if we try to reach higher quality in a policing or double-check mode. Instead, if you create and instill the right quality culture where every employee understands what needs to be done and why it needs to be done, and they execute flawlessly (through simplified, controlled and standardized processes), the heavy systems are not necessary, and cost and true quality do not need to be a choice. In my view, it starts with a clear definition, an aligned leadership team, clear direction and full engagement of every person in the organization, and a shared leadership and ownership of every issue along the way.

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How Much Transparency Is Too Much With Clinical Trials?

SUJAY JADHAV

Sujay Jadhav is CEO of goBalto. He has over 20 years of experience with leading Silicon Valley software providers with a life sciences focus. He was most recently SVP of global corporate strategy and development at Model N.

There is a growing movement by some researchers and regulators to increase disclosure of clinical trial results. According to advocates, the push for greater transparency would result in the publication of all clinical trial results, including those currently under investigation, as well as past trials conducted. In response, several pharmaceutical companies have publically embraced the concept of clinical trial transparency, notably AstraZeneca with the recent creation of a Scientific Review Board to independently assess requests for data.

At issue is the ability of researchers to independently verify study results and, consequently, improve patient treatments that can lead to better health and lower healthcare costs. This initiative has been gaining ground due to various safety scandals that revealed trial data for some products was never fully published or disclosed, and the efficacy of some recommended medicines has been questioned. It's not clear that patients would truly benefit from this level of transparency.

MORE INFORMATION MAY EQUAL MORE CONFUSION FOR PATIENTS

Too much transparency in drug development might be problematic for many patients facing difficult diagnoses, says Barry Milton, a seasoned clinical trial specialist with more than 25 years' experience in both the healthcare and pharmaceutical industries. "In particular, without the proposed lay level of communication, the disclosure of clinical trial data and results may intensify confusion for some patients," he comments. Initiatives under way by the Center for Information & Study on Clinical Research Participation (CISCRP) are a positive step toward addressing this concern. Yet, as the transparency movement builds, the availability of a layperson translation would have to be tempered with the fact that there are an estimated 781 million people around the world who cannot read or write, and the average reading level in the U.S. is grade nine. How do we expect the general population to read outputs crafted at the Master/Ph.D. level?

It's not just patients who sometimes have trouble interpreting clinical trial information. Even clinical trial specialists sometimes find it hard to distinguish between a result that is truly positive and one that is just a result, since the comparison of the information to real-life clinical practice is not always clear in scientifically driven reports. And there are additional challenges. In a recent article, W. Nicholson Price II of University of New Hampshire School of Law and Timo Minssen, researcher at the University of Copenhagen, warn that new regulations requiring clinical trial data disclosure might make it difficult for companies to patent new medical uses for known drugs. Without sufficient alternatives, this may inhibit the development of new medical uses toward market approval.

These issues tend to be of greatest concern when patients are overwhelmed by their diagnoses and rely on their physicians and caregivers to bolster their knowledge levels as part of making healthcare decisions. If they are presented with volumes of data regarding clinical trials of their current and potential future drugs, they would need to be given time and support to understand how the data affect them.

Everything we do in clinical trials is rooted in the human element. And the issue of transparency highlights that it's not just about technology, cost savings, and faster time lines. It's about making a difference to patients who want and need treatment. Milton drives this point home in a touching anecdote about his mother.

"My mother was diagnosed with stage IV colorectal cancer at the age of 67. She had an eighth-grade education and an excellent group of physicians to help her through her treatments. However, when it came time to talking about prognosis and treatments, she deferred to her doctors and me. The only time she provided input was when we discussed her prognosis — a 95 percent chance of her dying even if she did not take treatment A. Her response was 'Well, maybe I am part of that 5 percent.' She did not care about what made up the 5 percent, only that she had hope to be part of it. I believe that in some cases, our need to expose the data comes at the risk of removing hope, and sometimes, hope is the real drug of choice for some patients. That can't be explained in a clinical trial," Milton notes.

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The Hidden Factor Of Leadership

ALAN ZELL

In the past 30 years, having read many books, articles, and case studies about the theories and practices for successful leadership styles, I have found that there is a hidden theme which connects them all — *selling*. Essentially, this involves asking others to accept and do what one expects others to do. When they do what is asked, it is a result of a good leadership style.

But there is a problem when the subject of selling comes up for anyone who doesn't have that term in their job description. Almost automatically the word evokes a negative attitude. Hence, it is not unusual to hear someone state, "I'm not selling, I'm a manager or in finance or in operations or some other job description other than selling." To them, being accused of selling is an anathema. Such an attitude ends up as a disadvantage for both the individual and their organization. So, to be seen as a leader, you may need to change your attitude toward the concept of selling.

CHANGE #1
Don't consider *selling* a four-letter word. Instead, view it as an 11-letter term — a profession.

CHANGE #2
Understand that some decisions made by employees who are not directly related to sales may still affect a leader's reputation or even the company's reputation as a leader in its industry and with the public. Ultimately, those decisions could have a negative effect on the bottom line, which may, in turn, imply the organization is suffering from poor leadership.

CHANGE #3
Recognize the concept of "internal selling," where everyone at a company is involved in selling in some way or another. This involves "selling" things such as an organization's ideas, policies, procedures, and appropriate attitudes toward investors, advisors, associates, staff, and suppliers.

Alan Zell is the author of *The Elements of Selling*. For over 30 years he has helped his clients get better by adapting his attitudes-for-selling tenets into their internal and external communications.

Internal selling is not a unidirectional activity performed from the top down; it is a two-way street. The other direction occurs when the staff wants to sell their ideas, attitudes, and competency to their management and supervisors and then to their associates, staff, and others who may be outside the organization. Good internal selling happens when a person speaks with confidence and intelligence about a topic.

Unfortunately, everyone has been both the victim and the villain of poor internal selling. Often, the negative effects of poor leadership can be traced to poor internal selling. So, being a leader rests on how easy it for others to buy-into and do what is asked of them and how they relate the situation to friends, family, associates, vendors, or even the organization's customers/clients.

Leadership of all types and styles comes about for individuals, firms, and organizations when everyone involved sees there is a selling component to what everyone does no matter their job title. When you accept that attitude that selling is an integral part of leadership, then leadership will permeate your organization. Without it, though, leadership is only a word and not an action. L

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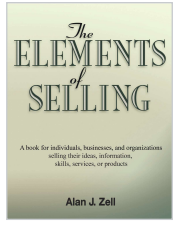

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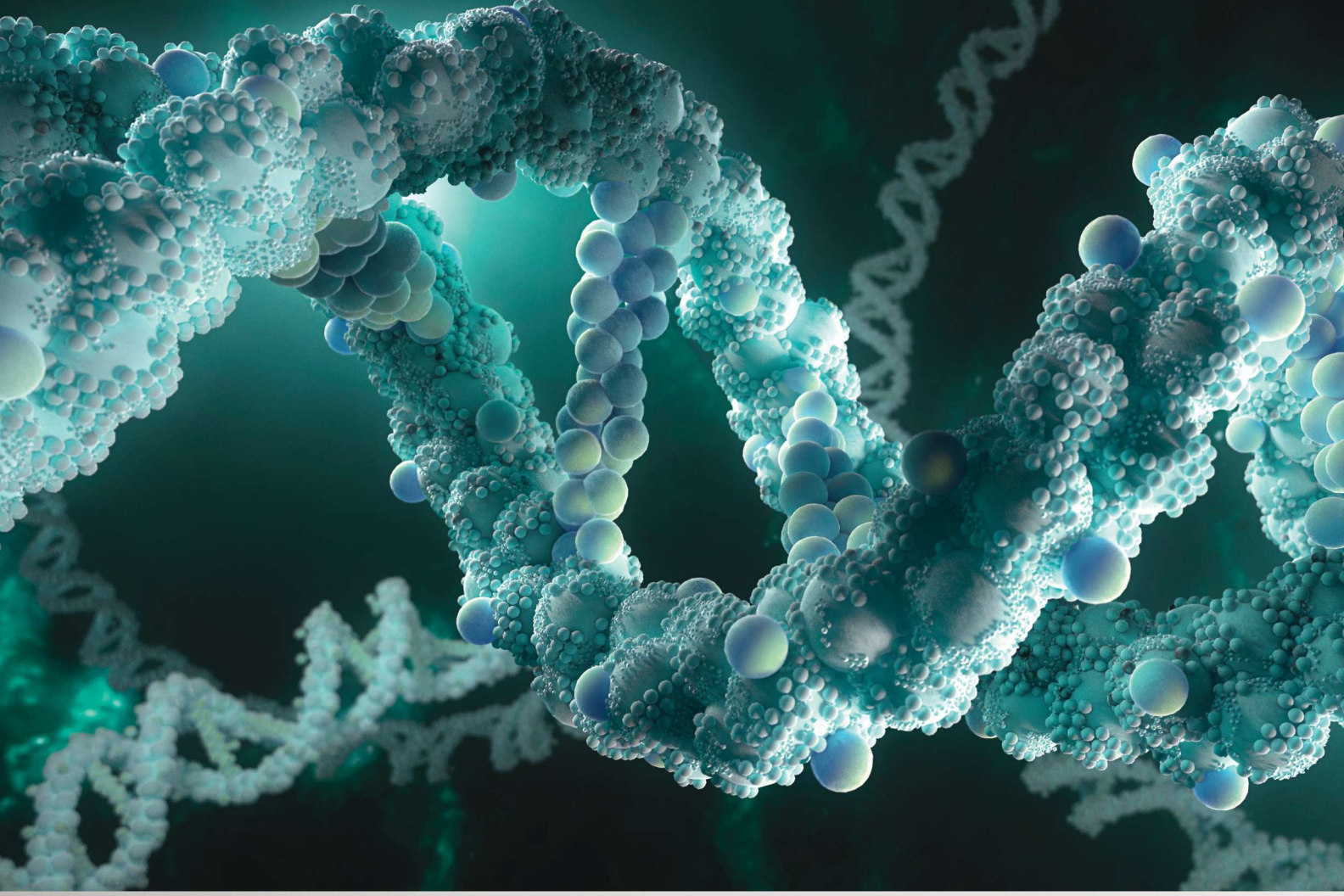

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