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Grünenthal's Entrepreneurial And Networked Approach

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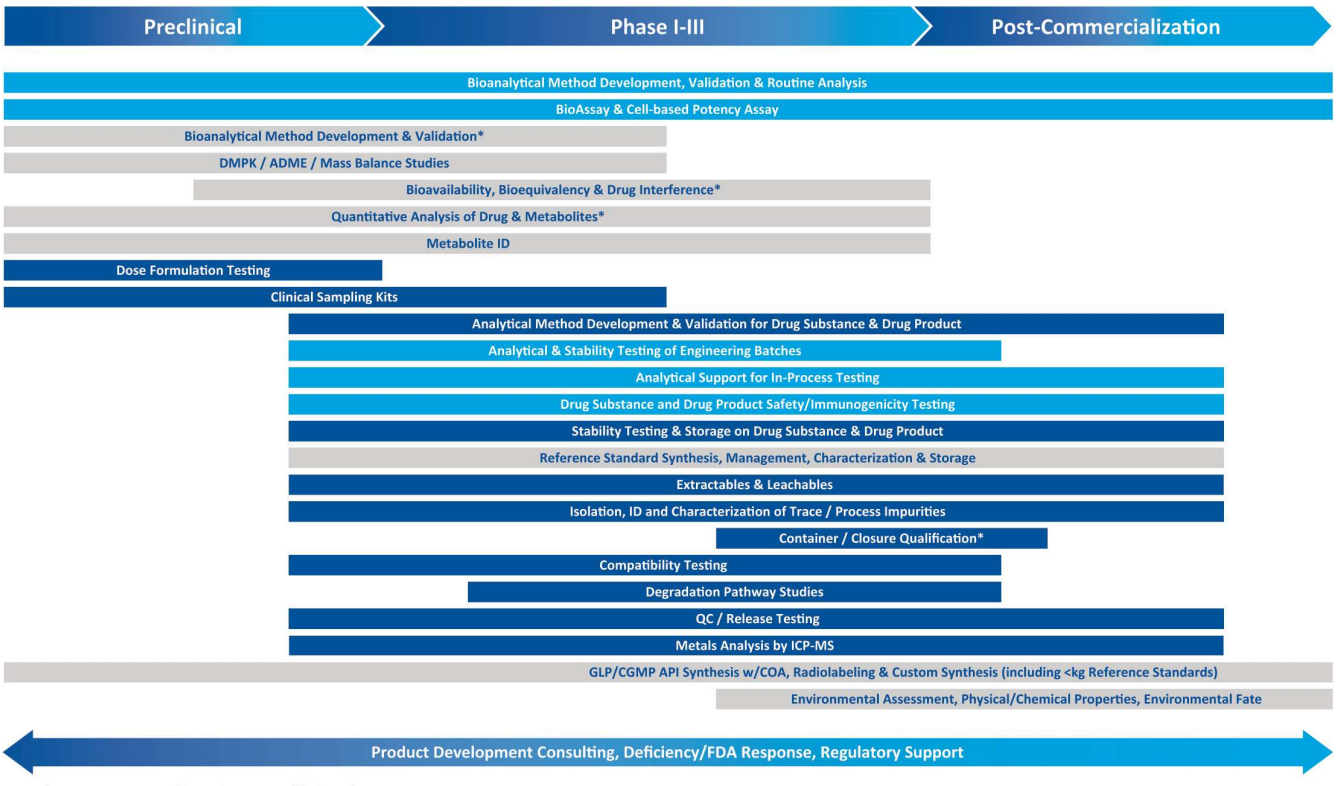

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Grünenthal's Entrepreneurial And Networked Approach To R&D

Grünenthal's CSO, **Klaus Langner, Ph.D.,** reveals how this $1.2 billion company plans to compete for collaborative R&D partners — and grow revenue. p. 20

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20 Cover Story: GRÜNENTHAL

"Yes, you need to be confident that you can develop compounds in areas of opportunity, but you don't necessarily have to do so alone."

Klaus Langner, Ph.D., Chief Scientific Officer of Grünenthal

Features:

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Ever Notice How Q1 In Biopharma Provides A Study In Contrasts?

ROB WRIGHT Chief Editor

The first quarter in the life sciences industry provides a wonderful study in contrasts. For example, in January at the 33rd Annual J.P. Morgan (JPM) Healthcare Conference, some of the largest pharmaceutical and biotech companies conduct presentations to packed rooms at the Westin St. Francis. Meanwhile, if you walk across Geary St. and into San Francisco's famed Lefty O'Doul's Restaurant & Cocktail lounge, you will see some of biopharma's start-up CEOs conducting multiple meetings in an effort to find funds to fuel their proprietorships. At the same time, at the Parc 55 Wyndham on Cyril Magnin, the Biotech Showcase conference is happening. While Shire's CEO, Flemming Ornskov, M.D., presents for 25 minutes at JPM in a room that can hold 1,100, at the showcase, Immunocore Limited's chief business officer, Eva-Lotta Allan, has 15 minutes to convince a room that would burst with 30 people why they should partner and/or invest in her clinical-stage company.

February brings you from the warm weather of the West Coast to the blustery East. The city that never sleeps, New York, plays host to the seventeenth BIO CEO & Investor Conference at the Waldorf Astoria. Boasting 1,400+ attendees from 26 different countries, lesser-known companies like Synthetic Biologics, Durect, Adocia, and Raptor Pharmaceuticals compete for investor ears and dollars during the same time slot allotted for fireside chat participant John Milligan, president and COO of one of the hottest biopharma stocks on the planet — Gilead Sciences.

March is the month when the Drug, Chemical & Associated Technologies Association (DCAT) celebrates DCAT week, March 16 to 19, which also takes place at the Waldorf. Considered one of the largest gatherings in the world for the pharmaceutical and related industries, DCAT week creates peripheral networking and partnering opportunities similar to JPM. For example, *Life Science Leader* magazine hosts a small, yet popular, gathering known as the annual CMO Leadership Awards on Wednesday evening (March 18) at the "W" Hotel, which just so happens to be right across the street from the Waldorf.

The first quarter of 2015 also has been a study in contrasts when it comes to which companies we've featured on the cover of *Life Science Leader*. January and February featured executives from Pfizer and Astellas — two of the biggest companies in two of the biggest pharmaceutical markets in the world (i.e., United States and Japan). This month, though, we chose a smaller, less well-known, family-owned business — Grünenthal. This company has been doing business for over 70 years in the EU, the second largest pharmaceutical market that's also one of the most restrictive and challenging. Grünenthal has traditionally conducted business with partners. However, the company's chief scientific officer, Klaus Langner, is seeking to involve collaborators even earlier than they have in the past. In the article on page 20, Langner shares how the German-based company is building a new entrepreneurial and networked approach to R&D, which in itself is an interesting study in biopharma contrasts.

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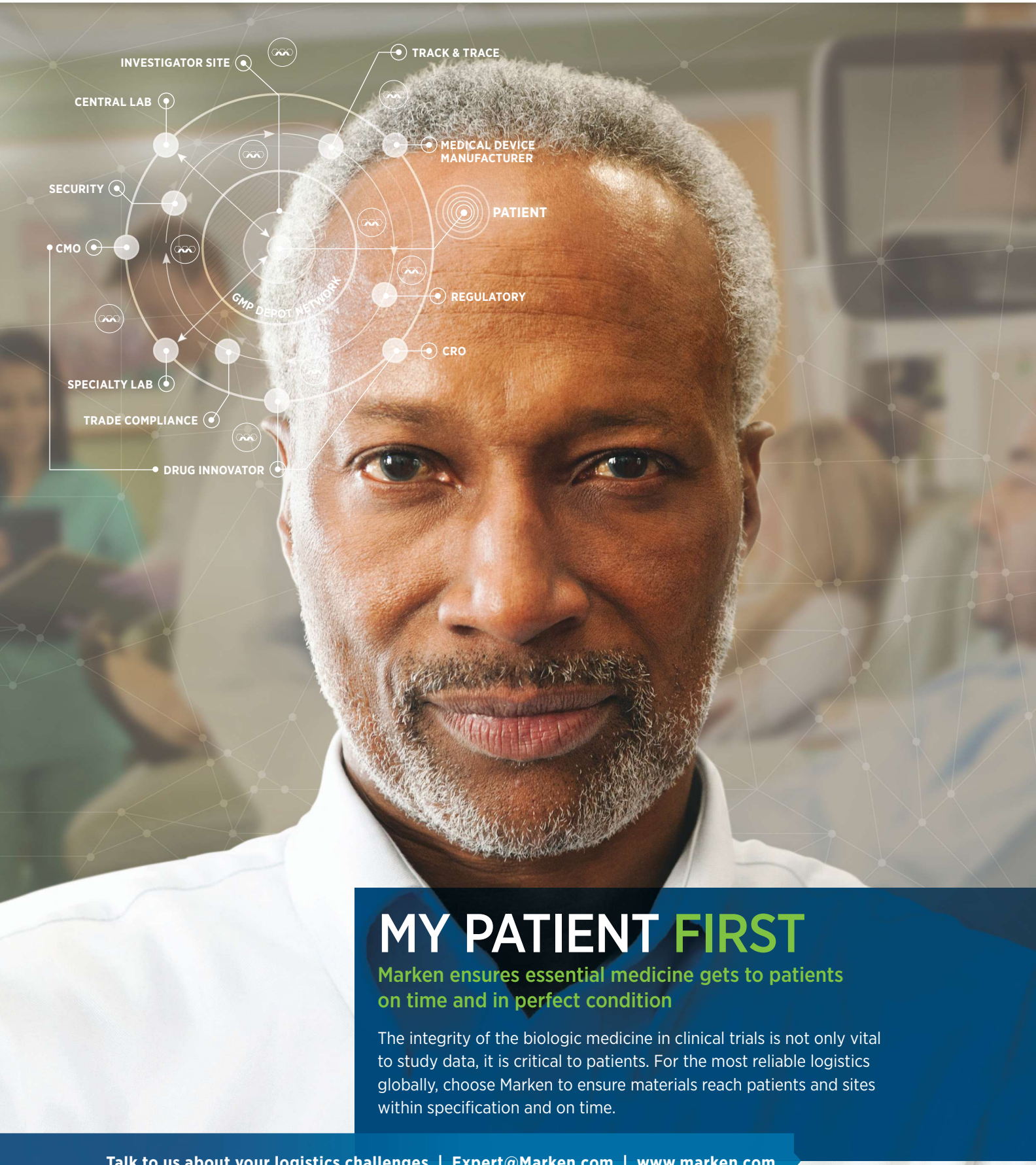

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Q What advantages will personalized medicine bring to patients, and what is its overall public health benefit?

A PERSONALIZED MEDICINE could trump the current one-size-fits-all approach to pharmaceutical interventions in certain cases. Some individuals fall on one side of the bell-shaped curve, and the rest will be okay with a general therapy. The closer to the top of the curve, and to the right (high responders), the greater chance the therapy will be successful. The outliers on the left will benefit the most from individualized therapy. For example, knowing specific tumor genotypes can focus chemotherapy on agents effective for such tumors. Understanding personal genetics will enable physicians to tailor therapy based on ability to respond to a specific chemotherapy and avoid treating individuals whose genetics make them poor responders. People metabolize drugs differently based on liver enzymes (Cyps), so understanding patient Cyp genotypes could help physicians tailor drug therapy to those with the ability to correctly metabolize prodrugs.

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

Q Who would you be most interested in reading about in *Life Science Leader*?

A MICHAEL JAHARIS has made three fortunes in pharmaceuticals. The first was when he and dermatologist Phillip Frost bought Key Pharmaceuticals in 1972. Jaharis was CEO until 1986 when it merged with Schering-Plough in an $836 million deal. Number two came when he founded Kos Pharmaceuticals in 1988 and sold it to Abbott Labs in 2006 for $4.2 billion. The third home run for Jaharis was when AstraZeneca purchased Pearl Therapeutics for $1.15 billion in 2013. At the time, Vatera Healthcare Partners, the VC firm cofounded by Jaharis, was the controlling investor in Pearl. As a biopharmaceutical entrepreneur, I think readers would be enlightened by his wisdom.

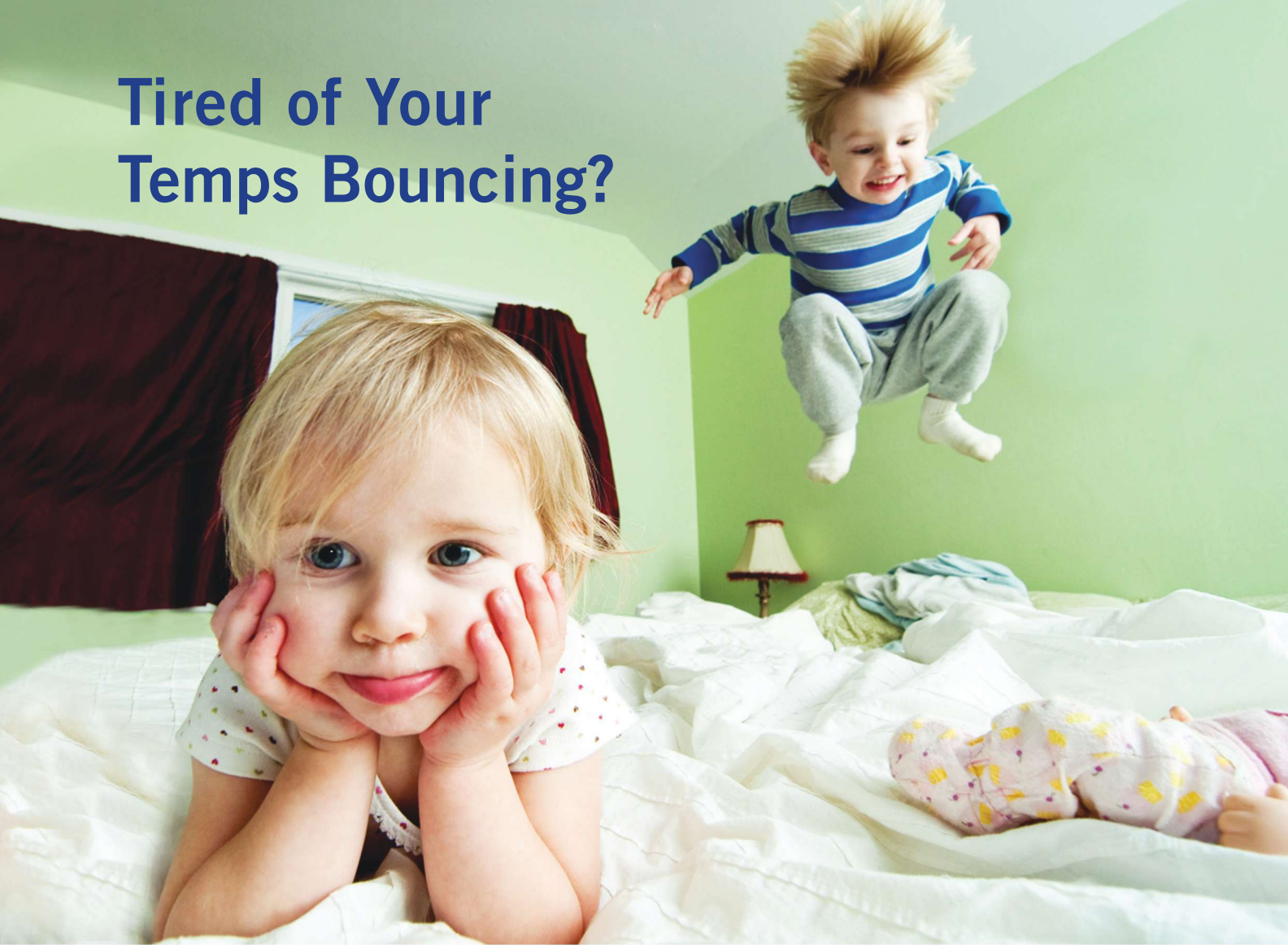
LESLIE WILLIAMS
Leslie Williams is president, CEO, and founder of ImmusanT, Inc., an early-stage company focused on peptide treatments for autoimmune diseases. She has more than 20 years of industry experience.

Q What macro trend have you noticed beginning to impact the way you do business?

A A RECENT LABOR STATISTIC NOTED 2015 as the year the millennial generation will become the majority in both the workforce and consumer space. I feel the shift. The things that motivated my staff 10 years ago do not resonate with current workers. Although I have no metrics to cite, I feel we are not training and developing enough clinical trialists. It takes me much longer to find a suitable hire. In a few instances, I have had positions open for months with only a trickle of applicants, and few of them qualified. It seems fewer and fewer have been adequately educated in the discipline of drug development. We need to ensure a steady stream of top talent is coming into our industry.

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

Tired of Your Temps Bouncing?



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Treasury Threatens Small Businesses For Providing Health Coverage In The "Wrong Way"

JOHN McMANUS The McManus Group

As if the challenge of providing healthcare coverage is not difficult enough for small businesses, the Department of Treasury is now threatening to penalize any employer who provides tax-preferred resources for their employees to purchase insurance coverage in the individual market with a $36,500 annual fee per employee.

You read that right — the penalty for providing such assistance is $100 a day per employee — or more than 12 times the penalty for large employers failing to provide coverage as mandated by the Affordable Care Act (ACA)!

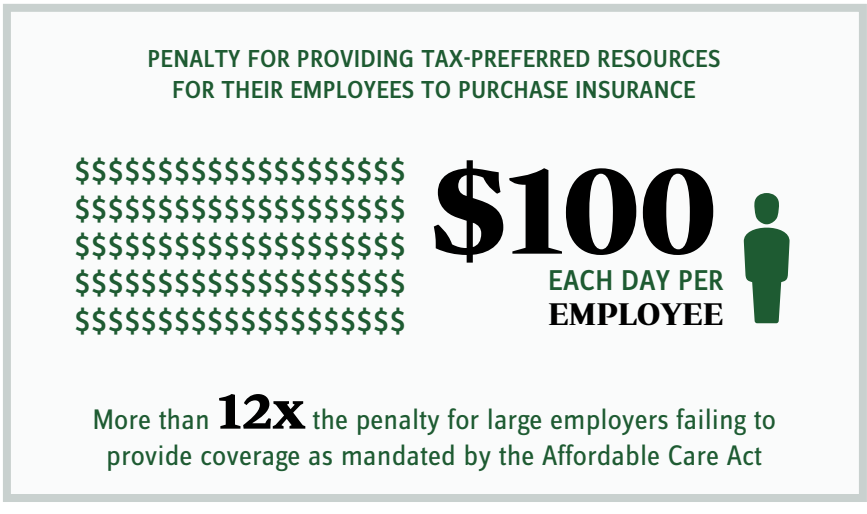
Small employers who are not even required to provide coverage are most likely to become ensnared in this punitive policy because they often do not have the sophistication, time, or resources to purchase group coverage for their employees. Rather, many fund tax-preferred Health Reimbursement Arrangements, which their employees use toward the purchase of coverage in the individual market or to simply pay for qualified health items and services, such as physician visits and prescription drugs.

But the Department of Treasury issued a vexing regulation stating that such contributions violate the ACA's market reforms, specifically the requirement that insurance policies must provide unlimited catastrophic protection and free preventive care.

The small business community met that regulation with bafflement and outrage. All were willing to stipulate that the discrete dollar contributions in themselves do not constitute an insurance policy. Those funds are resources to purchase an insurance policy in the individual market, which of course would be in compliance with the ACA requirements.

A backlash is now fomenting on Capitol Hill as constituents seek redress. At a recent Senate Finance Committee markup, Senator Grassley (R-IA) read an excerpt from a letter from a dentist in Sioux City:

"Help! I am a small business owner — seven employees. I have been helping to subsidize my employees' health insurance for 20 years. I just found out that the Market Reforms of the ACA have made that illegal … . Now all of my employees will have to pay taxes on the money I gave them for health insurance. They all live paycheck to paycheck and won't be able to come up with the taxes on this money. They also most likely won't qualify for the exchanges and any



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government subsidy. They are caught in the middle. I can't subsidize their health insurance because I risk a $100/day/employee penalty. Please hurry and do something to help the millions of middle-class, small-business employees who are caught between a rock and a hard place."

A homebuilder with 10 employees in Laplace, LA, received a similar notice from the IRS that the coverage he had been providing for his employees would result in a $100 a day penalty per employee. He was forced to drop the coverage and his employees are now paying more than $10,000 a year each to purchase health insurance, and his effort to raise their salaries to compensate for some of the difference increased his business's cost by $5,000 per employee.

What is going on here? Why penalize small employers with fines exceeding $36,000 per employee for providing coverage through the individual market?

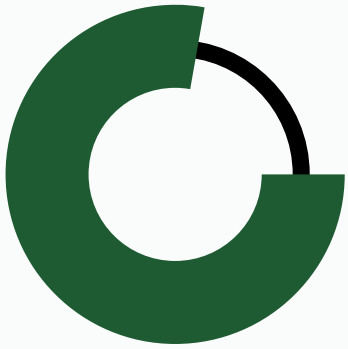
One can only speculate that the Obama administration is trying to coerce these small employers into the government-run and still dysfunctional small business "SHOP" exchange or trying to coerce their employees into the state and federal exchanges controlled by government.

Rather than speculate, Rep. Charles Boustany (R-LA), a senior member on the Ways & Means Committee who has introduced legislation to reverse the Treasury regulation, queried Treasury Secretary Jack Lew at a recent hearing, "Why would Treasury introduce this sort of draconian penalty?"

Lew's response: "Via the ACA, we have moved to a system that benefits individuals with affordable healthcare, and we are focused on that goal." How's that for a non-sequitur platitude?

Rumors are now swirling that implementation of the regulation may be briefly delayed but not withdrawn.

Rep. Boustany's bipartisan legislation that was introduced along with Rep. Mike Thompson (D-CA) has earned the plaudits of the National Federation of Independent Business (NFIB), the National Association for the Self-Employed, the National Association of Homebuilders, and the National Association of Manufacturers and remains the best hope to reverse this ill-thought policy. NFIB underscored the importance of the bill in its endorsement letter, noting, "Fourteen percent of nonoffering businesses utilize a reimbursement arrangement. In a recent NFIB ballot, 78 percent of small business owners support allowing employers to contribute pretax funds to their employees in order to purchase insurance on their own."



78%

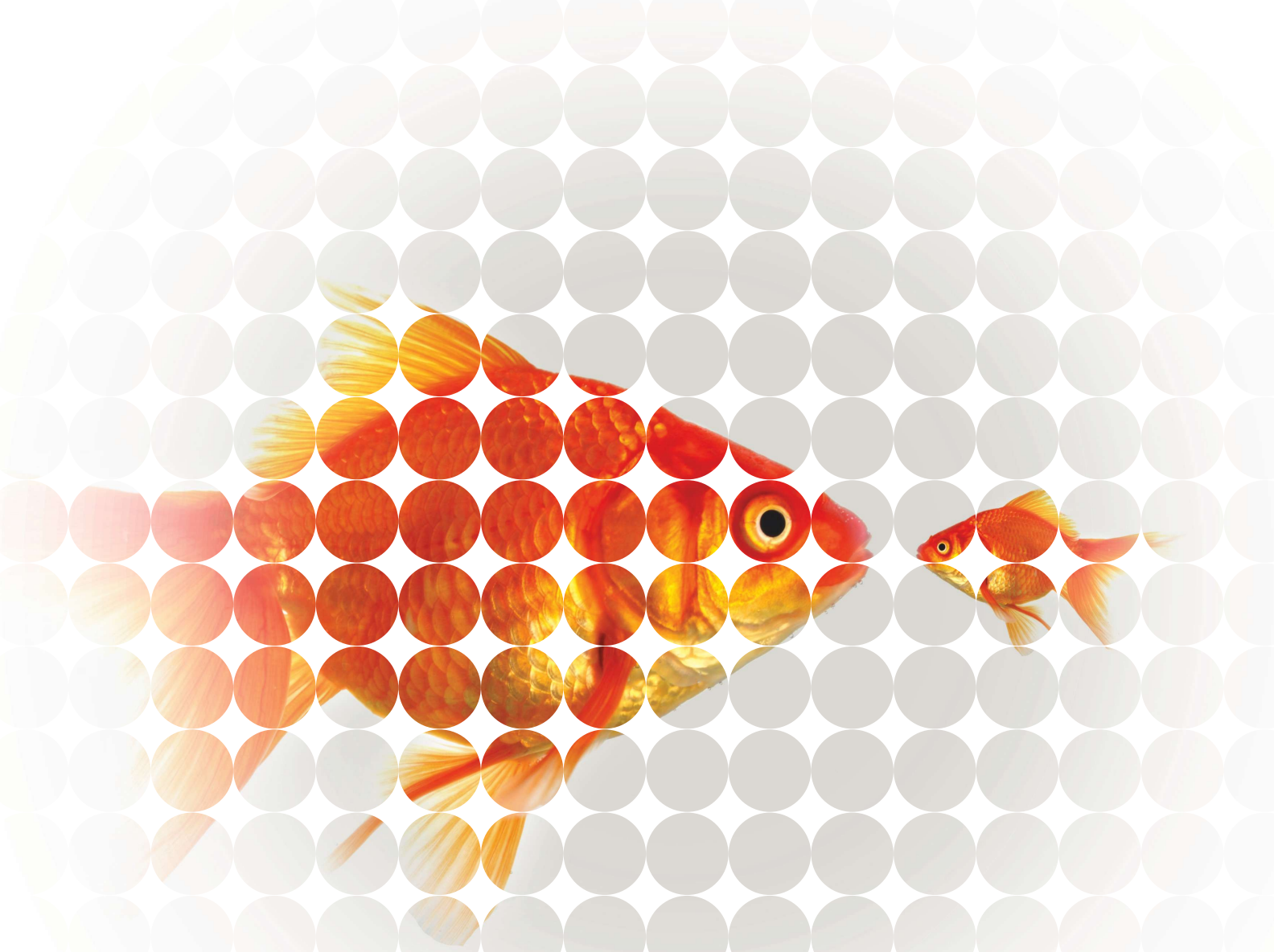
of small business owners support contributing pretax funds to their employees to purchase insurance **ON THEIR OWN**

Obamacare's employer mandate applies to large businesses with 50 or more workers. In February, the administration announced that it would once again delay the implementation of the mandate for employers with 50 to 99 employees until 2016 – two years longer than called for under the statute. And companies with more than 100 workers received a grace period if they offered coverage to 70 percent of their employees rather than 95 percent in 2015, as called for in the statute.

It is unfortunate that the administration does not have similar sympathy for small businesses that are not even subject to the mandate. They are vulnerable to massive fines that could put them out of business for providing healthcare assistance to their employees in a way that violates the administration's view of how healthcare should be provided.

A little paternalistic and pernicious, don't you think?

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.



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WAYNE KOBERSTEIN Executive Editor
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SNAPSHOT

NeuroPhage Pharmaceuticals is developing a novel approach to treating a number of disorders associated with protein misfolding, such as Alzheimer's, Parkinson's disease, and amyloidosis. Lead candidate NPT088 is based on the company's GAIM (General Amyloid Interaction Motif) technology, targeting and remodeling multiple toxic, misfolded proteins (Aβ, tau, α-synuclein) for clearance by the body's natural mechanism.

WHAT'S AT STAKE

When proteins misfold, many of them do it in the same way — aggregating to form amyloids all defined by a common structure, or "conformation." Amyloid formation can occur in any organ, and it is responsible for a wide range of diseases throughout the human body. According to NeuroPhage CSO Dr. Richard Fisher, a particular bacterial virus, or bacteriophage, holds the key to blocking the misfolding process, a mechanism for eliminating amyloid assemblies.

"We started by trying to figure out how this particular virus can have amyloid-targeting activity," says Fisher. "After several challenging years of investigation, during which we were learning how to develop a phage into a drug, we located the piece of protein on the phage apparently responsible for all the activities we observed, which include improving the condition of transgenic mice that model neurodegenerative conditions, such as Alzheimer's and Parkinson's. Those diseases are characterized by multiple misfolded proteins — usually not just one culprit — and with our approach, we can potentially target multiple misfolded proteins simultaneously."

Turning a bacteriophage into a drug was no easy task, NeuroPhage invented its own technology, GAIM, which mates the protein fragment to an antibody fragment, called an Ig-GAIM fusion, that neutralizes and mediates the elimination of the toxic amyloid plaque. The NeuroPhage drug does not discriminate by initial cause — misfolded proteins occur naturally and accumulate with age, or they can pile up much faster with pathological or genetic stimulus. What the drug essentially targets is the propensity of amyloids to act as a template for further misfolding, accelerating their own replication like a spreading fire. A second GAIM activity is binding to smaller aggregates, called oligomers, which can kill neurons outright; it remodels these structures into a nontoxic state. In the mouse models, says Fisher, treatment appeared to clear brains of up to 70 percent of amyloid plaque. "Now we have a new molecule that's very drugable — it can be given systemically, stays sufficiently long in the blood, and reaches the brain in the portions required."

CEO Jonathan Solomon says NeuroPhage plans to enter human trials by the end of 2015. Thus the company is poised at the edge of a classic test — going from preclinical models to proof of concept in humans.

One required element for approval of any brain-targeting neurologic drug is the ability to image the key biomarkers in a PET (Position Emission Tomography) scan. Several imaging agents for the two main aggregates in the Alzheimer's brain, amyloid beta, and amyloid tau now exist. Dr. Franz Hefti, NeuroPhage's current president and COO, previously played a key role in developing the imaging agents the company is using in its first human trials.

NeuroPhage has "a few very deep-pocketed investors," according to Solomon. Those include the venture arms of Merieux and Shire, as well as private individuals. "We can finance the company through completion of the imaging study, but another investor or going public could take us considerably further." Solomon notes a surge in the momentum of neuroscience development, attracting more attention from funding sources — and perhaps one new area stealing some of the thunder from cancer.

JONATHAN SOLOMON
CEO

Vital Statistics

20
Employees

Headquarters
Cambridge, MA

Finances

$61.4M
total to date from Shire, Merieux Development, and private angels

Research partnership funding

Michael J. Fox Foundation – received two grants totaling $1M to study GAIM's effect on Parkinson's disease

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What Does 2015 Hold For The Indian CMO Industry?

The last few years have been pretty rough for the Indian biopharmaceutical CMO industry. If 2013 wasn't enough, tougher unannounced surprise FDA inspections, warning letters, and import bans were carried on in 2014 and will continue in 2015. Some of the biggest names in the Indian CMO industry — Ranbaxy, Wockhardt, Sun Pharmaceutical, IPCA Labs, Dr. Reddy's, and others — have been hit with warning letters, import bans, and site shutdowns. To add to the misery, Europe has followed these steps and joined the FDA in banning manufacturing sites in India.

TJ LADAGE
MBiotech, Market Research Manager at That's Nice

> *"The overall offshoring trend hasn't slowed down a bit."*

If you ask the Americans, they will point out the lax nature of businesses in India, quality concerns, safety lapses, and violations such as data manipulation. While if you ask the Indians, they would call it differences in culture and disregard to business practices in India. But as an Indian working in the U.S. and having experienced some of the work culture nuances in both countries, I tend to agree with both. The argument can go on, but the fact remains that both the Indian pharmaceutical industry and the U.S. pharmaceutical industry need each other. Forty percent of the generics and over-the-counter medications sold in the United States are imported from India. (*New York Times* article, February 2014). And if India plans to export drugs to the U.S., they have to follow the rules and regulations set by the FDA for everyone. From the U.S. perspective, outsourcing to emerging markets, specifically India and China, is on the rise; the U.S. already relies on these two markets for the majority of its generics, APIs, excipients, etc. Both India and China, though termed "emerging" markets, have matured enough to be major stakeholders in manufacturing and exporting of generics to the U.S. and Western markets. It is vital for the U.S. to make sure these emerging markets up their standards and get their act together to maintain market stability and keep the domestic generics pricing in check. And with rising healthcare costs, it makes correcting the above a priority for the United States.

The overall offshoring trend hasn't slowed down a bit; in fact, the recently concluded Nice Insight 2014-15 annual CMO-CRO survey reveals a whopping 11 percent increase in respondents that are willing to offshore to emerging markets (70 percent in 2014 to 81 percent in 2015). The biggest jump was observed among "Specialty Pharmaceuticals," which increased from 61 percent to 83 percent in 12 months. Similar leaps were observed within Big Pharma (71 percent to 87 percent), Emerging Pharma (67 percent to 83 percent), and Biotech (70 percent to 83 percent). The smallest increase was observed among Emerging Biotech (86 percent to 89 percent), but of all the industry buyer groups, Emerging Biotech was the one willing to offshore the most to emerging markets. The small increase can also be attributed to the already high offshoring percentage in 2014.

If we look at outsourcing by region, we can

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see that the FDA warnings and shutdown of plants in India is reflected in the industry's outsourcing perspective toward India. The overall outsourcing to India fell from 13 percent in 2013-14 to 11 percent in 2014-15. If we further break down by industry category, we see that the pharmaceutical industry seems to have reacted more strongly than the biotechnology industry. The biggest drop, of 6 percent, was observed amongst Big Pharma (17 percent to 11 percent) and Specialty Pharma (18 percent to 12 percent) followed by a drop of 4 percent amongst Emerging Pharma (14 percent to 10 percent). Interestingly, there wasn't any change in outsourcing to India among the Biotechnology firms; however, there was a 2 percent drop among the Emerging Biotech group (13 percent to 11 percent).

For years industry experts have hoped India, an emerging economy, would become a major player in the global healthcare space. It has the ingredients for success and has demonstrated it with perhaps the most phenomenal growth the industry has shown in the past decade or so. It is encouraging to know the Indian government has taken up the issue of restoring the pharmaceutical industry's image by committing $511 million to double the number of inspectors at the central level and adding another 3,000 at the state level. The Central Drugs Standard Control Organization (CDSCO) has issued new guidelines for state regulators on how to conduct cGMP inspections (*Regulatory Affairs Professional Society*, August 2014). But if India plans to export pharmaceuticals to the EU and U.S., it has to stick to the guidelines set by the FDA, EMA, and other specific regulatory agencies. On the flip side, the U.S. needs to stick to the rulebook and invite Indian officials during surprise visits. Along with the warnings and sanctions, it would be beneficial if the FDA channels the appropriate resources and has cohesive open conversations with all the involved stakeholders to ensure high standards are upheld. Along with steps taken so far, both must immediately address one of the biggest concerns for both parties, cultural differences, as it seems to be creating a major hindrance. It's going to be a long way, but hopefully with some of the steps implemented in 2014, and with continued efforts, India can regain the lost trust and confidence it enjoyed in the developed markets over the years.

FIGURE 1

Percentage of Respondents Who Would Consider Outsourcing to CROs/CMOs in Emerging Markets

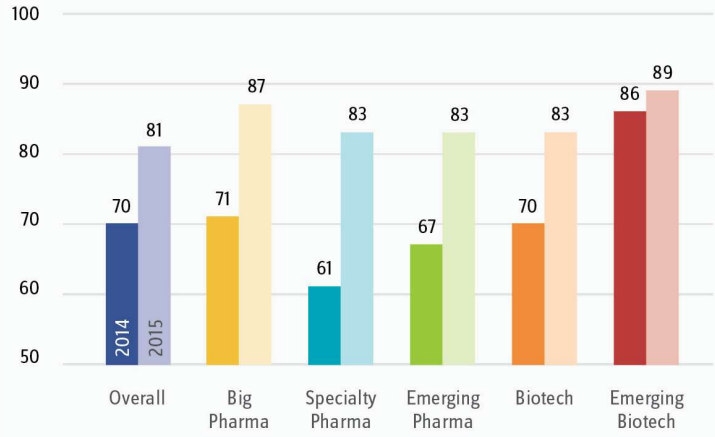
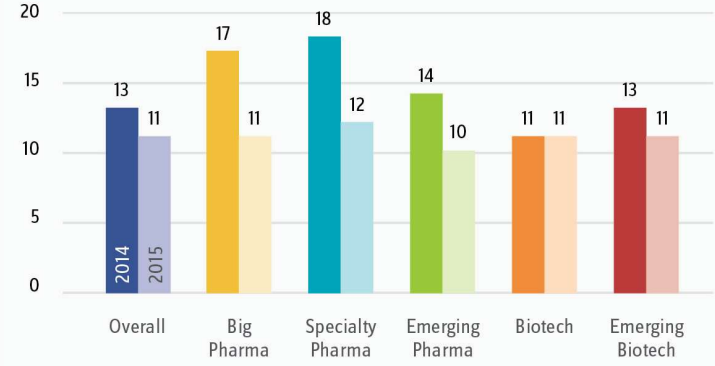


FIGURE 2

Percentage of Outsourced Projects Assigned to India



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 comprises 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.

N. WALKER

If you want to learn more about the report or how to participate, please contact Nigel Walker, managing director, or Kate Hammeke, director of marketing intelligence, at Nice Insight by sending an email to nigel@thatsnice.com or kate.h@thatsnice.com.

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GRÜNENTHAL BUILDS A NEW

ENTREPRENEURIAL & NETWORKED

APPROACH TO R&D

BY ROB WRIGHT

KLAUS LANGNER, PH.D. Chief Scientific Officer of Grünenthal

The German proverb, "Wer rastet, der rostet," loosely translates to, "He who rests grows rusty." This saying occurs to me as I sit across from Grünenthal's chief scientific officer, Klaus Langner, Ph.D. We are at the Omni hotel in San Francisco, and it is very late. However, since we are in town for the 33rd Annual J.P. Morgan (JPM) Healthcare conference, each of us knows this is far from our last meeting of the day.

Langner's dark suit still looks crisp, and his white shirt is still bright. I think to myself, "He has no 'rust' on him." Only the slight loosening of his tie provides any evidence his metal is beginning to fatigue. "It's pronounced Grew – nen – tall," he politely corrects in English laden with a German accent. "We are a fully integrated R&D company, having always a strong footprint in internal research."

"The U.S. is an important market for us, but only via partners."

KLAUS LANGNER
Chief Scientific Officer of Grünenthal

In 2013, Grünenthal, a nearly 70-year-old family-owned German drug developer that has primarily focused on discovering new ways to treat pain, invested approximately 27 percent of its revenues back into R&D. For the same year, that's five percentage points higher than Novartis, one of the most innovative pharmaceutical companies in the world. Like most companies in this industry, Grünenthal recognizes that to develop a sustainable business model, it must adopt an open and collaborative approach to R&D. But how is a company the size of Grünenthal, with revenues of approximately $1.2 billion (€1 billion) in 2014 supposed to compete for collaborative R&D partners so that it can continue to grow and remain "rust-" free? According to Langner, Grünenthal intends to broaden its business by implementing a new entrepreneurial specialist and networked approach to R&D built on the foundation of its focused drug discovery and development legacy.

REAP THE VALUE OF STRATEGIC PARTNERSHIPS

One of Grünenthal's first R&D success stories was tramadol, a narcotic-like pain reliever which was marketed by Janssen in the U.S. as Ultram. According to Langner, after Ultram, the company took an "opportunistic approach" to R&D, seizing opportunities not necessarily closely related to the development of pain-oriented therapies. "But from the 1990s onwards," he explains, "we began to focus more and more on pain." From then on, the company developed tapentadol, a centrally acting opioid analgesic. In the EU, Grünenthal markets the drug under its brand name, Palexia. In the U.S. however, tapentadol was, until very recently, marketed by Janssen under the brand Nucynta. "Tapentadol represented a real innovation in pain," Langner points out. "With respect to the development of a new chemical entity [NCE], prior to tapentadol, nothing new had happened in pain for 30 to 35 years."

Grünenthal's R&D approach reveals a pattern worthy of emulation, especially for small to midsize biopharmas. First, focus on your drug development niche. Second, when you are a small company seeking entry into the biggest and most stringent biopharmaceutical market in the world (i.e., the U.S.), seek highly reputable therapeutic category champions as your partners. "The U.S. is an important market for us, but only via partners," Langner states.

Grünenthal has other reputable pain management collaborators. Purdue Pharma, known for bringing pain relief to millions via OxyContin, licensed the technology patents from Grünenthal for their crush-resistant manufacturing technology which raises the hurdle for tampering and abuse. If you're a small pharma or bio company trying to grow, there are lessons to be learned from Grünenthal's partnering examples. For instance, don't put all your niche drug development into the basket of a single partner. And make sure you create strategic partnerships earlier than the out-licensing phase.

FOCUS ON CORE COMPETENCIES

During our conversation, Langner explains why it's important to adopt a focused approach to R&D. He says that if you wanted to develop an analgesic with a broad label, you would have to run up to nine Phase 3 trials in different pain subcategories, each with its own standard of care. "This broad approach increases your risk — heavily," he attests. Instead, to reduce risk, he advocates a more targeted approach, focusing on developmental compounds with smaller labels, as well as smaller patient populations. "Neridronate is a nice example of this right here in the U.S.," he states.

Neridronate is registered in Italy for the treatment of several diseases (e.g., osteogenesis imperfecta and Paget's disease of bone). CRPS (complex regional pain syndrome) is a progressive disease of the

autonomic nervous system that, according to the McGill Pain Index, ranks as the most painful form of chronic pain. Since pain management is a Grünenthal core competency, the company set out to obtain (which it did successfully) the licensing rights for Neridronate for the Americas. With less than 200,000 U.S.-Americans suffering from CRPS, Grünenthal executives knew this represented an unmet medical need, as well as a possible orphan drug indication for Neridronate. "Worldwide, two things we look for when assessing development, licensing, or commercial opportunities are drugs with niche and/or orphan indications," Langner states. Neridronate fits the bill. Apparently, the FDA agreed. On March 25, 2013, Neridronate was granted orphan drug designation by the FDA for CRPS-I, CRPS-II, and CRPS-NOS (not otherwise specified). "We think we can make a real difference in the treatment of patients suffering from CRPS-I, and we are highly committed to starting clinical trials in the U.S." The only thing missing is an R&D partnership to help bring Neridronate to patients in pain. Grünenthal will start clinical trials without a partner, but is seeking a partnership for future R&D and marketing activities. If successful, Neridronate would be the first drug on the U.S. market specifically approved for the treatment of pain due to CRPS-I.

Grünenthal's approach to creating a networked and entrepreneurial R&D program seems simple. Know what you are good at. Find synergistic opportunities that play to that strength. Then, find partners that complement your strengths and that also fill in your weaknesses. This is one of the main reasons for Langner's visit to J.P. Morgan. As Grünenthal's strength is pain, Langner sees complementary opportunities in conditions (e.g., certain inflammatory diseases), niches in neurology, cancer-supportive care, as well as various pain treatment settings (e.g., postoperative pain). "If we see an opportunity to bring something new to patients where there is a high unmet medical need and it fits to our target audience, we would go into the business," says Langner. For example, when California-based AcelRx Pharmaceuticals was seeking a European collaborator for Zalviso, its novel combination pain drug-delivery device, the firm picked Grünenthal. According to AcelRx CEO Richard King, though the search for an EU collaborator involved a number of large players, Grünenthal was selected because of its footprint in Europe's post-operative pain setting with tapentadol.

HOW DO YOU KEEP COMMITMENTS MADE TO COLLABORATORS?

Klaus Langner, Grünenthal's chief scientific officer, says time is one of the most important metrics when working with a collaborative partner — specifically, delivering to your partners on time. "We were developing a product for a partner that uses INTAC, our crush-resistant technology," he explains. "We had to make a technology transfer to the U.S. involving the new technology, the new formulation, and all of the machines necessary to produce the product." Keep in mind, Grünenthal was not the maker of the manufacturing machines used in the INTAC manufacturing process. "Nonetheless," Langner says, "we said we'd deliver everything, and therefore, we were responsible."

The initial time budgeted to complete the tech-transfer project was 18 months. "We had no previous experience conducting this size of a transfer, which included a completely new technology and completely new machines," he admits. Soon into the process, colleagues approached Langner to inform him they had seriously underestimated the time required, and shooting for 18 months was asking the impossible. Langner thought, "I am responsible. We have to deliver on time."

The first thing he did was to meet with the team to discuss options for meeting the delivery time period they had committed to. After the meeting, Langner sat down to do some analysis of the project and realized he needed some help. "We decided to hire two expert external consultants who were experienced in what I call 'bottleneck project management,'" he states.

At the next team meeting, Langner announced the decision to bring on the consultants, but was quick to clarify their role was not to take over the project's management. "Their job was to focus on analyzing the data to determine where backlogs could be eliminated," he states. "I reiterated that the responsibility for delivering the project on time remained with the Grünenthal internal project leads." The project team meetings became a routine, occurring early in the week and lasting an hour and a half. Although not necessary, Langner attended many of the meetings. "I made this project and these meetings my number-one priority," he says. "If I wanted people to take this project seriously and be committed, I needed to demonstrate the same level of commitment I was asking of them. It was visible." What wasn't visible was what Langner was doing outside of the meetings to help foster the project.

When most people are told a project will not be able to meet a deadline, their first inclination is probably to pick up the phone and ask the customer or partner for more time. Langner did pick up the phone, but not to call Grünenthal's collaborative partner. "I thought to myself, 'There are other industries with tough timelines; how do they do it?'" he shares. Having contacts at RWTH Aachen University, a prominent technical institution, who have done work with a number of industries external to pharma (e.g., automotive and aircraft), Langner set up several evening and dinner discussions to gain their insights on approaches to project management, cycle times, etc. "If companies in other industries are able to accomplish tasks just as difficult as the one facing Grünenthal and achieve success in even shorter time frames [than the typical 6-8 years for drug development], then so can we," he says.

At the beginning of the project, the team was measuring progress in months, first reducing the backlog to being only four months behind, then three, and eventually two. "All of a sudden we were at zero," Langner states. "In the beginning, nobody believed this possible, but we really adopted a can-do mentality." The end result was successful completion of the project on the last day at 12 noon. "This was a very important lesson for our organization," he shares.

How did they do it? First, the project was planned down to the last detail, and for each the critical path was analyzed. "We looked at literally everything: What is interconnected and in which way? Where are synergies, and how can these be used to speed up the timelines?" he shares. For each of these details, the time-critical steps were identified and intensely monitored. The progress of every detail was evaluated with a traffic-light system, and in the weekly meetings, everything – literally, everything – came to the table. "Sometimes these meetings were rough, of course; however, this approach created very high transparency, and we immediately saw if one activity was delayed, which other activities were affected. This was helpful also for prioritizing our actions," Langner explains. "It was also important that the team understood that this exercise was not meant as finger-pointing, but to ensure we can address delays quickly so the whole project was not in danger." Understandably, this process created a lot of emotions and pressure that needed to be managed. However, as the red traffic lights began to turn more to yellow and green, the team saw their commitment and personal engagement was paying off.

If you face a similar prospect of having to make the impossible possible, Langner has some words of wisdom. "As early as possible, look for the most critical steps that could derail the project's timeline, and pay close attention to them. Next, test and train your people. While my colleagues and I were familiar with project management, we had never undertaken this complex of a task before." Another piece of advice from Langner is to have a good project monitoring system in place. However, his most important tip, "You need a project lead who is willing to step on people's toes and be outspoken when things are not getting done." While you can probably find people like this within any organization, you are setting them up for failure if you don't empower them. It is important that they feel comfortable telling you, your boss, or even your boss' boss when someone on the team isn't pulling their weight on the project. "If you involve the people in the process, if the process is transparent and solution-oriented, if you manage emotions, celebrate milestones and if you are visible and approachable to everyone on the team, you can make it," he concludes.

But King noted it was also important to align with a company that "couldn't lose our product [Zalviso] in a sea of other products." Though the deal may seem small by Big Pharma standards — $30 million up front and potentially $220 million more in development, regulatory milestones, and rights to Zalviso in Europe and Australia — for a company the size of Grünenthal, this demonstrates not only a very significant commitment, but also a strong willingness to partner in R&D.

YOU CAN STILL TINKER WITH OPPORTUNITIES

It should be clear by now that Grünenthal is a pain company, first and foremost, that is seeking opportunities which build upon that competency or are adjacent to that area. Nevertheless, Langner contends that being strategically opportunistic does not mean being chained to your core. For example, Grünenthal has been in business in Latin America since 1968. About one year ago, the company nearly doubled its revenues in Latin America by acquiring Empresas Andrómaco, a Chilean company. "The acquisition of Empresas Andrómaco enriched and matched our portfolio that already included gynecology and CNS even before the acquisition. We now have more than 400 products — including oral contraceptives — in Latin America." In Europe, however, Grünenthal divested its gynecology business because of generic competition.

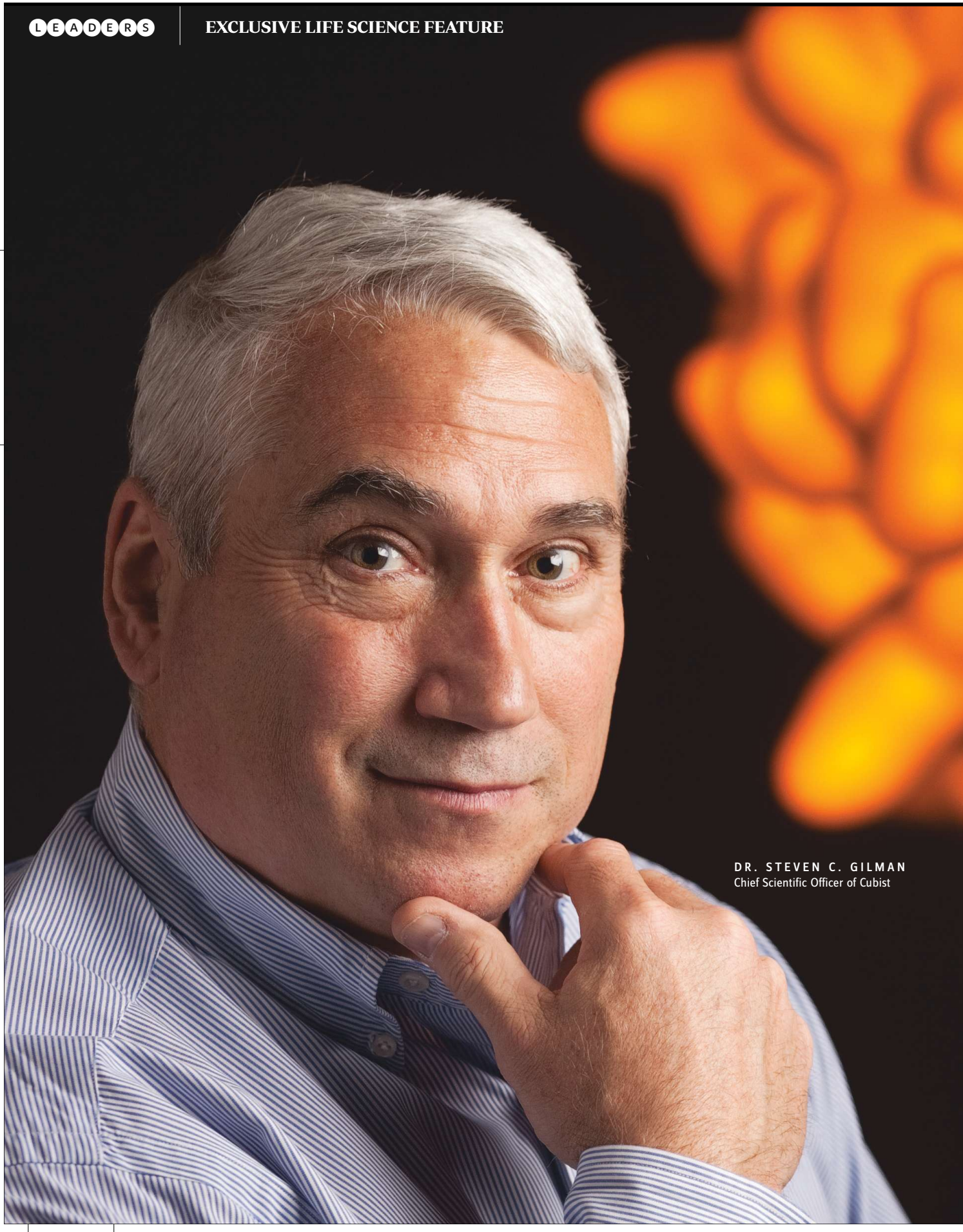
In other words, don't be so true to your core that you aren't open to tinkering with innovative opportunities. "When evaluating opportunities, the standard approach is to always focus on risk," Langner says. "But don't let risk overshadow how you assess an opportunity. Yes, you need to be confident that you can develop compounds in areas of opportunity, but you don't necessarily have to do so alone." To help foster this concept, Langner drove for the creation of the company's innovation medicine's unit (IMU). "The purpose of the IMU is to help us establish R&D entrepreneurial networks for assessing early-phase opportunities. We use the IMU to help find people outside our organization who can help with things like clinical profiling or the development of a biomarker that does not yet exist," he explains. The IMU consists of five people charged with identifying and assessing new late-stage discovery or early-clinical development opportunities from the external innovation community. "In creating the IMU, we wanted to bring a biotech atmosphere to Grünenthal — doing things fast and with a very senior, empowered, decision-making team," he explained. Started in 2014, Langner feels it is still too early to reveal the progress of the IMU. However, he is pleased thus far. "The IMU has been active in helping facilitate collaborations in Europe," he attests. "But we are also quite active in the U.S., interacting with potential partners in the San Diego and Boston areas."

One of the unique benefits afforded Grünenthal's IMU is the company's geographic location. Located in Aachen, in the western part of Germany, the city places Grünenthal in what is referred to as the North Rhine Westphalia — one of Europe's densest regions for research networks and nonuniversity research centers. "We are closer to the countries of Belgium and the Netherlands than we are to the German cities of Frankfurt or Berlin," Langner says. "We are at the heart of an entrepreneurial enabling ecosystem."

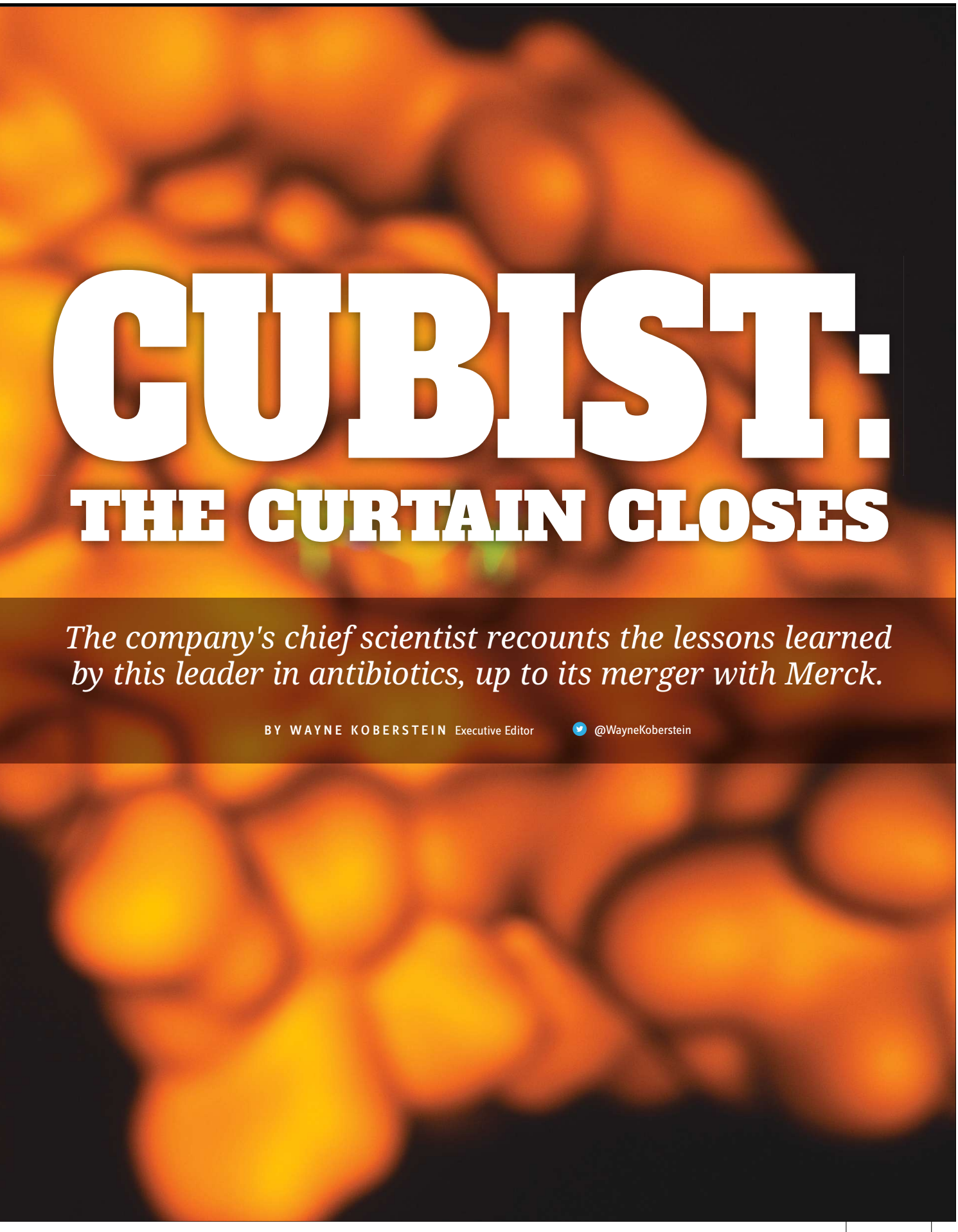
As Langner and I conclude our discussion and ready ourselves for our next meetings, I am struck by an American saying made famous by Mark Twain, "Actions speak louder than words." Interestingly enough, the saying is very close to the German proverb, "Taten sagen mehr als Worte," which translates to, "Actions say more than words." More than Langner's words, it is Grünenthal's actions which bode well for this midsize company's entrepreneurial, networked, and partnered R&D future. L

CUBIST: THE CURTAIN CLOSES

By W. Koberstein



DR. STEVEN C. GILMAN
Chief Scientific Officer of Cubist



CUBIST: THE CURTAIN CLOSES

The company's chief scientist recounts the lessons learned by this leader in antibiotics, up to its merger with Merck.

BY WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

The news gets better and better — right until the end. Such is the in-a-nutshell version of the story of Cubist Pharmaceuticals. In the spring of 2014, a year in which the famously independent company would score new drug approvals and acquisitions of its own, early signs of its demise began to appear.

In retrospect, the scenario seems familiar. The future CEO joined the board in April, and by late fall the board accepted a tender offer. By the end of the year, the company's fate was sealed but still uncertain in at least one respect: would it maintain its identity as Merck's wholly owned subsidiary or ultimately meld away into big-pharma Merck (MSD, outside North America), having left its indelible mark on the history of antibiotics?

"The merger certainly was not a planned event," says Cubist's chief scientific officer, Dr. Steven C. Gilman. "We have always operated with the mindset that the best way to create value for shareholders and patients is to run independently, and we have never put a 'For Sale' sign on the company. Obviously, our board has a fiduciary responsibility, and we cannot choose the time when a company will become interested in us, but we have to do what's right for shareholders under our fiduciary duties. Merck has been clear this is a value-driven deal to provide new therapeutic options for patients in the future. We believe Merck will keep the Cubist mission and our drive to provide new antibiotic therapies, and we'll see how that plays out over time."

In December of last year, the looming deal makes Cubist's announcement of another FDA approval — for Zerbaxa (ceftolozane/tazobactam), a treatment for "complicated," Gram-negative urinary tract and intra-abdominal infections — sound simultaneously proud and poignant. (See also "Zerbaxa — A Launch in the Limelight" on page 30.) We accepted an offer at that time to speak with Gilman about the approval and the significance of the product. But as context, we also discussed the acquisition from the larger perspective of Cubist's origins, strategy, and accomplishments over the years.

A LITTLE LIGHT HISTORY

Cubist began two decades ago with the mission to address a need that had become almost completely neglected by the large pharmaceutical companies. With a drug it licensed from Lilly, the company set out to navigate the development path from start to finish independently and with the determination to fully integrate itself into a commercial entity. Despite some notable setbacks, it succeeded well — well enough, indeed, to eventually attract a Big Pharma's attention.

When I asked Gilman to describe some key hurdles the company had overcome and lessons it had learned, his answer was interesting — and especially rewarding to this journalist. Coming up with a novel query is the writer's dream.

"I can't say I've ever had that question," says Gilman. "Probably the first big hurdle was the failure of our 2002 Phase 3 trial in pulmonary infections for the compound that would become our chief product, daptomycin [Cubicin]. We actually spent a lot of time and drove a lot of science around why that was, and that was very helpful for us and to others. Now researchers use the information we generated to make sure drugs they are developing will have a good chance of working in pulmonary infections. It is a good example of how we worked very diligently to ensure our science translated into benefits at the patient level."

"We need to question old pricing models because they are based on the incorrect assumption that antibiotics should be cheap and easily available."

DR. STEVEN C. GILMAN
Chief Scientific Officer, Cubist

Another hurdle Cubist learned to overcome was the typical, relatively slow ramp-up of sales for new antibiotics. "Despite investors anxious for the next quarter's earnings, we had patience and stayed the course," Gilman says. "With hard work and good products, you make the appropriate return, and shareholders will ultimately be satisfied. Sometimes it comes quickly, and sometimes it doesn't. But our science is about patients and patience — the actual patients, who are treated with our drugs; and patience, the persistence and perseverance it takes to develop our drugs. Our focus on science, patients, and patience has helped us build a now 20-year-old company."

Gilman sees the work of Cubist as trailblazing for companies, large or small, traversing the field with a new generation of antibiotics. "The whole industry has benefited, not only because of our success as a company acquired by another company, which generates a certain amount of buzz in the industry. We have spent a lot of time and effort working very closely with the FDA to create new policies and guidances that have streamlined some antiquated regulation, so now all companies' ability to develop antibiotics going forward is clearer and more defined." He notes Cubist's active role in contributing to the GAIN (Generating Antibiotic Incentives Now) Act of 2012, which offers incentives to stimulate overall industry growth in new antibiotics R&D.

LOOKING OUT

Contrary to the stereotype of a life sciences start-up lacking a sophisticated business team and inwardly focused only on its technology or product, Cubist needed to be outwardly focused only on its therapeutic area from the beginning, if it were to have any chance of being successful in the antibiotics space. Besides reaching out to the regulators, the company took time looking at the actual medical needs in the practice arena — not only of patients and practitioners, but also payers, key opinion leaders, and policymakers.

Similarly, as Cubist settles into its new subsidiary status, Gilman sees shared challenges for Merck and other new-antibiotics developers. The first set is scientific. "Only two novel classes of antibiotics have been discovered, both of which are represented in our portfolio: daptomycin is a lipopeptide, and tedizolid phosphate [Sivextro] is an oxazolidinone. We are trying to find

ZERBAXA — A LAUNCH IN THE LIMELIGHT

Just as Merck's acquisition of Cubist hit the veritable newsstands last December, the to-be-acquired company accomplished another FDA approval, for its new Gram-negative antibiotic Zerbaxa (ceftolozane/tazobactam). Cubist's long-time chief scientist at the time of the product's approval is Dr. Steven C. Gilman. He says Zerbaxa rounds out the company's fight against drug-resistant bacteria with the first antibiotic approved by the FDA in the U.S. under the GAIN (Generating Antibiotic Incentives Now) Act to address certain serious and resistant Gram-negative strains:

"Cubist has taken the charge and has worked quite diligently to come up with new therapeutic agents for certain Gram-positive and Gram-negative bacterial infections. With products, such as Sivextro (tedizolid phosphate), approved earlier in 2014, and Cubicin (daptomycin), on the market for more than 10 years, we have very significant agents against Gram-positives, but the emergence of resistant Gram-negative pathogens has been quite significant. Zerbaxa is the first new approval for drugs effective against drug-resistant Gram-negative pathogens under the GAIN Act of 2012. Zerbaxa is also the first of the Infectious Diseases Society of America's (IDSA) 10 x '20 Initiative, which in 2010 called for the development of 10 new antibiotics by 2020, to address certain serious and resistant Gram-negative bacteria. Zerbaxa is now approved in the United States for two indications, complicated urinary tract infections and complicated interabdominal infections, which are generally administered by IV in the hospital often to patients infected with drug-resistant pathogens; so we believe Zerbaxa will be a significant new addition to the physicians' armamentarium. We are now watching the drug's performance as we deliver it to the U.S. population with serious infections by multi-drug-resistant pathogens.

"We believe Zerbaxa therapy will help patients get out of the hospital more quickly, and, of course when you do that, you can save healthcare costs. Generally speaking, when you're infected with a drug-resistant pathogen but inappropriately treated, the duration of your hospital stay can double. The hospital costs can be double, and the risk of death is sometimes double, depending on the indication and whether the patient is infected with a drug-susceptible pathogen."

additional classes, and that is always challenging, but with drug-resistant pathogens and mechanisms changing all the time, there's always a need to stay one step ahead of the bacteria. There are also certain pathogens, such as Acinetobacter, that many drugs don't cover yet. And there are certain other holes in the armamentarium that scientists will be working on over time."

Antibiotics also continue to carry business challenges, and Gilman sees the need for additional incentives beyond the GAIN Act. "We need to question old pricing models because they are based on the incorrect assumption that antibiotics should be cheap and easily available. Most of the inexpensive antibiotics don't actually work against the most problematic pathogens nowadays."

Postmerger plans are short-term for Gilman at the time of our interview just before year's end, with the rest of the Cubist top-management team now mostly replaced. He is still discussing his future with Merck but wants to make sure he does everything possible to help in the transition, including the launch of Zerbaxa in the United States and its regulatory approval in Europe. His parting words likely capture the sentiments of the entire Cubist community as their company changes hands.

"We are proud to have built a significant company with multiple products, particularly now with Zerbaxa approved — a very exciting event, of course. We are proud to have built a company that's helped so many people, and we are looking forward to continuing that mission in the new arrangement with Merck."

We ended our conversation with hopeful wishes for the new year, knowing events will continue to unfold in unpredictable ways by the time this article is published. But those developments will play out in the context of this unique venture that stepped in to fill a gap in Big Pharma R&D and thereby opened new territory now drawing the industry back to a pressing medical need. L

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SUCAMPO'S DECLARATION *of* INDEPENDENCE

Scale-up continues long after start-up with this small but fully integrated company.

BY WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

PETER GREENLEAF Chief Executive Officer of Sucampo

Signing a deal can seal your fate. An exit for your investors may mean the end of your dream. What if you decided to forego the exit route, leapfrog to an IPO, and use commercial partnerships to fuel your scale-up into a fully integrated biopharma company? For an example in progress, look at Sucampo — a still-small company with two FDA-approved products, many more in the pipeline, a healthy balance sheet, and a commitment to maintain its long-term independence.

Heading Sucampo is CEO Peter Greenleaf, a biopharma veteran previously featured in these pages when he was president of MedImmune. (See "Antibacterial Drug Discovery And Beyond," July 2011.) Greenleaf left MedImmune in mid-2013 following a management restructuring by AstraZeneca and a tenure as head of Latin America. He says he wanted to reclaim the entrepreneurial spirit of leading a small company still in charge of its own fate. After a short stint helping the tiny start-up Histogenics, he went to a company where he saw the potential for growth with a go-it-alone strategy of full integration, joining Sucampo in March 2014.

At that time, Sucampo was already marketing the product Amitiza (lubiprostone) globally through partners. Amitiza is a chronic-care drug for chronic idiopathic constipation, irritable bowel syndrome with constipation (IBS-C), and noncancer opioid-induced constipation (OIC) in adult indications. The company was also developing other medicines in a potentially huge area of gastrointestinal (GI) therapeutics that could power its next stage of growth.

At the time, Sucampo also marketed Rescula (unoprostone isopropyl) for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. But under Greenleaf, the company has decided to terminate its promotion of Rescula in glaucoma, turning its attention to diversifying its pipeline into other high-value areas, starting with gastroenterology and ophthalmology, and to new modes of action that will move the company beyond its current prostone platform. Prostones are compounds derived from functional fatty acids that act as selective ion channel activators, according to the company.

Sucampo's story of independence is also one of repeated scale-ups. It covers all stages and issues in company development, from basic start-up challenges such as funding and finances, to best practices in managing partnerships, running virtual operations, removing drains on resources, and applying business-wise leadership in a small-company, science-driven environment.

BACK TO BASIC FUN, ONWARD TO ACCOUNTABILITY

When MedImmune began to operate less independently, melding into the AZ corporation, it was the third such experience for Greenleaf. Prior to his nine years at MedImmune, he was leading a commercial team at Centocor when J&J acquired it and working at Boehringer Mannheim during its acquisition by Roche. He sees the mergers at least partly in a positive light; the new parents helped the acquired-company organizations scale up to commercial capacity. But for Greenleaf and others who helped build the formerly independent enterprises, life in a large corporation lacked the dynamism, sense of discovery, and sheer business joy of working in an entrepreneurial environment.

His move back to "little biopharma" was no simple replay of his previous career, however. In his past run with small-to-midsize companies, the pattern had been successful in moving pipeline products forward, making the company an attractive target for takeover, and terminating in an acquisition by some large company. The AZ/MedImmune merger awoke his determination to break out of the too-familiar cycle.

"I learned a lot in the transition process of MedImmune growing within AstraZeneca," he says. "But on the day they decided to integrate MedImmune into the larger entity, I wanted to move on and go build another pharmaceutical company as the leader of that organization."

Greenleaf had been observing Sucampo since his time at Centocor, with a special interest because of Sucampo's base in Maryland where he has worked and lived for years. "Sucampo had a great foundation and a heritage built on strong scientific innovation," he says. "I knew about the development of Amitiza, and I'd been following the science. I knew a lot about the founders, Dr. Ueno and Dr. Kuno, and their philanthropic work here locally. I also knew the company had received heavy investment during the eight years since going public, but had not done much of the work needed to take it into the broader sphere. So I joined the company to raise it from the classic stage of scientific founders doing a start-up to the next stages of scaling, growing, and building a basic company architecture strong enough to support further growth."

Sucampo had already made some big strides from the start-up line. Greenleaf walked into a company with marketed products and a development pipeline. The company also had, and still has, exceptionally healthy financials for a development-stage company, he says. "We are bringing in around $100 million a year in revenue, and we carry very little debt. We have a very lean infrastructure. We still operate very much like a small start-up environment here, with less than 100 employees globally. And we have a passionate and innovative culture, much like a start-up. Our people are entrepreneurial, wear many hats, and are close to the pulse of the organization."

As the new leader, Greenleaf took hold of a company he saw as a basically sound ship and steered it in a new direction. He says some of the company's advantages were also the source of its main challenges. For example, because it had marketed products, its pure R&D culture had given way to a more commercial perspective. Full integration into commercial activities, as well as prolonged IP litigation, had also spread the company's resources thin.

"Over time, the company had taken on many battles across multiple fronts," he explains. "So establishing a central focus was absolutely crucial for the organization. In examining our strategy, it became clear that we needed to rebuild many areas of the company with new capabilities and world-class scientific leaders and

to secure some of the basic fundamentals in our financials." (See "Sucampo's Industry Brain Trust" on page 36.)

As Sucampo gathered management expertise, it dealt with IP and generic challenges to Amitiza by resolving lawsuits with Par and commercial partner Takeda — although, as partners, Sucampo and Takeda filed a patent infringement lawsuit against Dr. Reddy's late in 2014. Having passed one major IP hurdle, Sucampo entered 2015 with good revenue growth from Amitiza and a new deal in which Takeda will market the product globally.

Sucampo had thus exited "dilutive" activities, offloading its commercial work in sales and marketing through the partnerships, and focused on strengthening its pipeline. Greenleaf says his company also found ways to increase its margins on Amitiza not only through better financial management, but also through some key manufacturing and supply agreements for a lower cost of goods.

With a more-efficient and less-troublesome commercial setup in place, he says the company could then put more attention back into its drug-development function. "We wanted to ensure our development programs are not just carried forward, but also pressure-tested — with clear deliverables communicated externally in a very transparent way and for which we hold ourselves accountable. We will buffer, augment, and build up the pipeline with new science, bringing in a diversified approach to different therapeutic areas. Then, as our revenues grow and the pipeline becomes richer, hopefully investors can see the benefit of our efforts, the company's market cap will increase, and we can do even more transformative deals."

FROM COMPETITION TO COLLABORATION

A basic lesson in partnership lies beneath Sucampo's resolution of litigation filed by the company's former management against partner Takeda. In Greenleaf's view, ending the conflict over Takeda's commercial efforts for Amitiza was essential.

"Partnerships are pervasive in the pharma/biotech space; we live and die by our partnerships, and when you sign up with a partner, you make a long-term commitment. The goal should always be to make your partnerships work. In the rare occasion one is not working — and during the 20-plus years I've been in the industry, I've not yet experienced it — you end up sitting across the table from lawyers. It's better to try to drive your partnerships through alignment, by working together toward common goals."

Greenleaf put the Takeda alliance at the top of his agenda for his first 30 days in office. "I told the team that Takeda was critical to our current and future success, and we're going to make the relationship work." By the end of the first two weeks, he was on a plane to Japan to meet with

CEO Yasuchika Hasegawa. "Since then, we have rebuilt our relationship from the bottom up and the top down, and I do not think we would have been successful in signing the multiple agreements we did with Takeda without having done that basic building-block work."

One of the basic building blocks was simple trust, says Greenleaf. "Takeda is a global pharma company with presence in countries around the world. I believe that they have done a good job with the product Amitiza in the United States. They know the product inside and out, and our partnership has never been better. Takeda is the right company to take a product like Amitiza forward in the global markets, and we are excited not only about the extension and the expansion of our agreement, but also about how our relationship evolves in the future."

THE FOCUS INTERNAL

In addition to the changes with Amitiza, Greenleaf and his team saw other opportunities to shed resource-draining activities, such as the direct selling of Rescula in the United States, which Sucampo made the decision to terminate in the third quarter of 2014. The move reflected an overall strategy to focus more resources in development on the highest contributing areas, but Greenleaf says it also just made sense based on the "pure math" of cost versus revenue.

"Rescula was late in its life cycle. The market had significantly moved beyond the treatment of IOP associated with glaucoma. Most of the leading brands are either used in combination or are generic, and we had tried our best to sell the product through the infrastructure we built around it. But in the end, we were not able to sell enough product to make a decent return on investment, so we decided to try to find a partner who could leverage Rescula along with other products in its portfolio. It doesn't mean we will partner all future products, but right now it is better to use those resources to focus on maturing our pipeline."

Some advantages of being a commercial company with the sales burden largely partnered are obvious: positive revenue, ROI, and R&D resources. Of course, all of them are rare among small companies at the development stage, for whom operating at a loss is the normal mode. Greenleaf observes how investors have different sets of criteria for commercial and development-stage companies.

"A commercial company is examined for revenue, cash flow, profit, sales trends, and other objective factors. But investors look at a development-stage company by such terms as its product's market size, impact on the competitive set, and options for acquisition, as well as how to develop the company's valuation. Sucampo has the best of both worlds: inflow of resources to fund the pipeline without doing multiple dilutive rounds through investors to raise capital, and leveraging of resources through partnerships."

Greenleaf defines his main goal as leading the company and its investors toward large-scale growth and full integration. "We will have multiple products available in multiple therapeutic areas, significantly solving unmet medical needs and giving back significantly to our shareholders. As we evolve and revenue grows, we will always invest in the pipeline, but when we get a product that gives us a high enough rate of return, we will consider moving back into the commercial space."

PIPELINE EXPANSION

The next challenge for Sucampo is delivering on its pipeline-development strategy. Greenleaf is confident the company will succeed in maintaining the flow of new products in a timely way, following a practical strategy of short-term product acquisition and longer-term pipeline development.

He elaborates: "Securing Amitiza and its revenue, while ensuring it grows several million dollars during the next five to ten years, is critical. Most of our pipeline is about three to five years out, so any external deals we do will probably fall within that same window. Our hope is to have multiple shots on goal — and to produce new products over the next three to five years that replace the current and growth revenue of Amitiza."

Two other key parts of expanding Sucampo's product portfolio are widening its therapeutic focus and moving beyond its hitherto exclusive reliance on prostones. Both are essentially further steps in scale-up, requiring new investment and resource management as have other pivotal points of growth in the company's past.

"When we stopped doing Rescula's marketing, we did not simply take all of those freed-up resources and drop them to the

SUCAMPO'S INDUSTRY BRAIN TRUST

When Peter Greenleaf joined Sucampo as CEO in the spring of 2014, one of his top priorities was to beef up the small, mainly virtual company's management team with industry-experienced leaders. By fall of the same year, he had hired Peter Kiener, D.Phil., as its CSO and two other new executives for the management team, Matthias Alder to head business development and licensing and Steven Caffé, M.D., to run regulatory affairs. Another past MedImmune alum, Kiener came to Sucampo from his CSO position at Ambrx and had been president and cofounder of start-up Zyngenia. Alder hails from numerous small biotechs, and Caffé has a Big-Pharma and specialty-pharma background, having held key positions at MedImmune, Baxter, Sanofi, and Merck, as well as AMAG Pharmaceuticals.

bottom line," says Greenleaf. "We shifted resources from commercial activities to development capabilities, using them to build a strong clinical operation and medical organization and to establish internal processes that prosecute, monitor, measure, and manage the pipeline through the entire development process."

For the four prostones in the pipeline, mostly designated for indications in the company's core areas of gastroenterology and ophthalmology, the company also has earlier programs in supportive-care oncology and lumbar spinal stenosis. The supportive-care indication is oral mucositis caused by radiation and chemotherapy in patients with neck cancer. The lumbar indication is to alleviate the pain and disability of stenosis with a "proprietary ion channel activator." Sucampo has also stated its readiness to bring nonprostone drugs into the pipeline, which will take the company out of its comfort zone, into new MOAs (mechanism of action) — yet another way to scale up.

INTO EMPTY SPACE

Besides bulking up its product portfolio, Sucampo also plans to grow through expansion of its main commercial product into the huge unoccupied spaces of the GI market. New geographic markets, new indications, and new formulations will continue to unfurl for Amitiza.

Competition in such a large potential market for Amitiza in constipation also accelerates rather than impedes expansion of development, adoption, and use of the product, in Greenleaf's view. "The space in constipation is really wide open and undeveloped, and the majority of solutions are either over-the-counter, acute-use treatments or prescription-based generic acute-use treatments, for which tens of billions of prescriptions are written every year. Right now, innovative new products only account for a single-digit percentage of that market."

Sucampo and its competitors with innovative constipation therapies, such as Forest/Actavis and Ironwood with Linzess (linaclotide), have used patient and doctor education to create a rising tide that lifts all boats, he says, and adoption of the newer drugs is on the rise. "It would be wrong for us as innovative companies at this stage to focus on fighting each other when we are the minority of the market, and I believe all of the companies coming into this space with new solutions recognize that. A product that provides a more consistent solution and one that's been studied as a chronic solution, though it will take time to turn a market, is a better solution for patients."

THE FOCUS EXTERNAL

Greenleaf says the big picture of the market and the small-frame view of Sucampo and its products overlap. As competition drives market expansion for Amitiza, for instance, it will eventually put pressure on companies in multiple ways. More price competition will force more price-matching, negotiation with payers and managed care organizations, and adjustments in the product's cost structure. "We will be forced to continue to look at better ways to modify cost of goods and operations and how we bring new products to market through our manufacturing processes," he says.

Sucampo, its partners, and its competitors will also need to influence perceptions in the market about the disease and its treatment. "We need to continue to build awareness of the disease burden around constipation in general and make sure it is no longer qualified as a lifestyle problem, but truly as a problem with associated challenges. Patients miss work, live their lives in pain, and bear other consequences of constipation."

Like many start-up and scaling-up life sciences companies, Sucampo is challenging its own market with innovation. Perhaps its greatest advantage in developing further innovative treatments is its disruptive presence in the marketplace. Many small companies are now learning the benefits of venturing out early in development to visit their would-be customers. Sucampo already now occupies a space reserved for players, and according to Greenleaf, it will hold onto that space and continue to scale up its business — as an independent and free agent.

How An Executive's Health Challenges Can Make A Biotech Stronger

BRAD THOMPSON, PH.D.

Brad Thompson, Ph.D., is president and CEO of Oncolytics Biotech Inc., a Calgary-based biotechnology company focused on the development of oncolytic viruses as potential cancer therapeutics.

As the CEO of a biotech company since 1994, people often ask what has kept me focused throughout my 20-year (and counting) tenure. Aside from my firm belief in the value of the cancer treatments we are studying, there is another motivation: a personal experience with this terrible disease.

The year I assumed my current position at Oncolytics Biotech, my mother died of lung cancer. That was one year after I had an early-stage melanoma removed from my leg. As the chief executive of a company devoted to cutting-edge cancer treatment, these personal experiences have naturally strengthened my resolve to seek better solutions for patients. But they have done more than this: they have also given me the chance to think about the various ways an executive's past or present health issues can positively mold a company.

I can attest that a firsthand experience with serious illness — either your own or that of a family member — can provide unique insight into the plight of a specific patient population. Experiencing my mother's ordeal up close, and sharing with my family the anguish of being unable to find an adequate treatment for her, has allowed me to empathize more effectively with the cancer subjects enrolled in our clinical trials. I know how important it can be to seek a treatment that might extend a loved one's life, for any amount of time. Objectively, that difference might not amount to much, but subjectively, every day spent with a loved one with a terminal illness is a triumph.

Full disclosure about your illness is vital, and I've been completely open about my own brush with melanoma. Doing so can have multiple benefits. Most obviously, investors and employees alike will respect you for your honesty. Just as important, if you have been lucky enough to make a full recovery, as I did, they will be reassured that you are actively taking care of your health — so that the company is in good hands today and is likely to continue to be securely managed in the upcoming months and years. A physically fit leader is better equipped to handle the rigorous demands placed upon them. By sharing your story, you might also inspire your employees to look after their own health better — with obvious benefits to the company's health as a whole. Personal health absolutely influences professional performance.

When Warren Buffett publicly announced his cancer diagnosis in April 2012, he did so with characteristic courage and class. Even so, he made a preemptive strike at controlling the message before news of his illness could manage to leak out and be sensationalized. And when Herb Kelleher, the former CEO of Southwest Airlines, chose to disclose his treatment for prostate cancer, he actually made quips about his illness

"I can attest that a firsthand experience with serious illness – either your own or that of a family member – can provide unique insight into the plight of a specific patient population."

and the fact that his staff would be disappointed that he wasn't travelling more. Upon the "bombshell" announcement that he was sick, the company's stock stayed steady.

PERSONAL EXPERIENCE WITH ILLNESS CAN BE HARNESSED TO PRODUCTIVE ENDS

Additionally, personal experience with serious illness can not only allow biotech executives to shape their own company positively, but also allow them to serve as thought leaders for the field as a whole. For example, Neil Fowler, CEO of the small biotech Liquidia, was diagnosed with a tonsil tumor and was successfully treated. He used this experience to publicly voice his support for the wider development of Gardasil, a human papilloma virus vaccine that some believe might prevent the form of cancer he had from ever developing.

A serious illness can even spur a biotech executive to discern shortcomings in the healthcare system and work to address those issues. Consider Myrtle Potter. She had already successfully served as president and COO at Genentech, president at Bristol-Meyers Squibb, and vice president at Merck, when one night in 2005 she began slipping into a coma at home. Rushed to the hospital, she ended up with a failing liver and lungs as well as total kidney failure. Toxins flooded her body, and she lost close to 30 pounds, more than half her hair and even some skin. She spent a year recovering from what turned out to be a severe allergic reaction to a medication.

Harnessing this experience, Potter started two companies to help deal with gaps in healthcare — Myrtle Potter & Co., a B2B healthcare company, and Myrtle Potter Media Inc., a company that helps consumers navigate the U.S. healthcare system. She has established herself as a healthcare expert through her online content and media appearances, providing patients with practical information from how to get the right insurance to how to have a dialogue with their doctors. Now, that's turning a near-tragic outcome into a productive result.

Conversely, keeping your past health challenges a secret only runs the risk of having an intrepid reporter dig for the facts and spill the beans publicly — which won't be good for your reputation or, potentially, your company's bottom line. Even though Apple remained an industry leader through the period of illness and untimely death of Steve Jobs, the secrecy and obfuscation surrounding his cancer was criticized by numerous industry and media observers. Many ailing executives might be tempted to resist divulging a serious illness because they fear a loss of power, but current and potential investors have the right to know what's going on.

A biotech executive's personal experience with health issues isn't always completely negative. Instead, they can harness these experiences to make a company stronger. L

The R&D Tax Credit — A Catalyst For Life Sciences Innovation

YAIR HOLTZMAN

Yair Holtzman, CPA, MBA, MS, is a partner at Anchin, Block & Anchin LLP. He is the practice leader of the R&D Tax Credits Group, Life Sciences Industry Group, and Chemicals and Energy Industry Group.

Does your company develop new medical products, pharmaceuticals, or innovative production techniques in the United States? Does your company create software for the medical industry or for internal discovery or diagnostic tools? Does your company invest resources toward optimizing manufacturing processes? If so, your company may qualify for the Research & Experimentation Tax Credit (or the R&D Tax Credit), an often overlooked and misunderstood opportunity for taxpayers. The CEO at one of our longstanding clients, a New Jersey medical device company, champions the research credit as "the best way to refuel my innovation engine."

In 2011, a total of more than $9 billion in R&D tax credits was claimed by taxpayers around the United States. The tax credit can be used to offset income tax liabilities dollar for dollar, thereby lowering a company's effective tax rate and increasing cash flow. A pharmaceutical company client of ours with sales of $300 million claimed a federal credit of $500,000, as well as New Jersey and Iowa state credits totaling $500,000, which will enable them to substantially increase their R&D efforts going forward. Another client, a medical devices company with revenue of $10 million, was able to obtain a $100,000 federal tax credit.

For companies in net loss positions, the R&D credit can be carried back one year and carried forward for 20 years until it can be used. In addition, similar credits and other incentives are offered by 38 states, six of which offer refundable credits to attract new jobs and industries to the region. The research credit is more important now than ever before, as companies are pressured to improve their earnings per share and ROI in the face of increasing expenses, heightened regulations, and lower reimbursement rates.

Examples of typical qualifying activities in the life sciences industry include development of new or improved drugs, medical devices, diagnostic applications, and production techniques. Costs that can be considered for the credit include in-house wages of employees performing, supervising, or supporting the research activities. Also considered are costs related to supplies used or consumed during the development, as well as a percentage of contractor and consultant fees associated with the efforts. These costs encompass all phases of the development life cycle, from initial specifications and requirements to FDA approval. However, there are several areas that are often overlooked by taxpayers. In addition to revolutionary projects, the credit can be claimed for performing evolutionary projects involving products and processes. These initiatives may include increase in drug efficacy or stability of existing products; development of a new or improved production line to improve yield, purity, or quality; and other continuous improvement initiatives in a production or manufacturing setting.

One of the best features of the credit is that success is not a requirement. Even projects that ultimately fail can potentially qualify for the credit. After all, failure is the ultimate proof that a project involved R&D.

NEW INDUSTRY TRENDS AND HOW THEY APPLY TO THE R&D CREDIT

One way life sciences companies are combating higher development and commercialization costs for their products is through data technologies that increase productivity within their organizations. Companies are now mining information from tools in service, clinical trials, genetics, and demographics to perform analyses to gain insights on trials and new ideas while reducing costs by reaching conclusions more quickly. With the current proliferation of Big Data and cloud technologies, all companies have access to immense processing power to build models and generate analytics to create their next drug or device designs — or to scrap designs that don't meet standards. The costs related to the development of the data analytics

models and the personnel utilizing the data to make R&D decisions have potential to qualify for the research credit.

With recent data breaches and cyberterrorism cases, data security is now one of the major concerns for life sciences companies and governmental agencies such as the FDA, Federal Communications Commission, and Federal Trade Commission. In the FDA's recent draft guidance on software, emphasis was placed on ensuring confidentiality, integrity, and availability of information in medical software. The investments that companies make to further safeguard drug, device, and patient data is an area of opportunity for the research credit.

Consolidation among hospitals and insurers has made it necessary for a company to drive more than just marginal product innovation in order to justify product adoption. A strategy companies can implement to achieve higher product functionality and obtain reimbursement is to specialize in products incorporating service components, thereby offering higher quality of care at a lower overall cost for the health system. Development of these new integrated products and solutions can be technologically challenging and often requires expertise in areas such as material sciences, biochemistry, software, product strategy, design, manufacturing, materials selection, product testing, mold flow, failure effect and analysis, and predictive engineering. Work done by each of these cross-functional teams could qualify for the research credit based on its contributions to the final design. In different situations, a company may collaborate on research with outside institutions such as other corporations, college research labs, think tanks, and outsource organizations. The dollars provided to the company's collaborators may also qualify, subject to a review of the intellectual property rights and financial risk rules within the negotiated contract.

CALCULATING THE R&D TAX CREDIT

There are two methods for calculating the R&D Tax Credit; both reward taxpayers for increasing the amount spent on research over a base amount from earlier years. The traditional method (also referred to as the "regular" method) uses a base period from the mid-1980s if the company existed during these years. Under the traditional method, the R&D tax credit is equal to 20 percent of qualifying expenditures in excess of the base amount. The alternative method, called the Alternative Simplified Credit (ASC), became available in 2007. The ASC method uses the average qualifying expenditures from the three years prior to the credit year as a base period. Under the ASC method, the R&D tax credit is equal to 14 percent of qualifying expenditures in excess of the base amount. The traditional R&D Tax Credit benefit can be higher than under the ASC, but the recordkeeping and income restrictions can be onerous and may make the ASC method typically more attractive for clients.

To substantiate the credit, a taxpayer should gather documentation that creates a nexus between the costs incurred and the activities performed. Examples of supporting documentation vary from company to company, but can include lab notebooks, specification documents, computer-aided designs, status updates, presentations, white papers, test results, patent applications, and emails. Establishing the connection between specific expenditures and research performed by the taxpayer fulfills the supporting documentation requirement. In addition, there usually is a minimally invasive interview process of key scientists and engineers for collection of additional support. The interview process of key personnel allows the taxpayer's accounting department or outside consultants to effectively marry up the tax law with the qualifying scientific undertakings.

A QUALIFYING R&D EXAMPLE

An actual example we had in our life sciences practice included a small pharmaceutical company that undertook a project to synthesize a chemical compound and improve the related chemical synthetic processes. The compound was intended to be used to treat breast cancer that is advanced or has metastasized. The optimal synthesis pathway that would optimize yield and purity and the ability of the company to successfully implement the synthesis were unknown. Additional challenges that were unknown at the beginning of the development, but which presented themselves during the process, included loss of material on drying, optimization of crystallization temperature to increase yield, and yield loss when incorporating a wash after solids isolation. All of the activities involved in this project were technological in nature and relied on synthetic organic chemistry and analytical chemistry. The development involved substantial laboratory work. After extensive analysis of the expenditures and interviews with the key scientists involved in the project, it was determined it qualified for the purposes of the R&D Tax Credit. The client was able to obtain $176,000 in federal credits and an additional $128,000 in state research tax credits.

R&D CREDIT OUTLOOK

Although the credit has been extended 15 times since its inception in 1981, as of November 2014 it has not been renewed for tax years beginning after Dec. 31, 2013. The U.S. House of Representatives has recently approved legislation (H.R. 4438) that would permanently extend and simplify the R&D Tax Credit, as well as raise the percentage used in ASC methodology from 14 percent to 20 percent. The U.S. Senate has also passed legislation (S. 2260) that extends the current R&D credit through 2015 and allows some start-ups to claim the credit against payroll taxes and allows some privately held companies' owners to claim the credit against their alternative minimum tax (AMT). Neither piece of legislation has yet been enacted. Taxpayers should do the minimum groundwork necessary now to make an assessment as to whether or not they can qualify for the research credit, so if it is extended or made permanent they will be well-positioned to take advantage of this powerful opportunity. L

The Rise Of Digiceuticals – Can You Afford To Not Get Involved?

ED MISETA Executive Editor @OutsourcedPharm

When Heather Bell hears the term digiceuticals, she can't help but think about transformation. "I think that mobile health [the use of smartphones, tablets, and other mobile computing devices to record patient information] has the potential to be profoundly transformative for healthcare," says Bell, formerly AstraZeneca's VP of program management in IT/operations and now Sanofi's VP of corporate strategy and emerging opportunities.

"I believe it will usher in a realm of predictive medicine, complete with what we might call digital biomarkers and digital drugs. While that may sound futuristic, some of these are already on the market today."

While a lot of the hype in this area is focused on large tech companies, advances in technology will also present opportunities for pharma companies. "Bringing mobile health technology to clinical trials will certainly empower consumers," says Bell. "Patients have access to more information than ever before, and mobile technologies have also given them greater access to each other. Finally, wearable sensors and the promise of continuous monitoring have given pharma access to new sources of data."

MOVING FROM REACTIVE TO PROACTIVE

Bell believes we currently live in a medical world based on reactiveness. When patients have a disease exacerbation, they go to the hospital or their physician. But she envisions a different world, one in which we have more thoroughly studied what it is like to live with the disease through the eyes of the patient. What if, through the process of continuous monitoring and mobile technology, we understand how these diseases are experienced and develop new insights into what it is like to live with them?

"We might discover that 10 days prior to a major episode in a depression patient, their emailing, texting, and phone calls drop off dramatically versus a baseline," says Bell. "We might discover that three days before admission to the hospital, a child with asthma will start wheezing in the middle of the night. If it doesn't wake them up, the child, their parents, and their physician would never know. But a mobile device sitting on their bedside table would note the event and code changes in their breathing."

Having that information would enable physicians to take preemptive action, provide medications, and possibly avoid costly and painful hospitalizations. This scenario is not as futuristic as it sounds. Bell references a Medtronic study from 2004 showing data obtained from pacemakers in heart failure patients. The data revealed patients had a dramatic drop in heart rate variability 20 days before required hospitalization. Not every patient has a pacemaker, but continuous monitoring is certainly moving the medical community toward a world of predictive medicine.

FILL IN THE DOTS BETWEEN VISITS

Bell cites Ginger.io as another example of where the industry is heading. The company has expertise in predictive algorithms and the management of Big Data. She references a chart from the company's website that plots national health measures against time, which she believes illustrates a major challenge that exists in medicine today.

A doctor will see how a patient is doing when that patient visits the clinic. But if a physician wants to know how that subject feels between visits, they have to rely on the patient's account of what has occurred. While helpful, it generally does not tell the whole story. "Ginger.io is trying to fill that gap with continuous data," says Bell. "Having that information gives the physician a much richer picture of where the ups and downs are for any patient."

Ginger.io has built the platform that underpins UCSF's healthy heart study, a largely digitally powered, epidemiological study of a million people's heart health. They are also enrolling individuals in studies on neurological disorders. If patients have depression or bipolar disorder, that study is capturing data on how much they email, text, and phone to establish a baseline.

TECHNOLOGY ADVANCES FROM NONTRADITIONAL SOURCES

When discussing advances made in wearable technologies, Bell gives a nod to gaming developers. Quality of life initiatives exist within companies like Nintendo that are attempting to bring better fitness apps to the gaming generation.

"These companies are outstanding at rapid prototyping, creating user-friendly interfaces, and having profound customer insight," she says. "Samsung is involved in a partnership with UCSF, co-running a lab to validate sensor technology that is expected to lead to better preventive health solutions."

Bell adds, "I think we can envision a world in which there are companies that know a lot more about diseases pharma is interested in, as well as the drugs we sell. Technology presents opportunities for pharmaceutical companies to reinforce the core drug business and move into new and different spaces."

USE TECHNOLOGY TO ENGAGE PATIENTS

One aspect of the advances in technology that has Bell most excited is patient recruitment via websites and social media. She references a partnership between Biogen Idec and MyHealthTeams to illustrate her point.

MyHealthTeams is a Silicon Valley-based start-up that provides "mini-Facebooks" for specific disease communities. For example, a patient with breast cancer can become a part of the MyBreastCancerTeam. Similar teams are in place for autism, multiple sclerosis, lupus, and more. The teams are only open to patients who have the disease or, in some cases such as autism, those who are caring for someone with the disease.

The user communities are highly engaged with an interest in clinical trials. The monthly active use rate for most groups is more than 50 percent, and it's not unusual to get an 85 percent response rate when querying members about relevant clinical trials. This allows sponsors to target their outreach.

Bell notes Biogen Idec approached patients on MyMSTeam with relapsing MS who were in the relevant age demographic and on an existing specified therapy (Beta-Interferon).

"Patients were sent an email asking if they would be interested in the trial and speaking with a screener," says Bell. "At that time, Biogen Idec's baseline for trial screening was five patients a week. Within 24 hours of sending the email, 35 patients had been screened. This ability to tap into an incredibly engaged population and get quick responses has been encouraging." L

Biopharma Looks Into The Supply Chain Mirror: We're The Problem

LOUIS GARGUILO Executive Editor @Louis_Garguilo

It's like a scene from a Brothers Grimm folk tale. One late afternoon at an industry conference, a cross section of biopharmaceutical leaders gather in a room to take a hard look into a large mirror. It reflects that they — not their suppliers or service providers, as was assumed — are culpable for, and thus can control, many of the product reliability problems in their supply chains.

According to Marla Phillips, co-chair of PharmaLink Conference and director at Xavier Health, "It was a sudden and profound paradigm shift."

The gathering is a culmination of months of investigation into these questions:

Why isn't the drug product supply more reliable, and why can't we assure greater consistency in product quality for patients?

Attendees from companies such as Boston Scientific, Cook, Eli Lilly, General Mills, J&J, Kroger, Merck, Meridian Bioscience, P&G, and Shire know the data is conclusive; in fact, the data is culled directly from the manufacturers themselves.

"I remember the meeting clearly," says Phillips. "The silence when we said, 'Your own data is showing you are causing the lack of reliability in your products.' Then you heard comments like, 'Oh my gosh, it really is.'"

Perhaps some comments said under breath were a bit more colorful.

David Lowndes, senior vice president of supply chain management for Shire, was there. For him, what we'll document in this article boils down to this: "The industry should achieve the same results in safety, quality, and availability from a fully outsourced supply chain as from a vertically integrated one. Patients, practitioners, and regulators expect nothing less."

INTEGRITY OF SUPPLY INITIATIVE AND GOOD SUPPLY PRACTICES (GSPs)

"Fixing the supply chain" is a topic where seemingly the amount written about it is inversely proportional to the amount actually done to improve it.

However, what is coming out of the FDA/Xavier PharmaLink Conference, specifically the discussion about a set of GSPs regarding the Integrity of Supply Initiative, is substantial and important. The data mentioned above was derived via rigorous research and methodology, including detailed cause-and-effect matrixes, Pareto analysis, failure-mode models, and scientific surveying techniques.

The GSPs, being drafted as this article is written, could become recognized by the FDA and regulatory bodies as defining practices for biopharma, food, and medical device companies. For suppliers and outsourcing service providers, this process should usher in improved client relationships and performance. For patients, it means a safer and more reliable drug supply.

The GSPs address three categories determined by the data as the drivers for change. First is *Supply Chain Development and Management*. There is a need for more rigorous supplier selection processes. Currently, even when implemented, they don't get followed. Manufacturers then spend years managing unqualified suppliers that shouldn't be in the supply chain to begin with.

The second is *Product and Process Knowledge and Development*. The assumption at the outset of the Integrity of Supply Initiative was that suppliers lack reliability and quality. Instead, it was discovered manufacturers don't understand their own specifications or processes well enough to predict the impact of material variances on final products.

As the title suggests for the third category, *Driving Ideal Behavior*, manufacturers exhibit negative traits vis-à-vis their supplier networks. One-sided supplier-manufacturer relationships need to change to the "partnerships" often talked about but not practiced. The Initiative recognizes suppliers play an integral role in the success of the final product and bring applied expertise throughout the supply chain. It also stresses manufacturers need strong internal alignment of

goals and measurements *before* engaging suppliers.

CATALYSTS: FDASIA, AND AN OIL SHOCK?

Xavier Health hosts two annual conferences: PharmaLink for biopharma and MedCon for medical device. Discussions at both identified the need for the Integrity of Supply Initiative. Lowndes of Shire sits on the governing board. "The overall initial driver and why I got personally interested was because of FDASIA [Food and Drug Administration Safety and Innovation Act of 2012]. Embarrassingly for our industry, the FDA has *legislated* for us to pay more attention to our own supply chains," he says.

He adds, "It was important when the FDA came out with a clear message regarding what they saw as the issues, and their desire to work with us. I think back to the PharmaLink conference when we talked about why FDASIA was being put in place, specifically Title 7 for the safety and quality of supply and Title 10 for drug shortages."

Both Lowndes and Phillips bring up another seminal scene that unfolded during a 2014 meeting of Initiative leaders. Norman McLennan, VP of supply chain at Sasol Petroleum International (U.K.), presented on his industry's best practices for working with suppliers.

"He brought the whole upside-down nature of the way we look at our suppliers to light," Lowndes explains. "Here's oil and gas saying they treat their suppliers as if they are dependent upon them and need to look after them. Meanwhile, we often behave as though the opposite is true, as if they should be glad to have us as customers even while we are dependent on their performances to meet the profound needs of our patients."

READY FOR A NEW ATTITUDE… AND MODEL?

Lowndes presides over a fully outsourced supply chain for some Shire products. PharmaLink was a vehicle to interface with the FDA and fellow biopharma companies, and a way to share best practices. He also wants to change the entire supplier-manufacturer business model.

According to Lowndes, the current model was created by "Big Pharma moving late life cycle products out of their plants to make space and harvest as much residual value as possible. The process is frequently led by a part of a procurement organization. CMOs get negotiated down to small margins for large quantities."

Unfortunately, this leads to a need to standardize production and relationships to drive efficiency. It might have worked in the past with high-volume products, but with the increasing demand for specialty

and rare-disease products, more flexibility and agility are required. "In the current model suppliers can't respond to specific needs driven by our products," says Lowndes. "They may have 40 other customers and can't customize for everybody. We've created a model that has CMOs trying to make one-size–fits-all offerings to meet demand and stay profitable."

The status quo is supported by "specs wide enough to drive a bus through." Lowndes says manufacturers must provide a better understanding of how higher variability on processes and material impacts products. "As it turned out from the surveys and investigation of the Integrity of Supply Initiative," he says, "we often don't even share what we are using the material for. This is one reason why we get product variability. *We* own the specs; it's not the supplier's fault."

SHIRE'S APPLIED SOLUTIONS

Lowndes says the three categories for the GSPs — product and process knowledge and development, supply chain development and management, and driving ideal behaviors — are "pretty logical when you look at them. You want to say, 'It's common sense!'" But common sense, it appears, in large part, is not practiced. At Shire, some of what will come out in the GSPs is already in place. Lowndes believes the foundation for a new model is greater product and process knowledge and development — shared between sponsor and manufacturer.

"Shire's batch failure rate [for an outsourced small molecule supply chain] has gone down from 2 percent to 0.35 percent in a few years. My understanding is that for small molecule products 0.5 percent [in a vertically integrated supply chain] is about best practice," he says.

Shire shares a knowledge management system with its biggest partners. There's an overnight exchange of data and trending to proactively address potential issues at the manufacturing site, including such things as operator variability.

"We can identify the probability we will fail batches and the drivers for any excessive predictive failure rates," he says. "That helps us and the supplier. When failure happens in the old model, it's just an economic argument about who is accountable."

Shire adheres to its stringent supplier selection criteria. (Although Lowndes says the ultimate benchmark is simple: "If the FDA walks in there, will they be happy?") Supplier development is also important. "Issues in the industry creep up as technology and standards evolve," he says. "We work with suppliers to ensure we keep pace." For example, Shire recognized that difficulties in hiring and retaining skilled employees were causing production problems at a supplier. Shire sent its HR team to help the supplier with its HR systems, and instituted programs for attracting, retaining, and training staff.

Lowndes says he's most proud of bringing together Shire's supply chain partners for its biggest products the same way as if it were an internal supply chain. "We review everything from quality to product strategy and goals. We look at product performance amongst various sites and help each other with challenges."

Last year Shire conducted a business continuity exercise assuming a part of the supply chain had gone down. Suppliers strategized on how they would cooperate to address the situation so that patients would not be impacted by a shortage.

And for a supply chain, it's the well-being of patients that counts most. "We've actually taken patients to our CMOs to share our motivation with all their employees," says Lowndes. "In the current transactional model, Big Pharma is more apt to take their procurement group to the supplier."

LAST CHAPTER NOT WRITTEN

The endings in Brothers Grimm folk tales don't always turn out well. The Integrity of Supply Initiative is currently developing GSPs to increase the reliability and quality of drug supplies. GSPs will be tied to return on investment and take real-world business realities into account, according to Phillips of Xavier Health. They'll need to; adoption is not a foregone conclusion. As with any initiative raised to the level of best practices and potentially regulatory considerations, there will be tough negotiating over nuances in meaning. For example, while Lowndes is looking for a new industry model to facilitate flexibility and customization at suppliers, Phillips and others seem inclined to put the onus on the manufacturers for broader industry "harmonization" of parameters and specifications. Maybe a nuance, maybe a mountain.

The best practices themselves could prove controversial. An idea flowing from the aforementioned oil and gas industry is one of having a methodology for suppliers to rate manufacturers (not the other way around). Says Phillips: "If industry is really interested in improving product reliability, and know they are part of the problem, then suppliers should rate manufacturers so they can assess how they are doing." She quickly adds, by the way, there are ways to ensure the anonymity of the suppliers.

Timing is on the side of adoption. The need for change has become apparent to patients, their doctors, and healthcare organizations. Big Pharma and med device companies appear ready to face their shortcomings and are looking for solutions. The suppliers, certainly not without issues on their side as well, are caught in the middle of an untenable situation. The U.S. Congress has responded by passing FDASIA, and the FDA has come to the table to assist. Add the simple fact that outsourced supply chains, despite current issues, are on the rise.

Phillips says nobody involved in the Initiative will be satisfied with generating a set of GSPs. "These have to be adopted industrywide," she says. "We'll engage the manufacturers and trade associations to review and endorse the documents, and work with the FDA to have GSPs included in risk assessment of manufacturers and their suppliers. We'll give the industry every reason to adopt these measures." L

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A Recipe For Life Sciences Commercialization

ROGER HUMPHREY

As the landscape of the biopharmaceutical industry expands into growing regions, an exciting transformation is beginning to transfer commercialization "recipes" to emerging markets. All eyes are on small, specialty, and midsize players emerging at the forefront of innovation in the mature regions of Europe and the United States.

At the global level, the BRICK countries of Brazil, Russia, India, China, and Korea are aggressively investing in R&D, facilities, and scientist training, and vying for bigger roles not only as markets for medicines, but also as rich breeding grounds for R&D and manufacturing.

INGREDIENTS OF A SUCCESSFUL TECHNOLOGY TRANSFER

Successfully transitioning from bench to marketplace requires the support of a complex web of ancillary businesses, particularly for those companies that are scaling up rapidly. Mature life sciences clusters like San Francisco's Bay Area, for instance, offer vibrant financial, legal, marketing, and logistics infrastructures that further the industry's success. Some emerging markets have recognized this dynamic and are developing their own clusters accordingly, purposefully recruiting supporting businesses to life sciences research and development parks, and creating initiatives to help businesses with the commercialization process, according to JLL's 2014 *Global Life Sciences Cluster Report.*

Japan is one of the markets hungry to become a leader. The Japanese government is aiming to make Tsukuba Science City its flagship science and technology hub and a global center for public-private basic research partnerships in such areas as microbiology, next-generation cancer therapy, and plant genetics. Japan's *Revitalization Strategy and the Healthcare and Medical Strategy,* released in June 2013, will further support companies' efforts to strengthen R&D capacity, streamline approval processes, and commercialize innovations in regenerative medicine.

The United Kingdom, already a leading cluster, recently funded an initiative to attract more companies to the "golden triangle" encompassing London, Cambridge, and Oxford. The goal is to facilitate collaboration between the cities and the U.K. academic research base and to reinforce specialist infrastructure.

Ontario Canada's Centre for Commercialization of Regenerative Medicine (CCRM) is a network of academics, industry leaders, and entrepreneurs working together to accelerate the commercialization of stem-cell and biomaterials technologies. CCRM was part of the March 2014 renewal of an agreement with China to strengthen collaborations and fund new ideas and technologies.

PUBLIC SECTOR INVESTMENT

Low corporate tax structures, clear and developed regulatory frameworks, and minimal administrative obstacles are all critical to small and midsize enterprises, where so much of the growth in life sciences is occurring. Competitive tax rates lure life sciences companies of all sizes to certain regions, giving them the flexibility to put those extra resources toward other purposes. Many large pharmaceutical companies have moved manufacturing sites to Ireland, for instance, where the corporate tax rate is among the lowest in the world. Switzerland, the United Kingdom, Korea, the Netherlands, and Israel also offer attractive tax rates.

Depending on what a company needs, however, other advantages may outweigh the tax burden. Despite having relatively high corporate tax rates, countries such as the United States, Germany, and Japan continue to be very attractive to many

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life sciences innovators because they provide excellent regulatory systems, world-renowned research institutions, and highly transparent political and financial systems that allow for businesses to be conducted efficiently.

Mature life sciences clusters generally have developed policies that foster small, growing companies and help overcome barriers to market. For example, the U.K. Trade and Investment (UKTI) was created to help attract investment from overseas to domestic ventures, from early-stage development through product commercialization, and helps companies maximize government tax breaks and incentives.

In Korea, the government developed its "Pharma Korea 2020" strategic plan in 2012 to help the country become a top-seven global drug powerhouse by 2020. To establish Osong Bio Valley as a life sciences hub, the Korean government is relocating six government institutions to the region, including the Ministry of Food and Drug Safety and Korea National Institute of Health.

Biotechnology is one of seven strategic emerging industries identified in China's 12th Five-Year Plan, which calls for government spending of more than $1.9 billion on new drugs through 2015. While Big Pharma historically was interested in China as a low-cost manufacturing location, China now is focusing on expanding its capabilities into high-tech R&D functions.

REGIONAL COMPETITION FOR COMMERCIALIZATION HUBS HEATS UP

More life sciences companies are looking internationally at emerging clusters not only for market opportunities, but also as cost-effective locations in which significant investments are being made to design supportive environments that cultivate growing companies. More than one-third of life sciences companies anticipate reducing or consolidating their corporate real estate portfolios in European markets, while 63 percent and 48 percent plan to increase their portfolios in China and Brazil, respectively, according to JLL's *Global Corporate Real Estate Trends for the Life Sciences Sector*.

As regional competition intensifies to gain the coveted life sciences cluster status, businesses must carefully prioritize the most influential external factors that will help make their product or treatment the next billion-dollar idea. L

Roger Humphrey is executive managing director of JLL's Life Sciences Group. He can be reached at Roger.Humphrey@am.jll.com.

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6 Questions To Answer Before Considering A Carve-Out

STEVE SAPLETAL & JOHN NICOL

Carve-out transactions are no walk in the park. Forming an entirely new entity is extremely difficult, especially when you consider the many moving parts that have to be managed all at one time. While technical and financial aspects are usually at the top of executives' carve-out checklists, there is another crucial element that should be made a priority — the organization's people.

We all know that a company's culture is extremely important to the success of the business. Culture affects employee morale, performance, and ultimately how the company operates each day. But culture is especially important in the healthcare, pharmaceutical, and medical device industries where companies can have widely different attitudes towards R&D, quality, and compliance. That's why you should take culture into account before starting the carve-out process.

Here are six questions to ask yourself when undergoing a carve-out:

1 WHAT WAS THE COMPANY CULTURE LIKE BEFORE THE CARVE-OUT?

Clearly understanding the company's current culture is critical before you can even begin to define the culture of the new company. It's also important to understand that there are controllable, as well as organic, factors that impact a company's culture. For instance, leadership is able to control how employees communicate within the organization, but they can't directly control individual attitudes or team behavior.

2 WHAT'S THE NEW COMPANY'S VISION AND MISSION STATEMENT?

Employees should have a clear understanding of the new company's vision and how they fit into that vision. To do this, leadership needs to be as transparent as possible about any cultural differences and expectations for how the new company will operate. Recognizing and pointing out the cultural similarities and differences right away paint a more accurate picture for employees and better define expectations.

3 HOW SHOULD WE COMMUNICATE WITH EMPLOYEES?

Having open communication during a carve-out is simply a must, and developing a detailed communications plan in advance will allow executives to maintain consistency and fluidity when communicating with employees of both the new and parent organization. In addition to the plan, you should create a team dedicated to the internal and external communications of the cultural program. Conducting reoccurring check-ins through employee engagement surveys or small group discussions is helpful in gauging how employees are adapting to the new culture, and what's working and what needs improvement.

4 WHAT INCENTIVES ARE IN PLACE THAT PROMOTE HIGH EMPLOYEE PERFORMANCE?

Before determining what incentives to offer employees, first understand the types of employees who work for you and what motivates them. For instance, do your people like celebrating small victories as a team? Are they driven by monetary incentives? Behaviors and expectations will vary among various roles and levels, so using a behavior road map will help differentiate preferences and identify appropriate solutions.

5 WHAT DO EMPLOYEES THINK ABOUT THE TRANSACTION?

One of employees' biggest concerns during a carve-out is the impact it will have on their job. Questions like "Will my responsibilities change?", "Will I even have a job when this is all over?", and "How will this affect my benefits package?" are sure to emerge at some point during the carve-out. To ensure employees remain on board and productive, executives need to address these concerns right away.

6 WHAT CHANGES WILL THE NEW OWNER BRING?

With a new company comes a new owner and many more adjustments. Oftentimes, new owners will bring their own set of expectations, employees, and processes that will potentially impact the cultural development of the new organization. The expectations of the agreement between the new owner and stand-alone company are key in shaping and aligning the direction of the new company.

Carve-outs are complex and require much thought, especially when it comes to merging corporate cultures. Knowing ahead of time what to expect and how to tackle the cultural shift will make the transition smoother and much more successful. L

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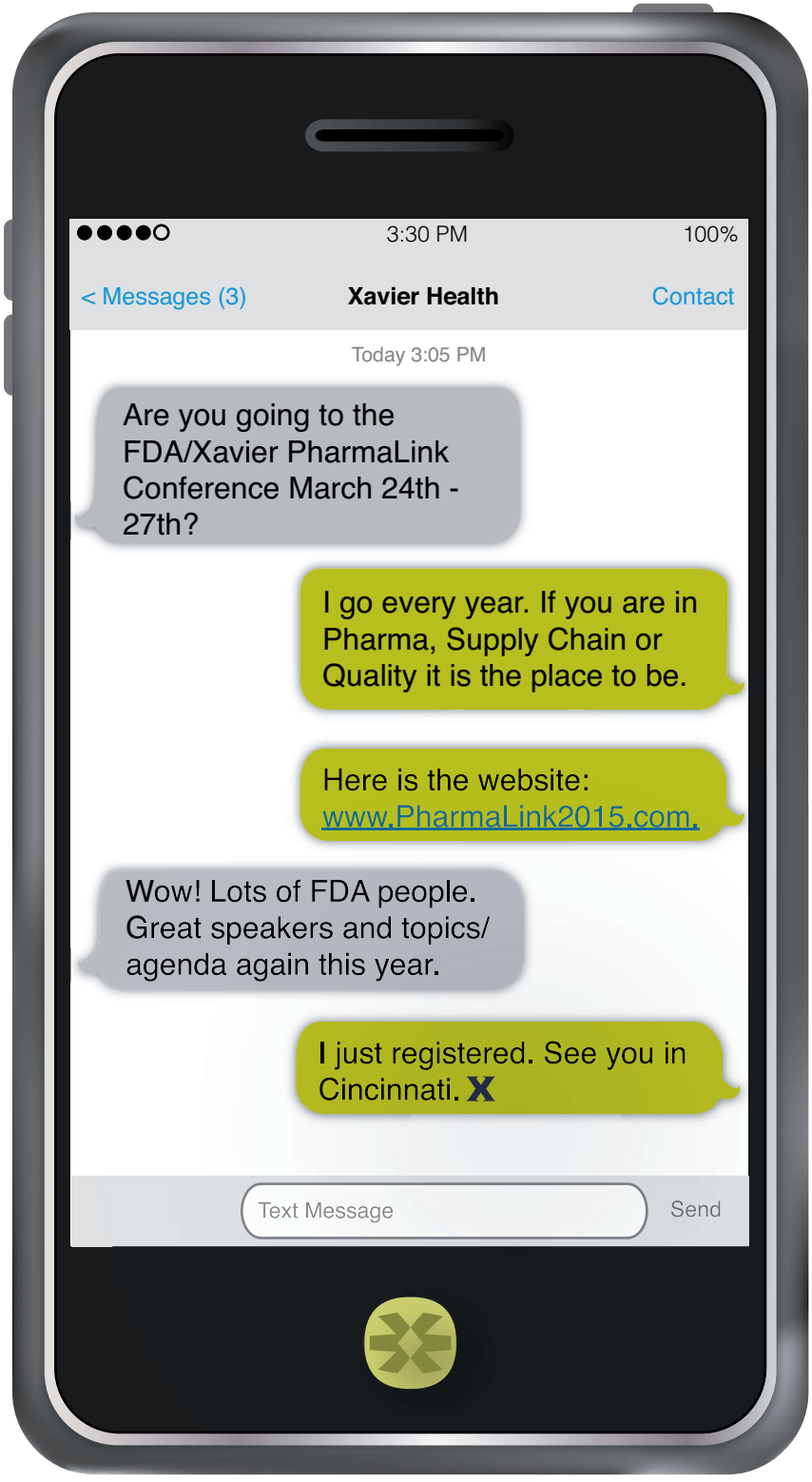
John Nicol is a senior consultant in West Monroe Partners' operations excellence practice.



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Give Them Something To Believe In

JESSICA MELORE

Whether communicating the benefits of a product or simply trying to keep employees motivated, how do we reach them? Give them something to believe in. People respond to what they feel is genuine. It may be an investment in a leader, a product, an organization, or a mindset they have never considered before, but if you can demonstrate that you have their best interests in mind, and that you believe in what you're proposing, they'll be more likely to listen.

BUSINESS IS PERSONAL

As the recipient of a lifesaving heart transplant, organ donation for me is personal. When I talk about it with people, I try to make it personal for them by asking how they would feel if a loved one needed an organ. I disagree with the saying, "It's not personal, it's just business." Your business should be personal. If you want to give your team something to believe in and take a more personal interest, try incorporating the following components into your communications:

VISION

This is not the company-approved vision plastered around the office and on websites, but your personal vision, for what you want the company, department, or your team to achieve. Giving them something to believe in requires a more personal approach and your willingness to boldly share your personal vision without fear of what others will think.

EMPATHY

Demonstrating an understanding of the challenges your team faces, either from observation, intensive research, or, ideally, firsthand experience is important to gaining believers on your team. The four components of empathy are perspective-taking, not judging, recognizing people's emotions, and then communicating that recognition (e.g., I know how you feel). Think of empathy as the fuel of connections, not an opportunity to one-up someone's feelings of being overwhelmed with your more difficult story.

COMMITMENT/INVESTMENT

These factors must go hand-in-hand. You can be committed to a project by going through the daily motions without putting forth the psychological, emotional, and financial investment to make it a true success. You can also be deeply invested without committing the time or discipline to getting it done. If you want your team to be committed to an effort, you need to be prepared to roll up your sleeves and do the same.

HUMILITY/FLEXIBILITY

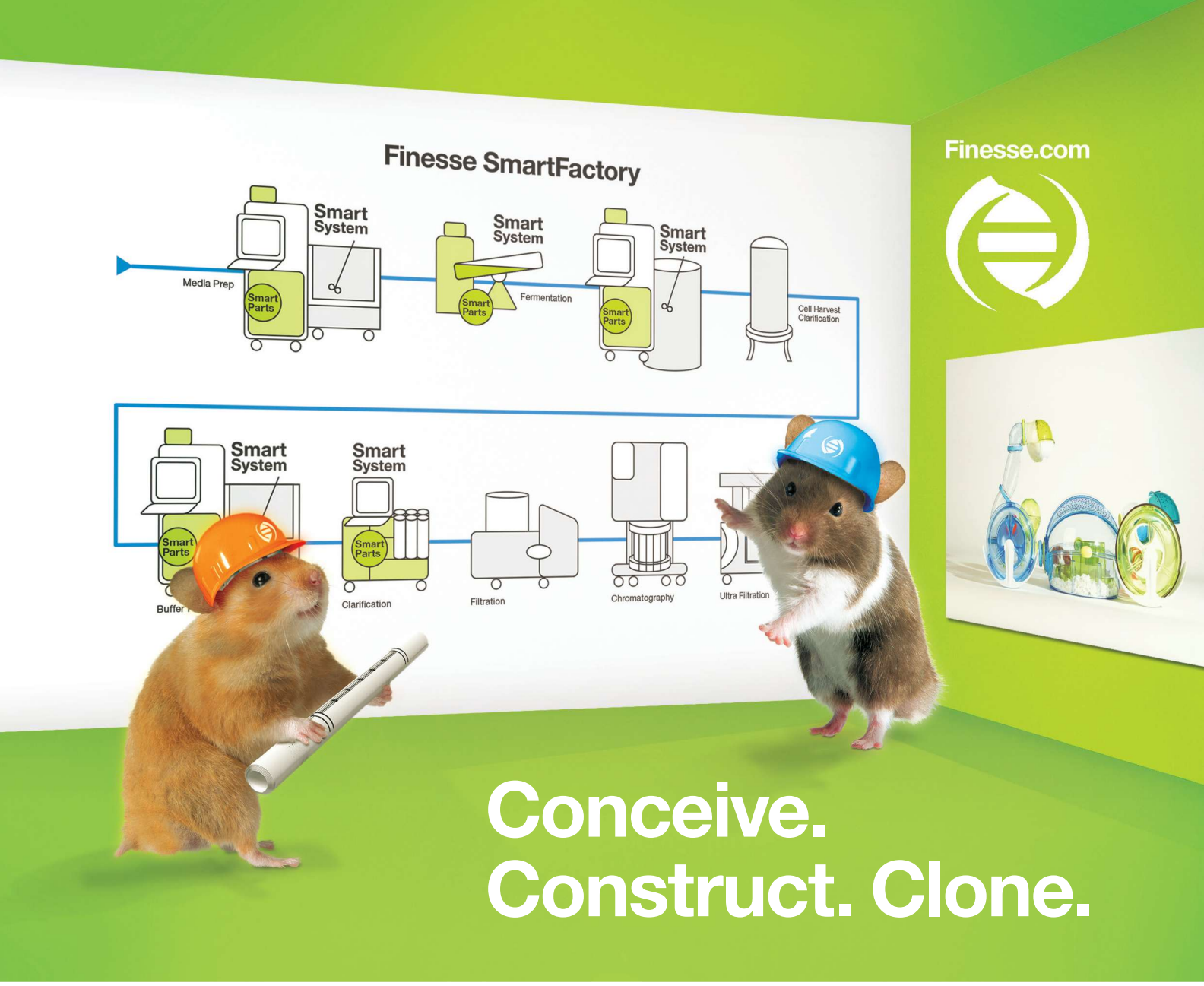
People value success, but they value transparency even more. Leaders who have the ability to admit failures and shortcomings can be endearing and win admirers. However, being flexible in addition to humble, and willing to make adjustments to better respond to the needs of your team, will win you commitment.

PERSONAL MOTIVATION

You may be doing all the right things. However, conveying your enthusiasm for your idea makes all the difference. Don't just talk about what makes you excited to get up in the morning. Instead, tell the stories of the people or entities your idea, products, or services will impact now and in the future.

People invest in ideas that are inspiring, well-thought-out, and backed with passion and commitment. People don't want to run through a brick wall for a company, but they will support a leader capable of giving them something to believe in.

A survivor of a massive heart attack, heart transplant, leg amputation, and two bouts of cancer, Jessica Melore is an international motivational speaker and public health ambassador for health organizations and Fortune 1000 companies worldwide. For more information, visit www.jessicamelore.com.



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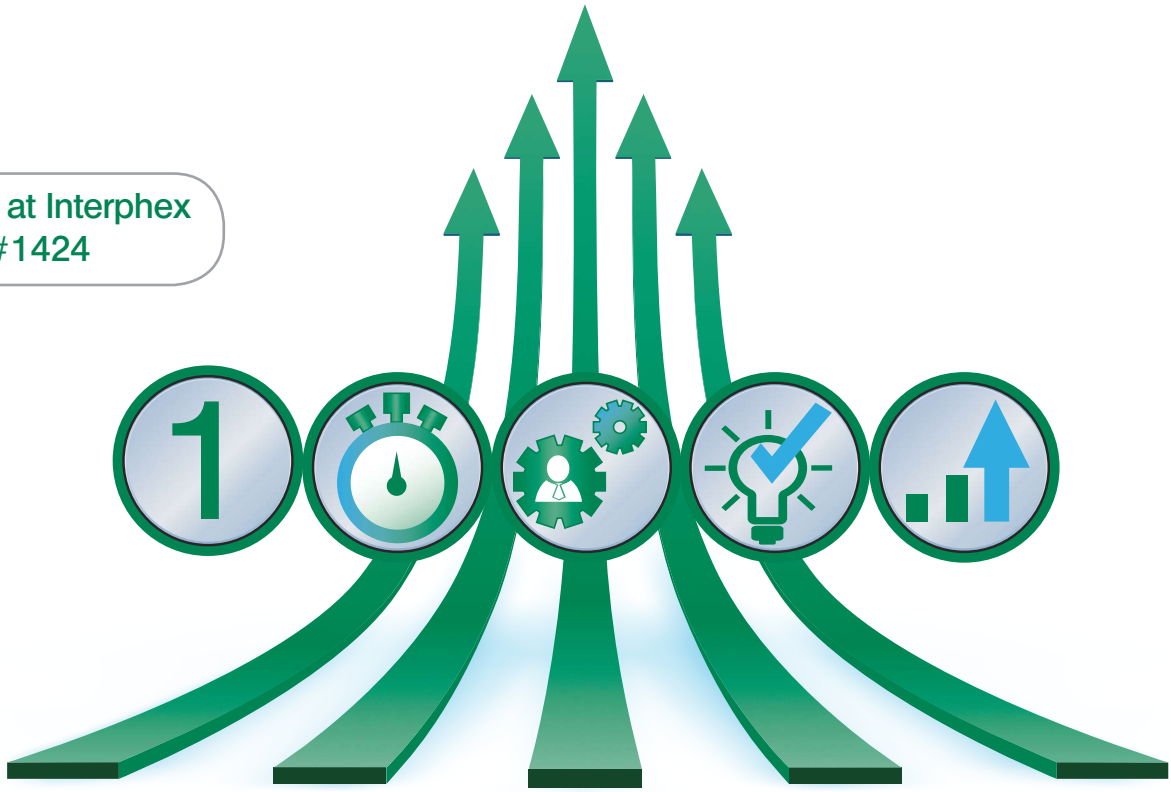

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